WOMEN'S HEALTH: THE ROLE OF NUCLEAR MEDICINE

A TECHNOLOGISTS' GUIDE

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Foreword

Over the years, nuclear medicine has evolved from a limited set of medical procedures for unspecified future applications into a well-established field of medical imaging, patient management and therapy. Although the availability of both the equipment and radiopharmaceuticals remains insufficient in view of the great demand for nuclear medicine applications, it is assumed that nuclear medicine tools will eventually become an integral part of standard clinical practice that is of pivotal importance for the detection, monitoring and treatment women's diseases.

WOMEN'S HEALTH — CURRENT STATUS AND FUTURE PERSPECTIVES

Recent rapid advances in drugs and technology have made it possible to manage numerous diseases beyond the past expectations of medical professionals, offering the opportunity to significantly improve detection and staging of oncological and non-oncological diseases in women and allowing individualised planning of therapeutic protocols. The rise of theranostics, the evolving nuclear medicine instrumentation and ongoing drug development are a direct response to the requirements of contemporary healthcare systems. Simultaneously, the field's expansion provides opportunities for female medical professionals from all specialties to develop both professionally and scientifically. Nevertheless, women's status in the nuclear medicine field requires attention, analysis, and effective solutions to address the situation.

Female patients and healthcare professionals experience similar challenges. Pregnancy, developing family life and the desire to maintain a work-life balance limit the possibility to ensure both physical well-being and career development. Similarly, both women undergoing procedures and those working in the nuclear medicine field must be protected from radiation overexposure, especially during pregnancy and breastfeeding. Both professionals and patients experience

limitations regarding their participation in studies or therapy, as the pregnant or breastfeeding patient cannot undergo the majority of procedures while the employee is excluded from their work environment. Novel technologies involving digital imaging and remote work tools support both the female patient and the nuclear medicine professional willing to remain active regardless of their ability to actively participate in the department's daily routine, but they do not resolve all the issues women experience. More often than men, women experience difficulties in regard to their age and/or religious or ethnic background in accessing both the appropriate healthcare and professional opportunities.

Modern nuclear medicine offers the possibility to undergo procedures performed by highly qualified, multidisciplinary medical teams, ensuring the intimacy and comfort which are vital for the management of female patients. However, it is crucial to ensure the involvement of large numbers of female professionals as a critical step towards improving women's level of security on their path to a full recovery. The expanding set of diagnostic and therapeutic procedures aimed at detecting and monitoring various gynaecological diseases entails many opportunities but also gives rise to a number of very specific concerns, including prevention and treatment of fertility problems post-radioisotope therapy or the oncological management of pregnant women. In these very specific areas, the presence of highly specialised female nuclear medicine experts appears to be not only an advantage, but indeed a necessity.

This year's *Technologist's Guide* looks at nuclear medicine from the perspective of female patients and employees, describing the procedures regulating their presence in the nuclear medicine department and presenting detailed analyses of both widely established and novel technologies and radiopharmaceuticals. Guiding the reader through all aspects of diagnostic and therapeutic management of female patients, it explains best practice in women's health from the point of view of nuclear medicine professionals.

The EANM Women's EmpoWErment Initiative recommends this book as a guide to the best practice necessities of contemporary nuclear medicine and the benefits that nuclear medicine offers women, both now and looking ahead to the future.

Laura Evangelista
EANM Women's EmpoWErment Initiative Leader

Agata Karolina Pietrzak
EANM Women's EmpoWErment co-Leader & Social Media Unit Head

Introduction

Nuclear medicine, as a branch of medical imaging and therapy, plays a crucial role in diagnosing and treating various health conditions. Its applications in women's health are not always accorded enough attention, however, despite harbouring a massive potential with regard to clinical impact and research. This edition of the Tech Guide not only aims to review and present well-established diagnostic methods, but also introduces new, innovative radiopharmaceuticals that could indeed revolutionise women's healthcare.

The nuclear medicine field could dramatically shift the current paradigm in terms of diagnosis and treatment of breast and gynaecological cancers and diagnostic profiling of endometriosis and shed greater light on cardiovascular diseases that disproportionately affect women. As such, investing in and studying nuclear medicine specifically tailored to women's health has the power to transform the way we approach diagnostics, patient management, and therapeutic options for female patients – something that technologists should be aware of and be champions for.

When planning this Tech Guide, the editorial team aimed to address critical considerations related to female workers in nuclear medicine, especially during pregnancy and upon their return to work, and likewise to focus on ensuring the safety of female patients undergoing investigations. In both contexts, technologists ought to be confident and

knowledgeable in discussing risks and benefits, in conducting risk assessments, and in implementing mitigation plans within their teams and departments. We hope that the information provided in this Guide empowers them to do so.

Our intention is also to ensure that the evolving needs of patients are acknowledged and honoured. Thus, please note that in this Guide, in the interests of simplicity, the term "woman" or "female worker" is inclusive of all who identify as female, were assigned a female gender identity at birth or experience physical health conditions associated with the female body.

Health and safety considerations are also critical in ensuring that the privacy, dignity and comfort of female patients are respected during nuclear medicine investigations, acknowledging cultural sensitivities and the need to cater to specific needs in an empathetic manner – this is key for the patient-facing part of the workforce: the technologists.

We are delighted to have assembled a multidisciplinary team of highly dedicated professionals to put together this Guide, making it relevant, contemporaneous, and well rounded. By integrating health and safety measures, radiation protection and patient-centred practices, the nuclear medicine community continues to contribute to advancements in women's healthcare while maintaining the highest standards of informed consent, safety and ethics.

We hope that readers will find this edition of the Tech Guide informative, both as a practical tool and as an open invitation to become involved in these remarkable developments, playing an active part in making these procedures a reality for patients everywhere.

Luísa Roldão Pereira,
Ângelo Rafael Felgosa Cardoso,
and Marta Coelho
The Editorial Team

1.1 CONSIDERATIONS FOR THE FEMALE PATIENT

by Sigrid Leide Svegborn

Medical Radiation Physics, Department of Translational Medicine, Lund University
Skåne University Hospital, Malmö SWEDEN

EXECUTIVE SUMMARY

Pregnancy and lactation are often contraindications in nuclear medicine due to increased radiation risk to the embryo/foetus of the pregnant patient and to the infant/child of the breastfeeding patient. When it is of vital importance for the patient, the responsible physician may, after a thorough justification assessment taking into account both the patient and the foetus or infant, consider the procedure to be appropriate.

Embryos and foetuses, infants and children exhibit a higher risk of suffering from severe health effects from ionising radiation than adults and the elderly. They have a longer life expectancy after the exposure during which long-term radiation-induced effects may occur, and they do not derive any direct benefit from the clinical procedure. Thus, significant efforts must be undertaken to protect them from unnecessary irradiation.

Most diagnostic nuclear medicine procedures are performed with short-lived radionuclides such as ^{99m}Tc or ^{18}F, which do not cause large foetal doses. Even though these procedures present no increased risk of severe acute health effects to the foetus, the risk of radiation-induced childhood cancer is not negligible. The foetal dose can be minimised by reducing the activity and prolonging the imaging scan time, as well as by encouraging the pregnant patient to drink more fluids than usual and to void frequently. A foetal whole-body dose of less than 100 mGy is no reason to terminate the pregnancy based on the radiation risk. For radiopharmaceutical therapy, on the other hand, pregnancy is an absolute contraindication, unless the treatment is lifesaving. Radioiodine (such as Na[^{131}I]I) may cause serious foetal thyroid harm and must be avoided.

Breastfeeding is important overall and should not be terminated if not necessary. In most cases, breastfeeding can be continued after a short interruption. Nuclear medicine staff should follow published recommendations on breastfeeding interruption. Breastfeeding must be stopped permanently before administration of radioiodine and other radiopharmaceuticals used for therapy.

Keywords:
Breast feeding; Foetus; Pregnancy; Radiation dose; Radiation exposure; Radiopharmaceuticals

INTRODUCTION

Pregnancy and lactation are often contraindications in nuclear medicine due to increased radiation risk to the embryo/foetus of the pregnant patient [1] and to the infant/child of the breastfeeding patient. When it is of vital importance, pregnant or breastfeeding patients may, however, be referred for nuclear medicine procedures. The performance of these procedures has to be preceded by a thorough justification assessment, weighing benefits against risks to the individual's health and that of the foetus or infant, and taking into account how time-critical the intervention is. For this reason, the techonologist or physician must always check the patient's circsumstances before initiating any procedure involving ionizing radiation.

In the early part of pregnancy, the formation of the human being is called an *embryo*. About 60 days after conception, most of the organs have been formed and a period of growth follows. During this period, it is called a *foetus* [2]. However, in the interests of simplicity and readability, the terms foetus, foetal exposure and foetal dose are used consistently throughout this chapter. Likewise, in the subchapter on breastfeeding the radiation dose to a young child who is breastfed is estimated and the terms *infant or child* are used consistently throughout, even though early childhood can be divided into several phases: newborn (approx. 0–3 months old), infant (approx. 2 months–1 year) and toddler (approx. 1–4 years) [3].

Embryos, foetuses, infants and children exhibit a higher risk of suffering from severe health effects from ionising radiation than adults and the elderly [1, 4]. Significant efforts must therefore be undertaken to protect them from unnecessary irradiation, and if the radiation exposure is indeed considered necessary, the rationale for the decision must be documented and the dose kept as low as reasonably achievable. It is important to have clear and proper recommendations in place on how to proceed when an embryo or foetus of a pregnant patient or an infant or child of a breastfeeding patient are exposed to ionising radiation, whether intentionally or accidentally.

PREGNANCY AND MEDICAL RADIATION

The risk of undesirable health effects due to exposure to ionising radiation sometimes gives rise to great anxiety, especially in pregnancy. Misconceptions around radiation may have led to misinformed decisions about the patient's health, including advice on medically-assisted abortion [1]. Patients, their relatives, carers and comforters, as well as healthcare staff, must be properly informed about the risks and their magnitude.

Radiation Risk to the Embryo or Foetus

The radiation-associated risks throughout pregnancy are related to the absorbed dose to the foetus. The higher the absorbed dose to the foetus, the higher the risk of unwanted health effects becomes. The radiation risks are also related to the stage of pregnancy at the time of irradiation. The radiation risk is most significant during the period when the organs are developing, i.e. in the early foetal period, whereas it is somewhat less in the second trimester and least in the third trimester [1].

The radiation dose of interest in this chapter is the absorbed dose to the foetus, i.e. the foetal dose. This is expressed in the unit milliGray, mGy. Dose limits are given as equivalent dose in the unit milliSievert, mSv [4]. For low-energy photon and electron radiation, which is the type of radiation emitted from the radionuclides used in diagnostic nuclear medicine and from many of the radionuclides used for treatment, as well as during CT, the numerical value of the absorbed dose [mGy] is basically equal to the numerical value of the equivalent dose [mSv].

At high foetal doses, i.e. approximately 100 mGy or more, deterministic effects, also called tissue reactions, may occur [1]. If the patient is in early pregnancy, not more than a couple of weeks after conception, there is a risk of failure to implant and thus of early miscarriage. High foetal doses may result in lethal effects to the growing foetus, including malformation and intellectual disability [1, 5]. These effects have a threshold dose of approximately 100–200 mGy, which means that if the foetal dose is below 100 mGy the effect will probably not occur.

In addition to tissue reactions, the exposure may result in stochastic effects such as radiation-induced cancer [1, 4]. It is well known that ionising radiation increases the risk of leukaemia and other types of cancer in children and adults. For stochastic effects the LNT (Linear No Threshold) model is assumed, which means a linear relationship between the risk of carcinogenic effects and the radiation dose, without a minimum threshold dose [4]. It has been shown that the risk of a radiation-induced cancer may be about 3–4 times higher for infants and small children than for adults and the elderly [6]. This is explained by fast cell proliferation and longer life expectancy during which a radiation-induced cancer may occur. The risk of carcinogenic effects to a foetus is assumed to be in the same order as for a child [1]. According to ICRP Publication 84, a radiation dose of approximately 10 mGy to a foetus will result in an absolute risk of cancer at age 0–15 years, equivalent to about 1 excess cancer death per 1700 foetuses irradiated [1].

It should be noted that the risk of spontaneous miscarriage (without any extra exposure to ionising radiation above natural background radiation) is more than 15%. The risk of incidence of genetic abnormalities in a pregnant population not exposed to ionising radiation is 4–10%, and the risk of prenatal growth deficiency and incidence of major malformations is around 4%. The

probability of childhood cancer is about 0.3% without any extra radiation dose above the natural background radiation [1].

Foetal Exposure from Radiopharmaceuticals

Before a radiopharmaceutical is administered to a patient of childbearing age (from the age the patient begins to ovulate until 2 years after menopause, typically between 12–55 years of age), possible pregnancy must be considered. Identification of a pregnant patient should be done orally and in writing through questions in the invitation letter to the examination, information posters in the patient waiting room (Figure 1) and repeated questions shortly before the administration of the radiopharmaceutical, when the technologist or physician is explaining the procedure and obtaining consent.

Some procedures deemed essential for the patient's health may be justified and appropriate also for a pregnant patient, such as lung scintigraphy for suspected pulmonary embolism or a tumour imaging examination, when the likely benefit far exceeds the risk incurred to the pregnant patient and the foetus. In these circumstances the procedure should be optimised to minimise the foetal dose while obtaining image quality good enough for proper and accurate interpretation of the examination. Such optimisation measures include a reduction of the activity and a corresponding increase in the scan time to ensure the same image

Figure 1. Examples of appropriate posters, situated in the patient waiting room, with information on the importance to inform the staff if pregnant or breastfeeding. Courtesy of A) International Atomic Energy Agency, https://rprop.iaea.org and B) Radiation physics, Region Skåne, Sweden.

quality, while considering the risk of motion artefacts if the scan time is too long to be comfortable for the patient.

In nuclear medicine, the foetus may be irradiated *externally* from activity in the pregnant patient. The majority of radiopharmaceuticals are primarily excreted through the urinary bladder system, and activity in the urinary bladder can be significant. The short distance between the foetus and the urinary bladder therefore entails a significant risk of exposure for the foetus. A recommended radiation protection measure is to encourage the pregnant patient to drink 1–2 more litres of fluids than usual and to void frequently after administration of the radiopharmaceutical.

Some radiopharmaceuticals have been shown to cross the placental barrier and concentrate in foetal tissue. Thus, the foetus is also exposed *internally*. This has been demonstrated for ^{99m}Tc-labelled diphosphonates [7], [^{18}F]FDG (2-[^{18}F]fluoro-2-deoxy-D-glucose) [8] and Na[^{131}I]I ([^{131}I] sodium iodide) [9] among others.

Nuclear medicine physicians need to obtain accurate dose estimates as part of the essential justification assessment before a nuclear medicine procedure. The magnitude of the absorbed dose to the foetus depends on what procedure is carried out. The biodistribution and retention of the radionuclide within the pregnant patient, the excretion pathways and possible placental crossing are different for different radiopharmaceuticals, consequently resulting in different foetal doses. Other parameters that have an impact on the foetal dose are the physical properties of the radionuclide, such as the type of ionising radiation and energy emitted during radioactive decay, as well as the physical half-life.

Determination of The Foetal Dose

It is not possible to measure the radiation dose to the individual foetus exposed. It is, however, possible to make a reasonably accurate estimate based on knowledge of the activity administered to the pregnant patient and dose coefficients calculated for the uterus of a reference pregnant patient and for a reference foetus in the 1st, 2nd, and 3rd trimester [10–13].

For a patient in early pregnancy, the dose to the uterus may be used as a substitute for the foetal dose, at least for the first two or three months before the embryo has grown too big. This approximation presumes no placental crossover. The uterine doses from some hundred different radiopharmaceuticals used in diagnostic nuclear medicine are given in ICRP publication 106 and publication 128, "Radiation dose to patients from radiopharmaceuticals" [10, 11]. It is, however, important to emphasise that these biokinetic models are based on a reference person and cannot be used for individual dosimetry.

Dose coefficients ($mGy_{foetus}/MBq_{patient}$) for foetuses **in the first, second and third trimester,** for many different radiopharmaceuticals are given in a paper by Russell *et al*. [12]. The foetal dose coefficients

are calculated using the internal dosimetry schema of MIRD (Medical Internal Radiation Dosimetry Committee) [14], defining the whole-body foetus as the target tissue and the organs and tissues of the pregnant patient containing the activity as source organs. The mean dose to the target tissue (in this case the foetus) is determined by multiplying the cumulated activity by the S-value. These two parameters include biological information such as the activity distribution and retention in the organs and tissues, as well as the mass of the target organ and data on the physical properties of the radionuclide. The specific absorbed fraction, SAF used in the dose estimation is based on a mathematical or computational description of the pregnant patient. For those radiopharmaceuticals where placental crossover has been recognised [15], the contribution to the foetal dose from the foetus itself (self-dose) has been added to the maternal part [12]. The foetal doses from some common nuclear medicine examinations in early pregnancy and at third trimester are given in ICRP publication 84 [1], with reference to the papers by Russell *et al*. [12, 15]. Intense development of a more precise description of a pregnant female has led to new SAFs. The computational phantoms for the pregnant patient by Stabin [13] and corresponding foetal dose coefficients for a great number of radiopharmaceuticals for early pregnancy (the uterus) and at the first, second and third trimester are a result of this. The publication by Stabin [13] includes both maternal dose and self-dose, when appropriate. Foetal doses for new substances since the publication by Russell *et al*. [12] have been added to the list.

Foetal Dose for The Pregnant Patient in Diagnostic Nuclear Medicine

Using the values for foetal dose coefficients presented in the paper by Stabin [13] and reference activities for the diagnostic nuclear medicine procedures [16], the whole-body foetal dose from an examination of the pregnant patient will be around 1-15 mGy for radiopharmaceuticals labelled with ^{99m}Tc, approximately 2-8 mGy for a procedure with 300 MBq [^{18}F]FDG, and about 7–24 mGy for 220 MBq of [^{111}In]In-pentetreotide administered to the patient (Table 1).

Putting these values into perspective with regard to the threshold doses for tissue reaction to a foetus, it can be concluded that prenatal doses from most properly performed diagnostic procedures using radionuclides with short physical half-lives, such as ^{99m}Tc and ^{18}F, present no noticeably increased risk of prenatal death, malformation, or intellectual disability. The risk of radiation-induced carcinogenic effects, however, is not completely negligible. Thus, it is highly recommended to keep the dose as low as reasonably achievable and encourage the pregnant patient to drink more than usual and void frequently during the day or days following administration of the radiopharmaceutical. If possible, the

activity administered to the patient may be reduced and the scan time in the gamma camera or PET-camera (positron emission tomography) prolonged accordingly.

Hybrid Imaging, SPECT/CT and PET/CT

Many nuclear medicine procedures are performed as hybrid imaging, i.e. the examination includes administration of a radiopharmaceutical followed by a PET or SPECT scan in combination with a CT scan. This CT scan contributes to the radiation dose to the patient and consequently to the dose to the foetus of a pregnant patient. Depending on the purpose of the CT scan, be it for attenuation correction, localisation or for diagnostic purposes, the foetal dose from CT varies from less than 1 mGy up to several tens of mGy [17]. Thus, it is important that the justification assessment for a nuclear medicine procedure also factors in a possible simultaneous CT scan. Regarding iodinated X-ray contrast agents, the central detrimental effect is their potential impact on the thyroid gland of the newborn [18].

A special case: Identification of acute pulmonary embolism in pregnant patients

Pulmonary embolism is the leading cause of pregnancy-related mortality, and clinical symptoms in pregnancy are not as typical as without pregnancy [19]. Most often the procedure is justified due to the serious condition of the patient. There is no crystal-clear evidence regarding choice of best strategy – lung scintigraphy or CT pulmonary angiography (CTPA). The foetal dose is low (< 1 mGy), regardless of modality, if the procedure is optimised. The foetal dose with CTPA is considerably lower early in pregnancy, but of the same magnitude later in pregnancy. The dose to the breasts of the pregnant patient is, however, lower with lung scintigraphy. Each hospital must take into consideration available optimised methods, professional expertise and local experience, as well as practical arrangements (e.g. prompt availability of scintigraphy and obtainability of the radiopharmaceutical if delivered by an external supplier). A missed pulmonary thrombosis is much worse than the possible radiation risk.

Foetal Dose for The Pregnant Patient in Therapeutic Nuclear Medicine

Regarding patients who receive radiopharmaceuticals for therapeutic purposes, the situation is quite different. The physical half-lives of the radionuclides used are longer and the activity administered is considerably higher, at least for β^--radiation-emitting radionuclides. Thus, pregnancy is an absolute contraindication in radiopharmaceutical therapy, unless the therapy is lifesaving. In radiopharmaceutical therapy, potential foetal health effects are severe and identification of pregnancy is vital. The possibility of pregnancy must be excluded before administration, preferably through *serum* β-hCG analysis (blood test),

and/or abdominal (vaginal) ultrasound examination [9].

Of special concern is the frequently occurring treatment of thyroid diseases such as thyroid carcinoma and hyperthyroidism. The radiopharmaceutical Na[^{131}I]I, which is used for these treatments, crosses the placental barrier and concentrates in the foetal thyroid. This concentration begins already 8–10 weeks post-conception [1]. The dose to the foetal thyroid due to this accumulation can become very high, in the order of hundreds of Gy, which can result in permanent hypothyroidism and risk of severe physical and mental harm to the foetus [9]. Even diagnostic levels of radioiodine for uptake measurements can cause serious health effects to the foetus due to the specific thyroid uptake, even though the foetal whole-body dose is low (Table 1). If pregnancy is discovered early after administration, i.e. within approximately 12

Radiopharmaceutical	Reference activity to patient, DRL (MBq)	Estimated whole body foetal dose (mGy_{foetus})			
		Early pregnancy	3-mo gestation	6-mo gestation	9-mo gestation
[^{18}F]FDG (Whole body tumour imaging)	300	7.8	5.7	4.2	2.1
[^{99m}Tc]Tc-MAA[1]	200	0.64	2.4	0.52	0.34
[^{99m}Tc]Tc-MAG3[2]	100	2.6	1.8	0.57	0.41
[^{99m}Tc]Tc-pertechnetate (Thyroid imaging)	80	1.1	5.0	0.88	0.46
[^{99m}Tc]Tc-sestamibi	800	14	9.6	5.5	4.5
[^{111}In]In-pentetreotide	220	24	17	8.1	6.6
Na[^{131}I]I* (Thyroid imaging/uptake)	0.2	0.015*	0.032*	0.058*	0.044*
Na[^{131}I]I* (Metastasis imaging)	400	30*	64*	116*	88*

*The values represent the foetal whole-body dose. The foetal thyroid dose however may become a factor of hundred or more higher. [1]FDG fluorodeoxyglucose, [2]MAA macroaggregated albumin, [3]MAG3 mercaptoacetyltriglycine.

Table 1. Foetal doses for a selected group of radiopharmaceuticals, for early pregnancy (the uterus) and at the first, second and third trimester, based on foetal dose coefficients from Stabin [13] and reference activity to a patient (Diagnostic Reference Levels, DRL) [16].

hours, and the foetus is old enough to have a functional thyroid, the effect can be reduced by rapid and repeated administration of stable potassium iodine to the pregnant patient [18].

Patients, both females and males, should avoid conception for a period following radiopharmaceutical therapy [16, 20–21]. The length of this period depends on the radiopharmaceutical concerned. Regarding treatment with Na[^{131}I]I, various radiation protection bodies recommend different lengths of time for avoiding conception, from approximately 4 months to 12 months after administration of the radioiodine [16, 20-21]. Other factors to consider include whether or not the patient also has other treatments as well as the individual life situation, meaning that pregnancy is something for patients to discuss with their oncologist and other specialists.

Unintended Administration of Radiopharmaceuticals to a Pregnant Patient

If a patient is discovered to be pregnant soon after administration, maternal hydration and frequent voiding should be encouraged to help eliminate maternal activity and reduce the residence time of the radionuclide in the urinary bladder. This will decrease the external dose to the foetus as well as the dose to the patient. The foetal dose should be estimated, and information should be provided to the pregnant patient, cautiously. Most diagnostic procedures are performed with short-lived radionuclides such as ^{99m}Tc and ^{18}F, which do not cause large foetal doses. Radioiodine, on the other hand, may cause significant foetal thyroid harm. If pregnancy is discovered within 12 hours of radioiodine administration, prompt oral administration of stable potassium iodide to the pregnant patient can reduce the foetal thyroid dose. This may need to be repeated several times. A foetal whole-body dose of less than 100 mGy is no reason to terminate the pregnancy based on the radiation risk [1]. Foetal doses in excess of 500 mGy can result in serious harm to the foetus, the magnitude and type of which is a function of dose and stage of pregnancy. At foetal doses of between 100 and 500 mGy, decisions should be based on individual circumstances.

Information to The Pregnant Patient

Communicating the risk is extremely important and should be done cautiously, so as not to increase anxiety or play down the severity. The pregnant patient has a right to know the magnitude and type of potential radiation effects that might result from in-utero exposure. Communication should reflect the level of risk. Communication that risk is negligible may be adequate for procedures that result in very low foetal doses (< 1 mGy). If foetal doses are above 1 mGy, a more detailed explanation should be given. The information should include the radiation risk to the foetus but also the risk to the pregnant patient if they refrain from the procedure.

BREASTFEEDING PATIENTS IN NUCLEAR MEDICINE

Administration of radiopharmaceuticals to breastfeeding patients is generally avoided, as the activity is secreted to varying degrees in breast milk. This may result in unwanted radiation exposure of the infant who ingests the milk and to enhanced external exposure due to the close contact between the breastfeeding patient and the infant. Occasionally, however, lactating patients are referred for acute clinical examinations and interruption of breastfeeding is recommended, either temporarily or permanently.

Breastfeeding is very important for the infant and also for the nursing person. There are several health benefits for the infant [22]. The breast milk contains antibodies that protect the infant from childhood illnesses such as diarrhoea and pneumonia. Breastfeeding has also been shown to reduce the risk of type 2 diabetes and the risk of becoming overweight or suffering from obesity. Furthermore, there are health benefits for the breastfeeding person [22]. It reduces the risk of breast cancer and ovarian cancer, as well as the risk of type 2 diabetes and postpartum depression. Breastfeeding should not be terminated unless absolutely necessary; instead, guidance on temporary interruption should be provided.

Following administration of radiopharmaceuticals to breastfeeding patients, activity can be detected in the breast milk to various degrees. When ingesting the radioactive breast milk, the infant is exposed to unwanted irradiation. This is of special concern, since infants are comparatively highly sensitive to radiation, have a longer life expectancy, and do not derive any direct benefit from the clinical procedure [18].

In diagnostic nuclear medicine, the radiation dose is of a magnitude that may cause radiation-induced cancer such as leukaemia or solid tumours, albeit with a very low probability. If radioiodine is involved, however, there may be a risk of serious thyroid diseases such as hypothyroidism or thyroid carcinoma, since the thyroid gland of young children, infants and foetuses is more sensitive to radiation than that of adults [4]. On the other hand, there may also be a risk to the breastfeeding patient if the procedure is postponed or not carried out at all.

The solution to the dilemma, weighing the importance of breastfeeding against the acute need for a clinical examination and the risk of serious health effects, is to interrupt breastfeeding – either temporarily for most radiopharmaceuticals, or permanently in the case of a very few.

Determination of The Dose to The Infant During Breastfeeding

The appropriate recommendation on interruption of breastfeeding is based on estimation of the radiation dose to the infant potentially ingesting the breast milk and a dose limit of 1 mSv (Effective dose), under the

assumption that the infant is a member of the public [4]. In order to determine the effective dose to the infant potentially ingesting the breast milk, information on several parameters is needed, namely:

- The activity concentration in several consecutive samples of breast milk obtained from the breastfeeding patient over several hours or days after administration;
- The estimated amount of breast milk ingested by the infant;
- Data on the biodistribution and retention of the radionuclide within the infant, among other factors;
- Absorbed dose coefficients (mGy_{infant}/$MBq_{patient}$) for oral administration.

The effective dose is estimated using tissue weighting factors defined by the ICRP [4]. Due to the lack of information regarding infants and children, the tissue weighting factors for adults must be used.

It is very cumbersome and difficult to determine the factors mentioned above for each individual case, hence various international radiation safety bodies, such as the International Atomic Energy Agency, IAEA, and the International Commission on Radiological Protection, ICRP, among others, have published general recommendations on breastfeeding interruption for various radiopharmaceuticals used in diagnostic nuclear medicine [11, 23]. These recommendations are based on data from papers published in scientific literature with original data, e.g. [24, 25], reviews [26, 27] and case reports.

Recommendations on Interruption of Breastfeeding

For many radiopharmaceuticals, activity can clearly be seen in the gamma camera or PET images of the breasts in lactating patients [24]. The amount of activity in the breast milk, however, varies between different radiopharmaceuticals because of the different molecular properties of the substances. Technetium-99m, as sodium pertechnetate, has been shown to be excreted in the breast milk to a significant extent, in total 10–20% of the activity administered to the breastfeeding patient [24–26]. Iodine-131, as sodium iodide, is another example of a substance with substantial activity excretion in breast milk, in this case 4–48 % [24, 27]. In contrast to this, for example, activity can clearly be seen in the breasts on the PET images immediately after an injection of [^{18}F]FDG , but almost negligible amounts of activity are found in the breast milk [24, 28].

With a dose limit of 1 mSv, recommendations on breastfeeding are divided into subgroups. Table 2 gives recommendations on breastfeeding interruption for a selection of radiopharmaceuticals frequently used in diagnostic nuclear medicine [23]. The recommendations are divided into the following subgroups:

a. No interruption needed at all;

b. Interruption for four (4) hours immediately after administration followed by manual emptying of the breasts and disposal of the breast milk;

c. Interruption for twelve (12) hours with manual emptying of the breasts every four hours, corresponding to three feeds, and disposal of the breast milk;

d. Total cessation;

e. No interruption of breastfeeding, but temporary avoidance of close contact between the infant and the patient.

If the nuclear medicine examination is not acute, the patient should be instructed to express breast milk in advance and keep it in the refrigerator or freezer for use during the interruption period. The infant should be breastfed just prior to the administration of the activity.

With most ^{99m}Tc-labelled substances it is not necessary to interrupt breastfeeding. However, there may be a risk of small amounts of free pertechnetate in the preparation, which has been shown to be largely excreted via breast milk. A four-hour interruption period during which one feed is discarded and not given to the infant will reassure the patient that the risk is negligible [24].

For some radiopharmaceuticals, the interruption period is estimated to be so long (several weeks) that it may be difficult for the patient to maintain her breast milk production, and in this case it is more appropriate to recommend permanent interruption. This is the case for sodium iodide with iodine-131, both for a diagnostic procedure as well as for treatment. Although the administered activity of Na[^{131}I]I is low when used for thyroid imaging and uptake measurements, the thyroid dose to the

Radiopharmaceuticals	Breastfeeding interruption	Radiopharmaceuticals	Breastfeeding interruption
^{99m}Tc-labelled: DMSA, DTPA, MAG3, MIBI, phosphate agents, Technegas, tetrofosmin	4 h	[^{18}F]FDG	Avoid close contact for 4 h
		[^{111}In]In-pentetreotide	60 h
^{99m}Tc-labelled: MAA, pertechnetate, RBC	12 h	[^{123}I]I-ioflupane and [^{123}I]I-mIBG	Cessation
		Na[^{131}I]I	Cessation

DMSA – dimercaptosuccinic acid, DTPA – diethylenetriaminepentaacetic acid, MAG3 – mercaptoacetyltriglycine, MIBI – methoxyisobutylisonitrile, MAA – macroaggregated albumin, RBC - Red blood cells, FDG – fluorodeoxyglucose, mIBG – meta-iodobenzylguanidine

Table 2. Recommended breastfeeding interruption for a selection of radiopharmaceuticals used in diagnostic nuclear medicine. Data obtained from IAEA Specific Safety Guide [23].

infant will be high, of therapeutic levels, due to the fact that a large fraction of the iodine is excreted in the breast milk and accumulates in the infant's thyroid, as well as the long physical half-life.

The excretion of activity in breast milk after administration of [^{18}F]FDG has been shown to be almost negligible [24, 28]. The PET images, however, clearly show activity in the breasts. The infant is thus irradiated externally, and the recommendation is to avoid close contact between the infant and the breastfeeding patient for approximately two physical half-lives, i.e. 4 hours.

For those radiopharmaceuticals for which there is no published information on radionuclide excretion in breast milk, the data have to be obtained before breastfeeding can be resumed. This is accomplished by collecting several consecutive samples of breast milk following administration of the radiopharmaceutical. The activity in these samples must be measured, the cumulated activity determined, and the radiation dose to an infant who potentially ingests the breast milk determined.

Breastfeeding and Therapeutic Nuclear Medicine

Breastfeeding is contraindicated after therapeutic administration of radionuclides [20], and should be avoided. Any therapeutic radiopharmaceutical administered orally, intravenously, or arterially is potentially hazardous to the infant, and breastfeeding must therefore be stopped completely. Furthermore, patients who have to undergo therapy with radioiodine should terminate breastfeeding up to eight weeks before receiving therapy [18, 29]. This is mainly because breast tissue that is producing milk will receive an unnecessarily high dose due to accumulation of activity in the breasts.

Radiation Dose to Breasts

The radiation dose to the breasts of a nursing patient has been estimated by Stabin and Breitz [26]. The breast dose varies significantly between different radiopharmaceuticals. For most ^{99m}Tc-labelled substances, the breast dose is of the magnitude of a couple of mGy and below. For Na[^{131}I]I, however, the breast dose is considerably higher. Stabin and Breitz reported a breast dose of approximately 1–2 Gy (i.e. 1000–2000 mGy) after a treatment of thyroid cancer with 5550 MBq. This data justifies the recommendation to a nursing patient to terminate breastfeeding well before receiving radioiodine therapy.

CONCLUSION

Most diagnostic procedures are done with short-lived radionuclides, such as ^{99m}Tc or ^{18}F, which do not cause large foetal doses. Prenatal doses from most properly performed diagnostic procedures present no increased risk of prenatal death, malformation or intellectual disability.

The risk of childhood cancer is not negligible, however. If the procedure is considered medically necessary, options include

reducing the activity to be administered and consequently prolonging the imaging scan time, encouraging the pregnant patient to drink more fluid than usual and to void urine frequently. A foetal whole-body dose of less than 100 mGy is no reason to terminate the pregnancy based on the radiation risk.

It should be noted that there is a *natural* risk of severe effects such as spontaneous miscarriage, incidence of genetic abnormalities and prenatal growth deficiency in a pregnant population not exposed to ionising radiation above the natural background radiation. This is also the case for the probability of childhood cancer, which is about 0.3% without any extra radiation dose above the natural background [1].

For radiopharmaceutical therapy, pregnancy is an absolute contraindication, unless the treatment is lifesaving. Radioiodine (such as Na[^{131}I]I) may cause significant foetal thyroid harm, and should therefore be avoided. The pregnant patient can be given stable iodine if pregnancy is discovered early after an unintentional administration of radioiodine.

Breastfeeding is important overall and should not be terminated unnecessarily. Nuclear medicine staff should follow published recommendations on breastfeeding interruption and advise that the infant be given breast milk just prior to the administration of the radiopharmaceutical. However, breastfeeding must be stopped permanently after administration of radioiodine and other radiopharmaceuticals used for therapy.

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1.2 CONSIDERATIONS FOR THE FEMALE WORKER

by Ana Patrícia Leite, Patrick J S Begley, Victoria Rowse

Nuclear Medicine Department, University Hospitals Sussex NHS Foundation Trust, United Kingdom

EXECUTIVE SUMMARY

Female workers are an essential part of the healthcare system. They are more vulnerable while pregnant and/or breastfeeding due to physiological changes and due to the involvement of another being (yet to be born), who is considered a "member of the public" under radiation protection categories. In order to protect these workers, the European Union has legislation and guidance in place that will advise what considerations are required and necessary. It is then the responsibility of each member state to incorporate this legislation into their national law.

In nuclear medicine, there are several hazards for pregnant and breastfeeding workers, such as ionising radiation, chemical agents and manual handling of heavy loads. As soon as the member of staff discloses to a department that they are pregnant and/or breastfeeding, a review of risk assessments for each hazard should be done. This will allow the hazard to be characterised, documenting what implications it will have for the worker's health and what can be done in order to protect them. Depending on the results of the review, an adjustment of worker responsibilities might be required, without prejudice to the staff member. Adjustments will need to be reviewed as the situation changes or with the progression of the pregnancy.

Keywords:
Risk assessment; pregnancy; breastfeeding; foetus; infant

INTRODUCTION

Health workers are an essential part of all healthcare systems. The World Health Organization estimates that around 70% of these workers are women [1]. In nuclear medicine it is crucial that the employer makes reasonable adjustments to protect staff against hazards in the workplace. This chapter will focus on considerations that the employer must take into account in order to protect a female worker during pregnancy, post-partum and while breastfeeding.

Legislation and Guidance

In the European Union (EU) there is legislation and guidance in place to protect ionising radiation workers and the health of female workers during and after pregnancy. Each EU member state has incorporated these directives into their national legislation.

The EU currently has two directives that provide guidance on how to protect female workers:

- **European Council Directive 92/85/EEC Guidelines** on the assessment of the chemical, physical and biological agents and industrial processes considered hazardous for the safety or health of pregnant workers and workers who have recently given birth or are breastfeeding [2];
- **European Council Directive 2013/59/Euratom** on basic safety standards for protection against the dangers arising from exposure to ionising radiation and repealing

Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/ Euratom [3].

RISK ASSESMENTS

During pregnancy, a woman's body undergoes a number of physiological and psychological changes. These should be considered as a natural process of the female body and not as an illness. Most women will work during and after pregnancy, and often while breastfeeding. Due to all these changes in a woman's body, some situations and conditions usually considered suitable in the workplace may no longer apply.

Health and safety in the workplace is achievable by applying rules and protocols to relevant hazards. In order to protect pregnant employees and their unborn children, risk assessments must be performed in order to minimise all hazards [2,4].

- The European Agency for Safety and Health at Work defines a risk assessment as "the process of evaluating risks to workers' safety and health from workplace hazards". It is a systematic examination of all aspects of work that considers:
- what could cause injury or harm;
- whether the hazards could be eliminated and, if not, what preventive or protective measures are, or should be, in place to control the risks [5].

It is worth noting in this context that pregnancy is a dynamic process. Thus, the subject being evaluated in a risk assessment might need reassessing as the pregnancy progresses.

In nuclear medicine, one of the main hazards to assess is the use of (and consequent exposure to) ionising radiation. For this reason, it is important that the employee informs the department of their pregnancy as soon as possible [6]. Without this notification, the department will not be able to protect the worker and their unborn child. The first trimester of pregnancy is the most vulnerable period; thus all necessary protective measures should start as soon as possible [2].

Although EU law requires that a pregnancy within the workplace remains confidential, in the nuclear medicine context it may become evident that a staff member is pregnant due to changes in their duties or the need for additional monitoring. Despite this, any disclosure of their condition should only occur with the worker's consent.

If a member of staff working in nuclear medicine is pregnant, returning to work after birth or breastfeeding, risk assessments should be in place to protect them. In the following two sections of this chapter, we will discuss considerations to be borne in mind while performing these risk assessments.

Considerations for radiation risk assessment

Member States of the EU were required by Article 106 of 2013/59/Euratom [3] to transpose the Directive into national law by 6 February 2018. Despite variations between nations, the general principles of radiation protection (Article 5) are universal: justification, optimisation and limitation. In the following, "Article" relates to a requirement of European Council Directive 2013/59/Euratom [3].

Nuclear medicine work is an established justified practice (Article 19(2)), benefitting workers by their employment [3].

Any existing practice involving exposures at work must have been optimised by the undertaking (hereafter employer) following prior evaluation (Article 32(a)); radiation risk assessment. National guidelines for performing radiation risk assessments may be available; paragraphs 70 and 71 of the Approved Code of Practice [7] apply to the UK regulations. These assessments must involve the advice of a competent radiation protection expert (Article 82(2(o))). This is so that appropriate control measures can be applied to meet the "as low as reasonably achievable" (ALARA) criterion from Article 5(b). Although the wording of ALARA may differ between national laws, the simplest solution is to apply relevant existing good practice [8] to control risks [3].

Employers must limit the dose to exposed workers (Article 9). However, the limit on equivalent dose to the unborn child is 1mSv for the remainder of the pregnancy (Article 10(1)); the unborn child must enjoy the same protection as a member of the public. Furthermore, in some nations it may be prohibited to categorise pregnant and breastfeeding workers in category A (Article 40(1)). The exposures detailed in existing risk assessments are unlikely to be insignificant and must not be intolerable. However, the tolerable range of exposures will be narrower for pregnant or breastfeeding workers due to the provisions of Article 10. Therefore, the range of duties they undertake may [9] need to be constrained [3].

In summary, working conditions must be established by the employer in cooperation with the pregnant and/or breastfeeding worker based on existing radiation risk assessments. This should be done as soon as the exposed worker has notified the employer of their condition (Article 10). Therefore, employers must always have suitably detailed and up-to-date radiation risk assessments available. An excerpt from an example is provided at the end of this chapter (guidance on page 34 onwards, with example from page 37).

Organisation

Workers exposed to radiation as part of their employment in nuclear medicine may consider their pregnancy or breastfeeding status to be a matter subject to input from their occupational health service, human resources service, radiation protection officer, or a radiation protection expert.

Therefore, the employer needs to specify whom exposed workers must inform, so that their working conditions can be immediately reviewed and adequately adjusted.

Designated radiation protection officers (Article 84) should pay particular attention to the working conditions and supervision of practices of pregnant and/or breastfeeding workers [3].

Radiopharmaceutical Production

The greatest need for effective control measures exists in production facilities, because that is where the largest quantities of radioactivity are handled.

Radiation risk assessments must therefore be robust, using measured dose rates to verify estimated or manufacturer reference dose rates where possible. It may be necessary to issue workers with multiple dosimeters to distinguish doses received in different areas. If significant variability in dose rates is expected, dosimeter readout may need to be made more frequent. The efficacy of shielding materials (e.g. lead glass) must be assessed for relevant radiation and particulate emission energies.

Consider the likelihood and magnitude of contamination of radionuclide generators under normal circumstances and after damage in transit. Cleaning the generator may involve high dose rates, depending on its construction. Without assistance (e.g. hoists), cleaning, transporting, loading and unloading of generators may not be physically suitable for pregnant workers. On-receipt duties will result in higher doses than duties required during return of spent generators. Likewise, elution of generators and preparation of radiopharmaceuticals will result in higher doses earlier in the generator activity cycle. There may be scope for dose reduction to the pregnant worker with careful scheduling.

Where national laws prohibit pregnant and breastfeeding workers from being categorised in category A, preparation of radiopharmaceuticals may not be appropriate due to high extremity doses. In this case, workers could be preferentially assigned quality control and release duties when these are assessed to result in lower extremity doses. Care must be taken to ensure that the operator with checking duties can use shielding intended for the operator preparing radiopharmaceuticals, otherwise effective doses to the pregnant worker may increase.

Cyclotron facilities should use automated synthesis where possible to eliminate exposure. Facilities handling radioactive gases or volatiles should use preventative systems (e.g. filters), and monitoring and alarm systems. Needlestick injury may result in significant intake of radionuclides as well as extremity doses, therefore needle-free devices or re-sheathing aids should be used. All handling of radioactivity should be done using suitable shielding, together with long-handled tongs where possible. Ancillary equipment (heater blocks, vial shakers) should also be shielded.

Methods of dispensing

Where pregnant and/or breastfeeding workers are involved in dispensing radiopharmaceuticals, consideration must be given to the type of radionuclide, its activity, concentration and physical form, in addition to the method of dispensing. Existing radiation risk assessment and dose monitoring records should indicate levels of external exposure from each practice. The method of dispensing will influence the risk of contamination, ingestion, inhalation or needlestick. Tasks involving syringe preparation rather than needle-free systems or pre-drawn syringes increase the chance of needlestick injury. Automated dispensing systems, where available, will reduce direct handling of radiopharmaceuticals and minimise contamination risks, making them preferable options.

The concentration of the radiopharmaceutical is likely to be high upon dispensing, therefore for a given volume ingested, injected or inhaled, this will reflect the highest likely foetal dose for a given radiopharmaceutical.

It is likely to be necessary to restrict the pregnant staff member's involvement in radionuclide therapy procedures, including dispensing of therapeutic radiopharmaceuticals. In particular, responsibilities involving the dispensing (or administering) of ^{131}I may need to be reassigned. This is due to the relatively high radiation exposure associated with ^{131}I and its volatile nature, which increases the risk of internal uptake through inhalation [10]. Additionally, ^{131}I has the potential to cross the placenta and accumulate in the foetal thyroid, posing a significant risk to foetal development.

Staff working in PET departments, where higher-energy radionuclides are in use, may be required to alter their working practices during pregnancy. For example, they may need to avoid dispensing and administering PET radiopharmaceuticals [9].

Routes of administration

Risk assessment for the pregnant and/or breastfeeding worker should include consideration of the method of administration for radiopharmaceuticals in use within the department. Many administration routes will be intravenous, and any risk of leakage or spray from administration systems should be carefully considered. Capsule-based diagnostic studies, such as SeHCAT administration, are generally low risk for contamination as the material remains contained, unless mishandled or damaged. Procedures involving the generation of radioactive aerosols, such as lung ventilation studies, pose a significant risk of inhalation exposure: in general, it will likely be necessary to restrict pregnant and/or breastfeeding workers from participating in these types of procedures. All iodine is volatile. It is also excreted in breast milk, and this should be considered in the risk assessment. Doses will be lower than for ^{131}I if there are any foreseeable intake scenarios.

Patient care

In adjustment of workload or duties, consider patients who require higher levels of close contact or care, such as those who are (or are likely to become) very unwell. Risk assessment may indicate that work with these groups of patients should be avoided by the pregnant worker so as to reduce exposure. For example, staff closely involved in cardiac stress studies, which require prolonged contact during and after administration, may need to alter their working practices. The risk assessment should consider which relevant duties are regularly undertaken (e.g. does the technologist participate in close immobilisation of paediatric patients during their scanning) In such cases, paediatric pharmaceutical activities may be lower, but the prolonged exposure should be considered, as well as contamination from other fluids). Caring duties for patients administered with high-energy radionuclides, or radiopharmaceuticals with high activities, may be reduced or restricted. In PET settings, for example, pregnant staff may avoid escorting patients to the toilet [9], and pregnant staff may also avoid assisting patients who need help with emptying urine bags.

Scanning/Measurement

In most diagnostic nuclear medicine procedures, exposure to radiation from patients during scanning and/or measurement is relatively low. This exposure is generally predictable based on historical dose records. Consider the magnitude of radioactivity and retention, and the proximity and duration of contact with the patient. For example, one day protocol cardiac scanning where the operator is next to the patient during the scan acquisition would not be appropriate, whereas taking bloods from glomerular filtration rate (GFR) patients is unlikely to result in significant radiation exposure. Tasks such as supporting patients during imaging may have to stop.

Waste

Waste that is likely to contain significant quantities of radioactivity should be adequately shielded. It is likely that full waste containers will need to be exposed in order to transport them to a waste store. Without assistance (e.g. trolleys) this task may not be physically suitable for pregnant workers and would not meet the criteria for ALARA practice. Scheduling waste container changes at the beginning of the day or week may reduce doses to the pregnant worker.

Consider the risk of contamination of the outside of sharps bins to determine the requirements for personal protective equipment when handling sharps bins.

Disposal of aqueous or gaseous waste is likely to carry a significant risk of bodily contamination and may not be suitable for breastfeeding workers. Furthermore, inhalation of gaseous radioactive waste should be considered in risk assessment for pregnant workers.

Contamination Monitoring and Decontamination

Procedures, personal protective equipment and training should mean that workers undertaking contamination monitoring are highly unlikely to become contaminated. Workers decontaminating low quantities of contamination are also unlikely to receive significant doses. Physical assistance may be required for pregnant workers to monitor and decontaminate floors (e.g. monitor trolleys).

Consider the possibility of bodily contamination leading to ingestion by the worker, resulting in radioactivity being transferred to their infant via breast milk. Although there is limited information on radiopharmaceutical transfer, iodine is known to concentrate in breast milk [11]. Routine decontamination of therapy suites is unlikely to be suitable for breastfeeding workers.

Use of Sealed Sources

Use of sealed sources for quality control may involve high dose rates, depending on source activity and working practices. Movement of heavily shielded containers for sealed sources may not be suitable for pregnant workers. Where multiple sources of different activities are used, there may be scope for dose reduction to the pregnant worker with careful scheduling.

Although periodic leak tests will be carried out (Article 86(4)), particular care should be taken and appropriate personal protective equipment worn by breastfeeding workers handling sealed sources [3].

Incidents and Accidents

Plans will be in place for responding to incidents and accidents. A coordinator will generally be responsible for gathering people and resources to ensure that plans are followed. This duty is likely to be most appropriate for pregnant and/or breastfeeding workers.

Rehearsal of plans with radiation protection officers and/or experts is critical. Pregnant workers can be instructed where to position themselves in order to reduce exposure (e.g. increase distance from unshielded sources and radioactive patients). Breastfeeding workers can be instructed how to reduce the risk of bodily contamination (e.g. do not directly assist contaminated people).

Emergency exposures (Article 53) are not expected in nuclear medicine departments. National laws may prohibit pregnant and/or breastfeeding workers from participating in emergencies. However, this does not preclude their involvement in planning for incidents and accidents [3].

Practical Example of a Radiation Risk Assessment

The following, with references from [7], can be used to guide radiation risk assessment. Consider the tasks involved in the work to be assessed. Then consider the areas where these tasks are done. Finally, consider the persons involved in doing the tasks and the areas they work in.

Per Task (e.g. production, dispensing, injecting, scanning)

- Describe sources and list useful protection data for use in assessment 70(a)
- Calculate or refer to published e.g. [12–15] external radiation dose rates and doses 70(b)
- Estimate likelihood of contamination arising and being spread 70(c), with aid of results of previous monitoring 70(d)
- Estimated levels of airborne or surface contamination 70(h), with aid of results of previous monitoring 70(d), and estimated radiation dose rates and doses 70(b) from this contamination e.g. using [16, 17]
- Dose constraint if task dose approaches relevant dose limit 71(d)
- Action needed to apply control measures 71(f), 70(g), 71(b) to ensure exposure is ALARA 71(a) e.g. relevant good practice [8]
- Maintenance and testing schedules 71(g), 70(e) of control measures including document management and leak testing 71(n)
- Effectiveness and suitability of PPE e.g. [18], and whether to provide it 71(c)
- Accident situations due to failures of control measures 70(l), their likelihood and severity 70(k) by estimation of equivalent dose to skin, effective dose from inhalation or ingestion, and steps to prevent or limit 70(m)
- Contingency plans to address accidents 71(h) e.g. relevant good practice [19]
- Training needs 71(i)

Per Area (e.g. Hot Lab, Dispensing Lab, Injection Room, Gamma Camera Room)

- List nature of sources 70(a) used in tasks that happen in this area
- List accident dose rates and doses 70(b) from tasks that happen in this area
- List estimated levels of contamination 70(h) from tasks that happen in this area
- List control measures 71(f), 70(g), 71(b) for ensuring tasks that happen in this area are ALARA 71(a)
- Use above data to determine whether Articles 37 and 38 of [3]: designation of areas 71(j), 70(j), 71(k) are met
- List contingency plans for tasks that happen in this area
- Use above data to determine whether Article 10 of [3]: change of working conditions for pregnant or breastfeeding workers 71(e) are met
- State responsibilities for managers and workers to ensure legislative compliance 71(o) e.g. Local Rules
- State programme for monitoring/audit of arrangements 71(p) e.g. number/scope of radiation protection officers (Article 84 [3])

Per Person (e.g. Category A, Category B, Pregnant, Breastfeeding, Non-radiation worker)

- List previous dosimetry 70(d), sum dose rates and doses under control measures, and accident dose rates 70(b) and doses from tasks that this person does

- List estimated levels 70(h) and resulting accident dose rates and doses 70(b) from tasks that this person does, or from tasks that happen in areas where this person works
- State relevant dose limit, compare with summed doses under control measures and accident doses
- Score 1–5 likelihood & severity (1 = <optimisation threshold; 3 = >investigation level; 4 = >dose limit; 5 = irreversible)
- Risk rating = likelihood * severity
- When severity = 5, disregard risk rating and improve control measures
- Apply locally defined ranges to determine acceptability, e.g.: Accept (<5); Tolerate (5–12); Reject (>12)
- Use above data to determine whether Article 40 [3] is met 71(l)
- Use above data to determine whether Article 10 [3] is met 71(e), recommend tasks that this person should not do
- Specify dosimetry programme 71(m) and ALARA dose investigation levels 71(f)
- List training needs from tasks that this person does 71(i)

For the purpose of this guide, one task is considered (Table 1).

CONSIDERATIONS FOR OTHER RISK ASSESSMENTS

Although a radiation risk assessment is crucial within a nuclear medicine department, there are also other matters the department should consider. Below we will describe other hazards that a pregnant and/or breastfeeding worker might encounter.

Postural problems

Fatigue from standing has been associated with miscarriage, premature birth and low birth weight [2].

In nuclear medicine, work activities can be time pressured, depending on how the department is organised. It is worth taking into consideration the work pace of the female worker during pregnancy. For example, during a session of dispensing radiopharmaceuticals, it might be worth considering, if appropriate, having a chair/stool for the employee to sit down. This will allow the member of staff to frequently change their posture during their work. If this is not possible, fatigue can be avoided by allowing the member of staff to have more frequent breaks during the session.

With the progression of the pregnancy and the increase in abdominal size, especially during the late stage of the pregnancy, some spaces deemed fit to work in may no longer be suitable [2]. For example, a worker in their third trimester might struggle to dispense radioisotopes safely due to the size of their abdomen. The risk assessment must consider how to avoid postural problems for the worker, as well as needlestick injuries or radioactive spills.

	Gamma Camera Quality Control – Extrinsic Uniformity
Source of The Radiation (70(a))	- 555 MBq ^{57}Co dispersed in a 64 x 45 cm epoxy matrix sealed in plastic with handles - Radionuclide data from [16]: • Half-life: 271.8 d • Gamma or X-ray emissions: 14 keV (9%); 122 keV (86%); 137 keV (11%); <1% omitted • Electrons: 6 keV (106%); 7 keV (70%); 11% omitted • No beta or alpha emissions • Betas and electrons total absorption: <0.1 mm glass or plastic • Gamma and X-ray absorption by lead: HVL <1 mm; TVL 1 mm
Task	Removing source from storage container, positioning the source on the detector, and storing after task → takes approximately 30 seconds
Dose	**1)** Measure the external dose rate from the ^{57}Co sheet source at arm's length, example: 0.2 μSv.hr^{-1}.MBq^{-1} **2)** Calculate the dose per task: $0.2\mu Sv.hr^{-1}.MBq^{-1} \times \frac{30}{3600} s \times A\,MBq = \frac{A\,MBq}{600\mu Sv.MBq^{-1}}$ where *A* is the activity in MBq. **3)** Consider a pregnant worker taking maternity leave at 37 weeks post-conception. Multiply the dose per task by how often the task is performed per week and the number of weeks exposed, for example: $3\,days/week \times 37\,weeks = 111\,days$ **4)** Multiply by the average source activity fraction: $\frac{1 + e^{-(\ln(2)\times(37\times7\,days)\div271.8\,days)}}{2} = 0.76$ **5)** Assume 3 weeks of leave are taken during the pregnancy. Multiply by this fraction: $\frac{37\,weeks - 3\,weeks}{37\,weeks} = 0.92$ **6)** Assuming the source activity was 555 MBq at conception, the total dose over the pregnancy is: $H_p(10)effective\,dose = \frac{555}{600} \times 111 \times 0.76 \times 0.92 \sim 70\mu Sv$ Repeat for equivalent dose to skin; 1.0 μSv.hr^{-1}.MBq^{-1} contact dose rate; ~360 μSv **Accident situation:** leaking source 10% source activity per unit area touched transferred onto fingers ~19.3 kBq.cm^{-2} Skin dose rate approaches 2.3 mSv.hr^{-1} 10% of this fixed to skin, leading to ~210 mSv skin dose (>150 mSv dose limit for category B worker) 10% of this may be ingested, leading to ~0.1 μSv effective dose

Routine Risk Ratings	**Likelihood :** 5/5 (this exposure is certain to occur) **Severity :** 1/5 (estimated radiation doses well below dose limits; low severity) **Risk Rating :** likelihood * severity = 5/25 (accept → no further mitigation necessary)
Accident Risk Ratings	**Likelihood :** 1/5 (this is very unlikely) **Severity :** 4/5 for Category B worker (control measures required e.g. leak testing) **Risk Rating :** 4/25
Contamination Risk	When in use, always wear impermeable gloves and hold the handles of the ^{57}Co sheet source. It is essential to ensure that the sealed source in use has been tested for leaks (as per standard good practice recommendations: after any incident even when there is no visible damage, and at least every 2 years) and is not likely to lead to spread to any surface that the worker touches, nor be transferred.
Control Measures	System of work for this source must include: • The application of time, distance and shielding principles of radiation protection. • Instructions to wear gloves and hold the handles of the source when in use. • Instructions to monitor gloves and hands after handling the source. • Instructions to immediately store the source once it has been used.

Table 1. Example of a sample risk assessment, looking into the daily task of performing quality control of the gamma camera (extrinsic uniformity), using a Cobalt-57 source.

Chemical agents

According to European Union Directive 92/85/EEC, some substances are considered dangerous for the human body, especially for pregnant women, unborn children or breastfed infants [2].

Some nuclear medicine departments may use lead brick shielding. Lead exposure has been associated with abortions, miscarriages and developmental problems [2]. A risk assessment will be required to make sure appropriate measures are put into place.

Some cleaning products may also be considered dangerous for a pregnant worker and their unborn child. Within radiopharmacy departments, hazardous cleaning products might be used to maintain good manufacturing practices. A risk assessment will thus be required to minimise the exposure of the employee, achievable through the usage of personal protective equipment, where appropriate. The EU Classification, Labelling and Packaging (CLP) Regulation identifies hazardous chemicals. These hazards are then identifiable by usage of symbols and phrases on the packaging labels [20]. The CLP Regulation therefore enables a department to make an informed decision regarding risk assessment of a chemical, making this crucial information to consider during pregnancy and/or breastfeeding risk assessment.

Manual handling

Manual handling may be considered a potential risk during pregnancy, as it may increase the chances of foetal injury or premature birth. Performing a health and safety risk assessment is crucial to protect both mother and unborn child. These risk assessments should take into consideration the strain (i.e. the weight of the load), how often lifting occurs, and how the load is lifted. It is also worth mentioning that the risk assessment might need updating throughout the pregnancy to reflect the physical changes undergone by the employee.

There is literature that sets manual handling weight limits for pregnant women [21]. These limits are categorised by infrequent or repetitive lifting, weeks of pregnancy, and from where in the body the lifting motion is taking place. The tables below summarise the weight limits suggested by the literature available. The data has been divided by frequency of lifting and stage of pregnancy (in weeks). It should be noted that past 20 weeks of pregnancy, body habitus will prevent lifting of objects close to the body. Table 2 shows weight limits suggested for infrequent lifting when a pregnant person does not perform lifting tasks more than every five minutes. Table 3 defines the weight limits suggested for repetitive lifting of short duration, where lifting occurs in a period less than one continuous hour and lifting is not performed more than three times per minute. Table 4 shows the weight limits suggested for repetitive lifting of long duration, where an hour or more of lifting is performed but lifting tasks are not done more than three times per minute. The current literature does not cover lifting that occurs more than three times per minute. The guidance provided below is only applicable for lifting with two hands while standing. Lifting with one hand, lifting while seated or kneeling, carrying, pushing or pulling is not covered since these can be categorised as high-risk tasks [21]. In this scenario, a risk assessment should be considered to evaluate the risk. The employee could also have a discussion with their gynaecologist/doctor, who will

be able to advise and, if required, write a recommendation letter to the department.

If a woman has recently given birth, especially if she has undergone a Caesarean section, there will also be some limitations regarding lifting and handling of loads. Breastfeeding mothers may feel discomfort due to breast soreness [2].

In nuclear medicine, the usage of shielded boxes to carry radioisotopes or the pulling of heavy shielded doors should be assessed to protect the pregnant or post-partum employee. The risk of manually changing collimator carts should also be evaluated. Collimator carts can weigh more than 100 kg, and this can be considered a high risk for the employee.

The Health and Safety Executive in the United Kingdom advises that employers must guarantee that pregnant women and new mothers are not lifting or carrying heavy loads [4]. Depending on the workload and structure of the department, employee duties may need to be adjusted to avoid future health complications for mother and/or child.

CONCLUSION

Pregnant and/or breastfeeding employees can continue to work in nuclear medicine, provided reasonable and tailored adjustments are implemented. This should be done following a review of risk assessments and in cooperation with the worker.

Weeks of Pregnancy	Area of The Body For Lifting	Distance of Lifting From Pregnant Body	Weight Limit (kg)
Less than 20 weeks	Shoulders	Close	13.5
		Mid	9.5
		Far	7.5
	Abdominal	Close	16
		Mid	11.5
		Far	9
	Knees	Close	14.5
		Mid	10
		Far	8
	Ground	Close	0
		Mid	
		Far	
Over 20 weeks	Shoulders	Mid	9.5
		Far	7.5
	Abdominal	Mid	11.5
		Far	9
	Knees	Mid	10
		Far	8
	Ground	Mid	0
		Far	

Table 2. Weight limits for infrequent lifting [21].

Weeks of Pregnancy	Area of The Body For Lifting	Distance of Lifting From Pregnant Body	Weight Limit (kg)
Less than 20 weeks	Shoulders	Close	11
		Mid	8
		Far	6
	Abdominal	Close	13.5
		Mid	9.5
		Far	7.5
	Knees	Close	12
		Mid	9
		Far	7
	Ground	Close	0
		Mid	
		Far	
Over 20 weeks	Shoulders	Mid	8
		Far	6
	Abdominal	Mid	9.5
		Far	7.5
	Knees	Mid	9
		Far	7
	Ground	Mid	0
		Far	

Table 3. Weight limits for repetitive lifting of short duration [21].

Weeks of Pregnancy	Area of The Body For Lifting	Distance of Lifting From Pregnant Body	Weight Limit (kg)
Less than 20 weeks	Shoulders	Close	6.5
		Mid	4.5
		Far	4
	Abdominal	Close	8
		Mid	5.5
		Far	4.5
	Knees	Close	7
		Mid	4.5
		Far	4
	Ground	Close	0
		Mid	
		Far	
Over 20 weeks	Shoulders	Mid	4.5
		Far	4
	Abdominal	Mid	5.5
		Far	4.5
	Knees	Mid	4.5
		Far	4
	Ground	Mid	0
		Far	

Table 4 – Weight limits for repetitive lifting of long duration. [21]

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2.1

BREAST SENTINEL NODE PROCEDURE

by Carolina Rodrigues

Nuclear Medicine Department, Imperial College Healthcare NHS Trust, London, UK
London Imaging Academy, London, UK

EXECUTIVE SUMMARY

The sentinel lymph node (SLN) procedure has transformed breast cancer staging by reducing the need for axillary lymph node dissection (ALND) with its associated complications. The SLN is the initial node receiving lymphatic drainage from a tumour, making its evaluation critical for accurate staging. Techniques for SLN identification include radiopharmaceuticals, dyes, imaging, and gamma probes, with innovations like ^{99m}Tc-based tracers and SPECT/CT improving accuracy. Combining lymphoscintigraphy with blue dye optimises detection, achieving high sensitivity and minimal false negatives. This procedure is now the standard for axillary evaluation in early-stage breast cancer, offering precision during the surgical intervention and improved patient outcomes.

Keywords:
Sentinel node biopsy; breast cancer; lymphoscintigraphy; radio-guided surgery

INTRODUCTION (HISTORY & PRINCIPLE)

Over the years, our comprehension of the sentinel node and its influence on breast cancer management and prognosis has advanced remarkably [1]. Various concepts, including Halsted's and Fisher's theories, have been explored and tested. In 1923, the term "sentinel lymph node" was first introduced by surgeon Braithwaite, who investigated lymph drainage [1,2]. In the late 1980s, surgeon Donald L. Morton proposed the concept of "lymphatic mapping with Sentinel Lymph Node Biopsy (SLNB)" specifically for melanomas. Since then, research has confirmed his hypothesis that lymphatic dissemination typically occurs in a sequential manner. *Morton et al.* defined an SLN as "the initial lymph node which the primary tumour drains". However, the term "initial" led to some misinterpretation, prompting a revision of the definition to "an SLN is any lymph node on the direct drainage pathway from the primary tumour" [3].

In early-stage breast cancer, the status of axillary lymph nodes remains a crucial prognostic factor, providing information that is important for patient management and treatment [3]. Axillary lymph node dissection (ALND) has been an integral part of the management of breast cancer and considered the most accurate method for assessing metastatic spread of disease to the lymphatic system. However, it is associated with several significant morbidities and complications such as lymphoedema,

nerve injury, shoulder dysfunction and decreased range of motion, among others, that may compromise the quality of life of patients. With the introduction of the SLNB procedure, it is now possible to remove only a few lymph nodes, and if the sentinel nodes are negative, it then minimises the number of unnecessary ALNDs, reducing the risk of associated complications [1,7]. Conversely, if the sentinel node shows evidence of metastasis, an axillary dissection may be required to evaluate the degree of axillary spread [5].

The process for detecting and localising SLNs involves a combination of radiopharmaceutical, coloured or fluorescent dye, preoperative scintigraphy imaging, intraoperative gamma probe localisation, and the surgical removal of the identified SLNs [2,8]. While there is agreement on certain clinical indications and protocols for SLNs in breast cancer, some areas remain contentious. These include the choice of radiopharmaceutical, particle size, optimal injection route, time of scintigraphy imaging and intraoperative detection [2,8-10]. This chapter will explore these procedures in detail.

CLINICAL INDICATIONS

The SLNB procedure is widely recognised as the standard of care for assessing axillary lymph nodes in breast cancer patients. Clinical indications and recommendations from organisations such as the European Association of Nuclear Medicine (EANM), the Society of Nuclear Medicine and Molecular Imaging (SNMMI), and the American Society of Clinical Oncology (ASCO) are typically adhered to globally in the management of early breast cancer. However, there are several clinical indications, outlined in Table 1, that remain controversial, as they are not universally accepted and/or lack sufficient evidence [2]. Additionally, the latest update to the ASCO guidelines has expanded the recommendation to include SLNB for patients with operable breast cancer under specific conditions, which are also detailed in Table 1 [5,11].

International guidelines concerning the use of SLNB in pregnant and breastfeeding patients present inconsistencies. The EANM and the SNMMI endorse the procedure, citing its low-risk status compared to the risks associated with axillary dissection. Conversely, the American Society of Clinical Oncology (ASCO) recommends against SLNB in pregnant patients. Additionally, according to EANM and SNMMI guidance, nursing mothers are recommended to suspend breastfeeding for 24 hours following the administration of radiopharmaceuticals [2]. However, there are alternative guidelines suggesting that such a suspension may not be necessary [12].

Acceptable	Not Recommended	Contraindications
Early T1-2 invasive breast cancer and clinically negative axillary nodes [2,4,5,9,14,16]	Multifocal/multicentric tumour* [2,3,5,9,11,16]	Inflammatory breast disease [2,4,9,11,16]
DCIS undergoing mastectomy [4,5,9,13,14]	Recurrent breast cancer following breast conservative therapy or recurrence after mastectomy [9,14]	Positive axillary nodes [4,14]
Prior preoperative/neoadjuvant systemic therapy [2,5,11,16]	Pregnancy [2,5,11,16]	
Male breast cancer [2,5]	Breastfeeding [2,5,11,16]	
Obese patients (SLN detection rate unaffected) [2,5]	Internal mammary chain lymph nodal involvement [2,3]	
Elderly patients (SLN detection rate unaffected) [2,5]	DCIS without mastectomy [2,4, 11-16]	
	After preoperative systemic therapy* [2,3,5,9,11,15,16]	
	Large or locally advanced invasive breast cancers (T3-4 tumours) [2,4,9,11,16]	
	Prior axillary surgery** [2,5,11]	

Notes: DCIS: Ductal Carcinoma in Situ; * Strength of recommendation: moderate; ** Strength of recommendation: strong

Table 1 - Recommendations on the use of SLNB

PATIENT PREPARATION AND AFTERCARE

No special preparation is necessary before the patient arrives at the Nuclear Medicine department [2,8]. Recent exams such as mammograms, breast ultrasounds and magnetic resonance images should be available, ideally not older than one month. These images should be reviewed by a nuclear medicine physician and/or radiologist, or a delegated practitioner such as a technologist/radiographer operating under an established protocol, when authorising the procedure [2]. For female patients, it is essential to assess pregnancy and breastfeeding status in order to implement appropriate measures to keep the exposure of patient, foetuses and infants as low as reasonably practicable [2].

For patients undergoing breast wire localisation as a preoperative procedure, it is essential that this step is completed prior to the administration of the sentinel node injection [5]. This practice helps prevent contamination of the staff member inserting the wire and minimises unnecessary exposure for the healthcare personnel involved.

Some departments may perform imaging, while others only administer the injection of the radiopharmaceutical (further details in the **Imaging Protocol** section (page 56). In the departments that perform imaging, patients are required to wear a gown and remove all clothing and jewellery above the waist that could interfere with the images [2,15].

There are relatively few restrictions or aftercare requirements, as the aftercare typically coincides with the surgical procedure and has its own specific guidelines to follow. Nonetheless, it is crucial for patients to adhere to the advice provided by the medical team both before and after the surgery.

RADIOPHARMACEUTICALS

The optimal radiopharmaceutical should demonstrate rapid transit to SLNs while maintaining extended high retention within the first draining lymph node and low uptake by distal lymph nodes [2,5,10,17,18]. The lymphatic system's drainage, distribution and clearance of radioactive colloids can differ and are influenced by the size of the particles. Smaller particles are drained and cleared first, while larger particles are drained and cleared last and may be retained longer at the injection site. There is widespread consensus that the radiocolloid should be a good compromise between fast lymphatic drainage and effective retention in SLNs [2-5,10,17]. Consequently, the particle size will influence the timing of preoperative scintigraphy and intraoperative detection of SLNs, as well as the activity administered to the patient [2,5,10]. SLNs can be identified 1–2h post injection (p.i) of the radiopharmaceutical and the surgery should be scheduled within a 2–30h timeframe p.i., depending on the facilities [2,10]. If the surgery is planned for early morning, the injection and imaging can

be conducted safely on the afternoon prior to the surgery [2,5].

Throughout the years, various ^{99m}Tc-labelled compounds have been studied and used for radio-guided SLNB for breast cancer, as illustrated in Table 2 [2–5]. The most common radiopharmaceuticals include colloid particles such as [^{99m}Tc]Tc-sulphur colloid, [^{99m}Tc]Tc-nanocolloidal albumin and [^{99m}Tc]Tc-antimony trisulphide [2–5,10,17]. In recent years, new radiopharmaceuticals have been developed, showing promising results, with some achieving a detection rate of 100% and a minimal ratio of false negatives [18]. These promising new tracers include a novel receptor-targeting small molecule, [^{99m}Tc]Tc-tilmanocept [2,18,19], and a monoclonal antibody, [^{99m}Tc]Tc-rituximab [10,18,19].

However, some studies have shown that the success rate in identification of axillary SLNs is not significantly affected by the particle size of the radiopharmaceutical. As a result, the choice of radiopharmaceutical is often primarily determined by local availability rather than variations in detection efficacy [2].

^{99m}Tc-Based Radiopharmaceuticals	Region Where It Is Frequently Used	Particle Size (nm)	
		Maximum	Mean
Nanocolloidal albumin (Nanocoll®)	Europe	100	5–80
Human serum albumin	Europe	7–23	3–16
Sulphide nanocolloid (Lymphoscint®)	Europe	80	10–50
Rhenium sulphide nanocolloid (Nanocis®)	Europe	500	50–200
Sulphur colloid	USA	15–5000	100–220 (filtered)
Tilmanocept (Lymphoseek®)	USA	7	7
Antimony trisulphide	Canada and Australia	80	3–30
Stannous phytate	Japan	1200	200–400
Tin colloid	Japan	800	30–250
Calcium phytate	Japan	150–2000	150–1500
Rituximab	China	N/A	N/A

Table 2 - Characterisation of common ^{99m}Tc-based radiopharmaceuticals [2-5]

Activity and Volume Administered

There is no universal agreement on the activity to be administered in an SLN procedure [20]. In current practice, a total injection activity of 5–30 MBq is typically considered sufficient for surgery scheduled on the same day, depending on the interval between injection and surgery. If injection is performed on the day prior to the surgery, the activity should be increased accordingly; potentially up to 150 MBq, as referenced in literature [2,5]. However, the specific activity injected often varies from department to department.

When it comes to the volumes used, the literature indicates a consensus that small volumes with high specific activity should be used to enhance SLN detection. The selection of volume will depend on the injection technique used. For superficial injections, large volumes may disrupt normal lymphatic flow, so volumes of 0.05–0.5 mL are preferred. In the case of peritumoural injections, volumes of 0.5–1 mL can be used. Additionally, when using small volumes (e.g. 0.1 mL), it is recommended to introduce a small amount of air (0.1 mL) to eliminate any dead space within the tip of the syringe and the needle [1,2]. Typically, 25–27G needles are used for injection to reduce pain and discomfort to the patient [1,3].

Injection Technique

The ideal injection technique continues to be a topic of worldwide debate [1–5]. The different injection techniques that can be utilised are superficial injections (intradermal, subdermal, subareolar and periareolar) and deep injections (intratumoural and peritumoural) [2–4,19]. The number of injections can range between one and four depending on the technique selected [3].

Additionally, each breast is divided into four quadrants, along with a central portion that includes the areola and nipple. The tumour's position within the breast is typically indicated using either clock-face notation or quadrant designation. Therefore, the administration of the injection should be directed to the specific breast quadrant in which the tumour is located, as shown in Figure 1.

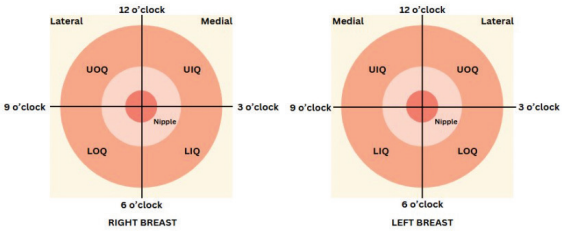

Figure 1. Breast quadrants diagram and clock-face positions: UOQ (Upper outer quadrant), UIQ (Upper inner quadrant), LOQ (Lower outer quadrant), LIQ (Lower inner quadrant).

In recent years, superficial injections have become increasingly popular due to their high practicality: they require less complex training, have better interoperability and consistency, and achieve a high SLN detection rate in the axilla [1,2,5,7]. They offer other advantages as well, including simplicity and a shorter time frame between injection and imaging [1,2,5]. In contrast, deep injections necessitate a thorough examination of the patient's clinical history and prior imaging, along with a more precise understanding of the tumour's exact location compared to superficial injections [1,2]. Additionally, if a tumour is in the upper outer quadrant, the increased activity at the injection site may complicate the identification of a less active SLN [1,2,7].

Nonetheless, superficial injections primarily facilitate the identification of axillary nodes. If the aim is to stage both extra-axillary nodes and the axilla, deep injection is advised [2,5]. The combination of both injection techniques, superficial and deep, in the same patient may enhance SLN detection [2,5].

However, numerous studies have demonstrated that the choice of injection technique does not significantly impact the identification of axillary SLNs, as all methods are capable of effectively detecting these nodes [2].

The patient is positioned supine or reclined, with their arm raised and adequately supported to facilitate access to the breast/axillary region. To ensure comfort and minimise movement during the injection, pillows or foam supports may be used.

Regardless of the administration site, after the injection, the patient is instructed to gently massage the breast to facilitate drainage of the tracer. Massage may be utilised if there is any delay in the passage of activity from the injection site during the study [2,5].

Special Considerations

There are several critical considerations that technologists/radiographers must take into account prior to injection. During this procedure, it is essential to reinforce patient privacy, ensuring that patients feel respected and secure. This aligns with best practices for maintaining dignity and trust within the healthcare environment. It is also important to communicate the option of having a chaperone present during the injection procedure. Such measures not only enhance the patient experience but also reinforce the commitment to patient-centred care.

Additionally, thorough assessment is essential due to various factors, including the presence of inserted wires before sentinel node injection, scar tissue, and breast or nipple deformities [2].

Staff must carefully manage areas with recently inserted wires prior to sentinel node injection. Patient positioning should be gentle and secure to prevent any disruption of the wire placement [5]. Additionally, scars can significantly alter lymphatic drainage patterns, making it crucial to administer the injection away from scar tissue to ensure

accurate radiopharmaceutical migration. In cases involving nipple inversion or deformities, the injection may need to be performed around the nipple-areolar complex or in the subcutaneous tissue adjacent to the lesion [21].

Collaboration with the referring physician or surgeon is often advisable to determine the optimal injection site, particularly in more complex scenarios.

Radiation Protection

Staff members are required to wear personal protective equipment, including aprons and gloves, to safeguard against radiopharmaceutical contamination and ensure sterility. While eye protection is optional, it is recommended, particularly if there is a risk of splashes during procedures. Furthermore, staff should wear radiation badges (both whole-body and finger badges) and use syringe shields if possible.

To prevent any radiopharmaceutical spillage, an absorbent cover should be placed beneath the injection site to capture any drops that may leak during or after the procedure. After needle removal, a cotton ball or gauze must be applied to the injection site to absorb any residual radiopharmaceutical and prevent it from contacting the skin. If it spills on the skin, it must be promptly cleaned to avoid misidentification with SLN. The initial absorbent material should be discarded, and a fresh one secured with tape before the patient leaves the department [1].

IMAGING PROTOCOL

Imaging is typically advised prior to surgery due to the variability in breast lymphatic drainage into both the axilla and extra-axillary nodes among patients [2]. Preoperative imaging serves as a quality control measure, ensuring the correct radiopharmaceutical and injection technique are utilised [5]. In certain departments, however, imaging may not be performed for logistical reasons, in which case the surgeons depend solely on the injection and detection using a gamma probe.

As previously noted, the interval between injection and imaging is influenced by the specific radiopharmaceutical and injection technique employed [5]. With superficial injections, the lymphatic drainage and subsequent lymph node visualisation typically occurs within 20 to 30 minutes. In contrast, deep injections may require 2 to 3 hours for effective imaging [5].

Gamma Camera Parameters and Image Acquisition

A single or dual-head gamma camera system with large field-of-view (FOV) detectors is recommended to acquire dynamic, static and single-photon computed tomography (SPECT) or SPECT/computed tomography (SPECT/CT) images. Low-energy high-resolution (LEHR) or low-energy ultra high-resolution (LEUHR) collimators should be used. The energy window should be 15% (±5%) centred on the 140 keV photopeak of ^{99m}Tc [2,5].

Dynamic imaging is not considered essential for SLN procedures for breast cancer and is often omitted in clinical practice [2,5,8,17]. Static images are typically acquired 15–30 minutes p.i., with additional imaging at 2–4 hours p.i. in selected cases [2,5,17]. Planar imaging effectively identifies the lymphatic drainage pathways leading to the SLNs; however, it lacks the ability to precisely localise the detected lymph nodes anatomically. To obtain more detailed information, SPECT/CT images can be utilised as a supplementary technique [2,5,8,17].

Table 3 below presents examples of acquisition parameters recommended by numerous studies and guidelines [2,5,8]. It is important to note that these parameters should be tailored to and optimised for the specific equipment and protocols available in each clinical setting [22].

	Dynamic	Static Images	SPECT/CT
Matrix Size	128 x 128	256 x 256	128 x 128
Zoom	1	1	1
Views	Anterior and Posterior	Anterior, Anterior Oblique (45°) and Lateral	To be determined (usually axilla)
Time per view	N/A	3–5 min	N/A
Number of Frames	90	N/A	128
Frame Duration	10 sec	N/A	10 sec
Projections	N/A	N/A	360°
Eff mA	N/A	N/A	Low dose: 2.5 Conventional: 30–150
kV	N/A	N/A	140

Table 3 - Gamma camera acquisition parameters [2,5,8]

Transmission Imaging

When acquiring planar imaging, certain departments may utilise the patient's body contour for positioning and referencing areas of activity (Figure 2). To achieve this, a ^{57}Co or Tc^{99m} flood source can be placed on the side of the body opposite the camera, or a ^{57}Co or Tc^{99m} point source can be employed to trace the body's contours [2,5,7].

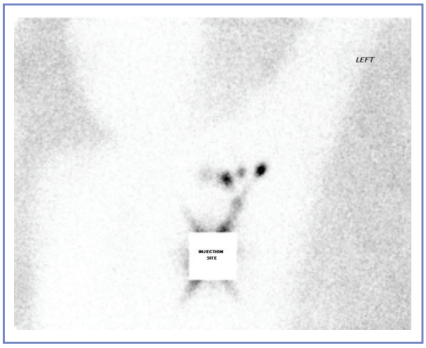

Figure 2. Example of Co-57 flood source to contour the patient's body. Courtesy of Northwick Park Hospital, London North West University Healthcare NHS Trust

Skin Marking

Skin marking is a practice that some surgeons find beneficial when imaging is performed. The location of the lymph node should be marked on the skin with ink, and the depth of the node should be noted. Ideally, the patient should be positioned as they would be for surgery. If multiple nodes are found in the image, some departments may choose to highlight the hottest node and describe and display the other nodes on accompanying reports and images. In cases where SPECT/CT is performed, co-registered images should be accessible at the time of the surgery [2,5,7].

Image Interpretation

Early and delayed planar images effectively identify SLNs in most patients. The major criteria for determining lymph nodes as SLNs include the timing of their appearance and, in some cases, the visualisation of lymphatic channels if dynamic imaging was performed [2,5,17]. Typically, SLNs cannot be easily distinguished from second tier lymph nodes [2,5]. While the SLN is often the hottest node, that is not necessarily the case for every patient. Separate lymphatic channels that drain to different lymph nodes identify each of these as distinct SLNs, even though they may be in the same anatomical region. When drainage to more than one anatomical region is seen, each of these regions has at least one SLN [2,5,17].

The report to the referring physician must include details about the radiopharmaceutical, the method of administration, the dose and volume of activity administered, the orientation of the images acquired, the location and intensity of the SLNs on each image and any potential sources of error or inaccuracies in the procedure. The images should be available by the time the patient reaches the surgical

suite. A strong collaborative relationship between the Nuclear Medicine department and the surgeon is essential for accurate dissemination of information regarding numbers and location of the nodes [2,5].

Clinical Case

A patient presented with recurrent breast cancer in the left breast, scheduled to undergo a mastectomy with repeat SLNB. Preoperative lymphoscintigraphy was requested to guide the procedure. The patient attended the imaging department in the afternoon prior to surgery, where 44 MBq of [^{99m}Tc]Tc-nanocolloid was administered via periareolar injection at the 3 o'clock position of the left breast. Imaging included dynamic acquisition (Figure 3), static planar imaging (Figure 4A), and SPECT/CT imaging (Figure 4B–D) to localise the sentinel lymph nodes.

Early dynamic imaging (Figure 3) revealed two sentinel lymph nodes located in Level I and Level III of the axilla. A third, smaller lymph node became visible during subsequent dynamic imaging. Additionally, there was a potential intramammary node. Early dynamic imaging (Figure 3) revealed two sentinel lymph nodes located in Level I and Level III of the axilla. A third, smaller lymph node became visible during subsequent dynamic imaging. Additionally, there was a potential intramammary node near the injection site; however, its visualisation was obscured by radiopharmaceutical activity at the injection site. It was presumed that this node would be included in the planned mastectomy. The Level I and Level III nodes were successfully localised and marked on the skin for surgical guidance. The smaller node, located in the Level I/II region, was not clearly visualised and could not be marked due to its indistinct appearance.

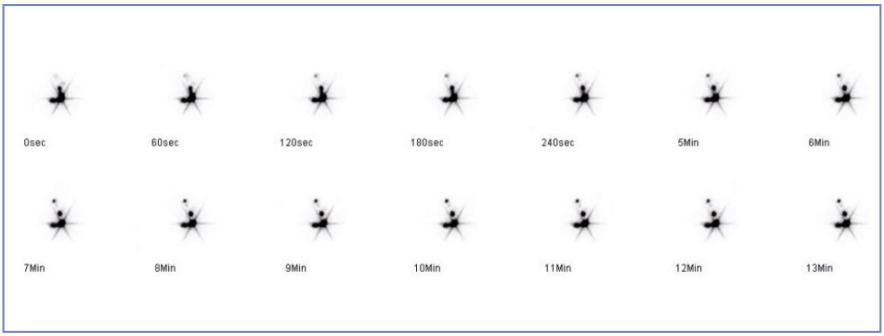

Figure 3. Dynamic images. Anterior view acquired with 10 sec per frame with a total of 90 frames. Courtesy of Hammersmith Hospital, Imperial College Healthcare NHS Trust, London.

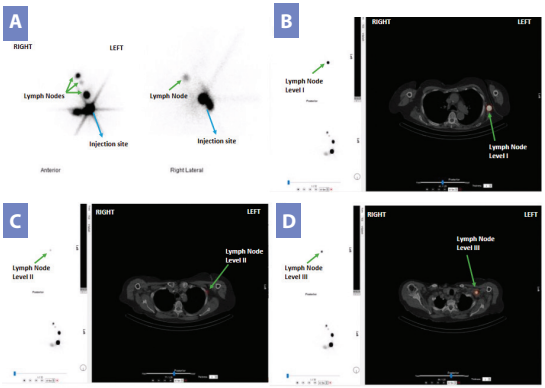

Figure 4. A: Anterior and right anterior oblique planar images, acquired with a duration of 3 minutes per image, demonstrate the distribution of radiotracer uptake and sentinel lymph node localisation. B: SPECT and fused SPECT/CT axial images clearly identify a sentinel lymph node at Level I. C: SPECT and fused SPECT/CT axial images highlight the presence of a lymph node located at Level II (unable to skin mark). D: SPECT and fused SPECT/CT axial images delineate a lymph node at Level III. Courtesy of Hammersmith Hospital, Imperial College Healthcare NHS Trust, London.

PATIENT PATHWAY AFTER NUCLEAR MEDICINE PROCEDURE

Blue-Dye Node Visualisation

The combined use of radiocolloid and blue dye improves the accuracy of SLN detection in breast cancer surgery, reducing false-negative rates [2,20]. While radiocolloid imaging and gamma probe guidance offer precise SLN localisation, blue dye provides a visual aid during surgery. Blue dye independently achieves 75–80% SLN detection, injected 10–20 minutes before surgery and enhancing SLN identification with gentle massage [2].

The dual-modality approach, combining lymphoscintigraphy and gamma probe with blue dye, maximises sensitivity and reduces false negatives. However, blue dye has limitations, including temporary skin discoloration, allergic reactions in 0.5–1.0% of patients (should not be used in pregnant patients), and limited use for extra-axillary nodes [2]. Proper timing and injection technique are essential for optimal results, and surgeons must weigh up its benefits and drawbacks when it is used alongside radiocolloid techniques.

Radio-guided Surgery

Intraoperative SLN detection relies on handheld gamma-detection probes, which must be sensitive enough to detect weakly active SLNs through up to 5 cm of soft tissue [2,5]. The probe should be well collimated to ensure precise detection, with high shielding to avoid interference from surrounding radiation, and be regularly quality-control tested. Ergonomically designed for use in sterile surgical fields, the probe provides real-time count data, supported by audio signals for immediate feedback [2,5]. The probe is used to locate SLNs based on preoperative imaging and skin markings, guiding dissection to the hot nodes. After excision, the surgical bed is scanned to confirm removal and assess residual activity [2,5,20].

SPECT/CT imaging is helpful in identifying clusters of lymph nodes, especially when SLNs are located closely or deeply, which may be obscured by the injection site [2,5,22]. The choice of SLNs to remove is based on radiolabelling and empirical thresholds, such as 10% or 20% of the count rate of the first removed node or at least ten times the background count [5]. While removing more than five nodes does not significantly enhance sensitivity, blue dye can aid localisation [2,5].

Previous breast surgery or radiation can alter lymphatic drainage patterns, increasing the risk of false-negative results. To mitigate this, thorough palpation and node harvesting should be conducted even in the absence of visual or radioactive confirmation [2,5].

In 1–2% of patients, SLNs remain undetected, leaving the axillary node status uncertain. Factors such as age, obesity, and tumour location are associated with failed localisation [2,5]. Despite persistent SLN non-visualisation, studies show no correlation with higher nodal metastasis or worse outcomes when preoperative ultrasound and fine needle aspiration cytology are used [5]. If SLN is not identified, ALND is recommended [2].

Additionally, all radioactive waste, including SLN, sponges and tissues, must be handled in accordance with institutional radiation safety protocols. Surgical and pathology staff should be trained in proper disposal techniques to ensure safety and efficient processing [2].

Histopathology

Specimens should be evaluated ex-vivo with a probe to confirm radioactivity [2]. Histopathological assessment of SLNs remains the "gold standard" for surgical management, however it is highly variable within hospitals [2]. Intraoperative techniques such as imprint cytology, frozen sectioning, or a one-step nucleic acid amplification method help identify SLNs, minimise false negatives, and ensure thorough evaluation for breast cancer staging and treatment [2,5].

Postoperative Follow-up

The results of SLNB are vital in informing decisions regarding adjuvant therapy. Patients with negative nodes can avoid unnecessary axillary surgery, while those

with positive nodes require further evaluation for additional treatment options [23]. To prevent or manage complications such as lymphoedema or restricted shoulder mobility, physiotherapy may be performed. Additionally, breast care nurses provide holistic support, addressing both the physical and emotional needs of patients [23,24].

QUALIFICATIONS AND RESPONSIBILITIES

SLN procedures must be performed solely by Nuclear Medicine practitioners (such as technologists, specialist radiographers, or physicians) and surgeons who have received specialised training in these techniques [5,25]. It is recommended to start with a supervised learning phase to foster collaboration and improve interaction among these specialists [2,5,25]. Key parameters used to assess the effectiveness of this multidisciplinary team include the percentage of successfully identified SLNBs and the rate of false negatives [5,25].

CONCLUSION

The breast SLN procedure has transformed axillary staging in breast cancer, reducing morbidity and enhancing diagnostic precision. Effective SLN procedures require seamless interdepartmental coordination, with precise scheduling of imaging and surgical interventions to avoid delays in patient care.

Ongoing training and education for multidisciplinary team members are essential to maintain proficiency in radiopharmaceutical handling, advanced imaging techniques, and radio-guided surgery. Access to specialised resources such as gamma probes and SPECT/CT scanners is critical for successful implementation. Additionally, strict adherence to national and international guidelines ensures standardised practices, fostering consistent and high-quality patient outcomes.

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2.2

GYNAECOLOGICAL SENTINEL NODE PROCEDURES

by Raquel Massa and Thomas Westwood

Department of Nuclear Medicine, The Christie NHS Foundation Trust, Manchester UK.

EXECUTIVE SUMMARY

» Sentinel lymph node (SLN) detection using ^{99m}Tc-labelled colloids during preoperative imaging significantly enhances the accuracy of lymph node evaluation, enabling the targeted removal of nodes that may harbour metastases.

» It is a well-established procedure for vulval, endometrial, and cervical cancers, with a growing body of research supporting its use in ovarian cancer and other gynaecological cancers. The primary objectives of SLN procedures are to improve staging accuracy, inform treatment decisions, and reduce the morbidity associated with unnecessary extensive lymphadenectomy.

» The standard SLN detection protocol includes a peritumoural injection of ^{99m}Tc-labelled colloids prior to surgery, complemented by an intraoperative intradermal injection of blue dye.

» The accuracy of SLN detection and localisation in gynaecological cancer is significantly improved with a cancer-specific injection technique, along with the implementation of both planar and SPECT/CT imaging studies.

Keywords:
Sentinel lymph node; sentinel lymph node biopsy; gynaecological cancer; scintigraphy; SPECT/CT; preoperative imaging.

INTRODUCTION

This chapter focuses on the vital role of sentinel lymph node (SLN) procedures in the assessment and management of various gynaecological cancers, including vulval, endometrial, and cervical malignancies. It outlines the development of SLN mapping and its impact on staging accuracy and treatment decisions, particularly with the use of ^{99m}Tc-labelled colloids. The chapter also discusses clinical indications, presenting a nuanced understanding of patient selection based on current guidelines. Patient preparation and care related to SLN imaging processes will also be discussed, equipping specialist healthcare professionals with best practices for patient interaction and procedural efficiency. A comprehensive review of imaging protocols, including SPECT/CT and conventional methods, highlights the technical complexities and the essential multidisciplinary collaboration required for successful implementation. Finally, real-world case studies illustrate the favourable outcomes associated with effective SLN assessments and explore their impact on clinical pathways.

HISTORY & PRINCIPLE OF THE SCAN

Accurate staging of gynaecological cancers relies on the assessment of the primary tumour, lymph node (LN) status, and the presence or otherwise of distant metastases. In this context, lymph node status is a key

factor on account of its prognostic and therapeutic implications regarding lymph node dissemination [1]. The concept of the sentinel lymph node (SLN) was initially introduced in the 1970s as the first lymph node or group of nodes that receive lymphatic drainage from the primary tumour. The SLN or SLNs may therefore harbour metastatic cancer cells before other lymph nodes in the regional lymph node chain [2,3]. The status of the SLN is thought to reflect the condition of the entire lymphatic region; if the SN is negative, it is expected that the non-SLNs will also be negative [1,4]. Thus, SLN detection has emerged as a less invasive alternative to complete lymphadenectomy in the surgical staging of specific solid cancers, including breast cancer, melanoma, and certain gynaecological cancers, aimed at reducing surgical extent and minimising the complications associated with more extensive lymphadenectomies [5–8].

Levenback et al. [9] were the pioneers in applying SLN detection to vulval cancer. This advancement led to the development of nuclear medicine techniques for SLN detection with ^{99m}Tc-labelled colloids administered during preoperative imaging. The implementation of these techniques for managing gynaecological tumours, particularly in vulval, cervical, and endometrial cancers, has significantly reduced morbidity, especially the occurrence of lymphoedema, by eliminating the need for a full inguinofemoral lymph node dissection [10–12]. A large study conducted by Van Der Zee et al. [5] found that vulval cancer patients who underwent SLN biopsy with confirmed SLN invasion had lower morbidity—both short and long-term—compared to those who had conventional inguinofemoral lymphadenectomy. It discusses treatment-related morbidity in early-stage vulvar cancer, noting that SLN dissection is associated with fewer complications such as wound breakdown, cellulitis, recurrent erysipelas, and lymphoedema. The findings suggest significantly lower morbidity rates in patients who had SLN biopsy compared to those needing more extensive lymphadenectomy.

The detection and localisation of SLNs begins with preoperative lymphoscintigraphy, which informs the surgical incision site. During the surgery, a dye agent—typically Patent Blue V, Isosulfan Blue, or Methylene Blue—is administered, alongside the use of a handheld gamma probe for precise localisation. This process enables the targeted removal of the identified lymph nodes. Subsequently, the excised SLNs undergo histopathological analysis to evaluate the presence of metastases [11].

The scan involves a multidisciplinary approach, often requiring the collaboration of a minimum of three professional groups. Typically, surgeons administer the injection of the radiopharmaceutical, prepared by the technologists who also perform the scan, and nuclear medicine physicians are responsible for interpreting and reporting the results of the scan. There may be variations in the staff groups who perform the tasks

below, depending on the dynamics of the department (e.g., in some departments where a high number of these scans are performed, technologists may be trained by the surgeon or nuclear medicine physician to perform the administrations).

In summary, the SLN mapping technique has revolutionised the accurate staging and surgical management of gynaecological cancers, offering vital prognostic information and enabling more personalised surgical interventions that enhance patient quality of life. The clinical indications for SLN detection in various gynaecological malignancies will be discussed next, together with how these advancements shape patient-centred oncology care.

CLINICAL INDICATIONS

Detection of SLN has been incorporated into the National Comprehensive Cancer Network guidelines for endometrial, cervical, and vulval cancer as an acceptable technique for lymphatic assessment in certain patients [13]. Recent findings have confirmed the high sensitivity and negative predictive value of this technique in appropriately chosen patients, while maintaining survival rates [13,14].

SLN mapping has become a standard practice in the management of early stage vulval cancer. It allows for the assessment of lymphatic spread without the need for complete inguinal lymphadenectomy in cases where the risk of lymph node metastases is low [5,8]. The GROINS-V-II study protocol was adjusted to require inguinofemoral lymphadenectomy for patients who present with SLN macrometastases larger than 2 mm, following an interim analysis that revealed unacceptably high rates of groin recurrences [8]. Clinical indications for SLN mapping include unifocal tumours confined to the vulva, those measuring less than 4 cm in diameter, stromal invasion greater than 1 mm, and negative findings in clinically and radiologically assessed inguinal lymph nodes. These criteria were supported by the GROINSS-V study and the GOG 173 protocol, which established SLN localisation as the gold standard for early-stage vulval squamous cell carcinoma, leading to improved patient outcomes by reducing the morbidity typically associated with more extensive lymphadenectomy procedures [5,8,15]. Additionally, while there is limited reported experience, SLN biopsy in vulval melanoma is also considered acceptable under the same criteria as in cutaneous melanoma [16].

In the context of endometrial cancer, SLN mapping is recommended for patients with uterine-confined disease, particularly those classified as having a low to intermediate risk of metastases. For patients within this risk category, SLN mapping can serve as a viable alternative to complete lymphadenectomy, especially for those who cannot safely undergo full lymphadenectomy due to medical or surgical considerations. The Society of Gynecologic Oncology (SGO) specifically endorses SLN mapping for

patients with clearly uterine-confined, low-grade endometrioid tumours. The British Gynaecological Cancer Society (BGCS) supports the use of SLN algorithms if imaging evaluations rule out metastases and there is no evidence of extrauterine disease observed during surgery, even in cases involving high-risk pathologies [11,17].

The SENTICOL study has underscored the significant role of SLN mapping using ^{99m}Tc-labelled colloid in the management of early-stage cervical cancer, particularly stage IB1 and selected IIA cases. This technique is crucial for accurate staging and assessing lymphatic spread, which informs treatment planning in early-stage cases for patients with squamous cell carcinoma, adenocarcinoma, and selected cases of adenosquamous carcinoma. In parallel, early cervical cancer (IA2/IB1, IIA1) also includes instances of high-risk endometrial cancer characterised by endometrioid histology, especially those with over 50% myometrial invasion or poorly differentiated (grade 3) tumours, along with serous papillary, clear-cell, or carcinosarcoma subtypes. Together, these findings highlight the importance of advanced mapping techniques in improving the management of early gynaecological cancers [11,14].

While SLN detection is not standard of care for ovarian cancer as it is for other gynaecological cancers, it is currently being explored and may be appropriate in specific clinical situations, particularly in early-stage disease and within the context of fertility-sparing treatments [18].

CONTRAINDICATIONS

SLN detection in the context of gynaecological cancers is contraindicated if there is a reasonable suspicion of cancer spreading beyond the uterine area. Additionally, the presence of abnormal pelvic or paraaortic lymph nodes identified through imaging studies serves as a contraindication for this procedure. Other contraindications that prevent a patient from undergoing SLN imaging include a previous history of surgical interventions or radiation therapy in the lymph node regions being evaluated, as well as factors related to the patient's age or other accompanying medical conditions that may pose risks for surgical treatment [11].

Pregnancy is generally not considered a contraindication for SLN biopsy. However, the EANM guidelines advise nursing mothers to pause breastfeeding for 24 hours following the administration of radiopharmaceutical [11], while ARSAC suggests that this suspension may not be required [19].

PATIENT PREPARATION & AFTER CARE

No special preparation is required for SLN imaging. However, patients should remove all clothing and jewellery from the waist up to facilitate the imaging process [11].

Before administering the radiopharmaceutical, the technologist must verify the patient's identity and ensure compliance with legal and regulatory requirements pertaining to the safe use of

radioactive materials in medical procedures. This includes assessing the pregnancy status of patients of childbearing age prior to the administration of radiopharmaceutical, obtaining either written or verbal consent for the procedure, and providing personalised guidance on radiation protection measures [19,20]. For patients with cognitive impairment who cannot provide consent, it is advisable for a member of the referring clinical team to conduct a capacity assessment in advance.

Patients should receive written confirmation of their appointment time, typically the afternoon before or the morning of the surgery. If the scan takes place on the day of surgery, patients are required to fast and suspend any medication necessary for surgical preparation. To minimise the risk of wasted radiopharmaceuticals and last-minute cancellations of surgical theatre slots, it is crucial to ask patients to confirm their attendance, emphasising the importance of punctuality. In some European countries, the imaging procedure is omitted, and the radiopharmaceutical is administered on the surgical table.

RADIOPHARMACEUTICALS

Prior to radiopharmaceutical administration, it is essential that the technologist provides a thorough explanation of the SLN imaging procedure, ensuring that the patient feels reassured and can ask any questions they may have. A summary of the procedure, including radiopharmaceutical administration, activities, injection technique, and imaging acquisition parameters and protocol, is given in Table 1. The technologist should prioritise the patient's comfort and privacy, ensuring that they feel at ease throughout the procedure. Additionally, a chaperone should be provided upon request to support the patient and maintain a respectful and secure environment.

An ideal radiopharmaceutical for SLN detection should display quick transit to SLNs while maintaining persistent retention in the nodes. The most common radiopharmaceuticals are ^{99m}Tc-labelled colloids, including [^{99m}Tc]Tc-sulphur colloid and [^{99m}Tc]Tc-albumin nanocolloid, as well as receptor-based tracers like [^{99m}Tc]Tc-tilmanocept [11,21,22]. The drainage, distribution, and elimination of radioactive colloids by the lymphatic system can vary depending on particle size. Smaller particles are cleared quickly, while larger particles are drained more slowly and may remain at the injection site. This characteristic can be advantageous if the imaging procedure is conducted the day before surgery. In Europe, [^{99m}Tc]Tc-nanocolloidal albumin (Nanocoll) is the preferred licensed agent, consisting of particles sized between 5–100 nm, while [^{99m}Tc]Tc-sulphur colloid, with particles ranging from 100 – 220 nm range, is commonly used in the United States. The tracer should be radiolabelled with [^{99m}Tc] pertechnetate following the manufacturer's guidelines, achieving a labelling yield greater than 95% prior to injection. Standard quality control procedures for radiopharmaceuticals should be adhered to [11].

^{99m}Tc-labelled colloids	[^{99m}Tc] Tc-sulphur colloid	[^{99m}Tc]Tc-albumin nanocolloid	Additional Note	
Particles Size	100 – 220 nm	5 – 100 nm	Lymphatic drainage of radioactive colloids varies by particle size: smaller particles are cleared quickly, while larger ones drain slowly, potentially remaining at the injection site—beneficial for imaging before surgery.	
Clinical Indication	Cervical Cancer	Endometrial Cancer	Vulval Cancer	Note: SLN detection is not standard for ovarian cancer as it is for other gynaecological cancers but is being studied for specific cases, especially in early-stage disease and fertility-sparing treatments
Activity Administered	110 MBq	40 – 185 MBq	20-150 MBq	
Injection Technique	Cervical peritumoral	• Endometrial peritumoral via hysteroscopy • Myometrial/ subserosal injections	2 to 4 intradermal or intramucosal peritumoral injections	
Acquisition Parameters & Imaging Protocol	Collimator type	Photopeak & Energy Window	Planar Imaging	SPECT Imaging
	Low Energy High Resolution	140 keV (15 ± 5%)	• 3-5 minutes • Anterior & Lateral views • Matrix 256 × 256 or 128 × 128 Zoom level of 1 • Patient in supine position with arms down	• 120 projections (60 for each detector) with 3° angular increments • 15–25 seconds per projection • Matrix size of 128 × 128 Zoom level of 1 • Patient in supine position with arms raised overhead

Table 1: Sentinel Lymph Node procedure in gynaecological cancer: A Summary [11, 18, 21, 22]

INJECTION TECHNIQUE, ACTIVITY AND VOLUME

For radiopharmaceutical administration, the patient is positioned on the scanner bed supine with their knees bent and legs abducted to optimise access to the area around the vulva, ensuring accurate injection into the appropriate tissue. In some instances, the patient's legs may be placed in stirrups to enhance visualisation and access to the surgical site.

In gynaecological SLN imaging, the radiopharmaceutical injection techniques vary depending on the type of cancer, and are typically administered by the surgeon. Figure 1 illustrates injection locations for SLN detection in cervical and vulval cancers. For cervical cancer, approximately 110 MBq is injected in 2 mL, usually at 0.5 mL per injection, into the cervix using a 20 or 22-gauge spinal needle. If there has been previous conisation, pericicatricial injection is preferred [11].

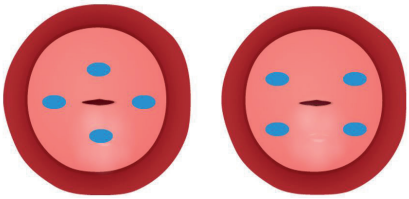

Figure 1: Injection locations for sentinel lymph node detection in cervical and vulval cancers are as follows: On the left, injections into the cervix are made at the 3, 6, 9, and 12 o'clock positions. On the right, injections are administered at the 2, 4, 8, and 10 o'clock positions. *Courtesy of The Christie PET/CT Academy, Manchester.*

In endometrial cancer, total doses range from 40 to 185 MBq, with volumes from 0.5 to 8 mL. Primary methods include cervical injection, endometrial peritumoural injection via hysteroscopy, and myometrial/subserosal injection. Cervical injections yield detection rates of 70% to 87%, while hysteroscopic injections show lower rates of 40% to 65%. Myometrial/subserosal injections have detection rates of 45% to 92%, with a promising 88% detection rate noted for ultrasound-guided injections [11].

For vulval cancer, the administration process is more straightforward due to the superficial nature of the tumours. The protocol normally involves administering two to four intradermal or intramucosal peritumoural injections, typically delivering 20 to 150 MBq in 0.4 mL per injection (0.1 mL per injection). Before the procedure, anaesthetic cream or spray, such as lidocaine or ethyl chloride, is applied to minimise discomfort [11].

Following the injection of the radiopharmaceutical, SLN visualisation typically occurs within two hours. Patients are usually scheduled to enter the surgical room within four to twenty hours post-injection, depending on departmental protocols [11]. However, it is essential to recognise that improper administration of the radiopharmaceutical can adversely affect the diagnostic value of the scan. In the authors' experience, there was a case involving a patient with vulval cancer where neither the scan performed the

day before surgery, nor the intraoperative gamma probe detection revealed any focal uptake of [^{99m}Tc]Tc-albumin nanocolloid. This lack of uptake was attributed to an inadequate injection technique, which resulted in significant radiotracer spillage. Such incidents underscore the critical importance of proper injection technique, as both incorrect administration and spillage can significantly compromise the scan's diagnostic efficacy and impede the identification of SLN. Figure 2 shows the setup for injection administration.

RADIATION PROTECTION

Staff are required to wear personal protective equipment (PPE), including aprons, gloves and arm covers, to protect against radiopharmaceutical contamination. While eye protection is optional, it is strongly recommended, especially if there is a potential for splashes during procedures. In addition, staff should wear radiation badges (whole-body and finger badges) and, where possible, use syringe shields, as shown in Figure 2.

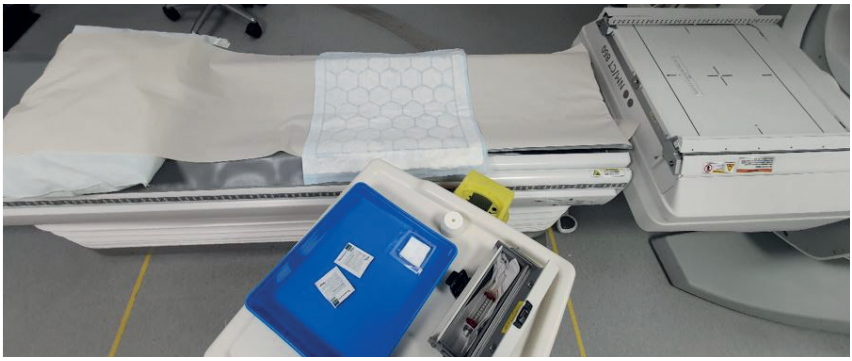

Figure 2: Injection Administration Setup. An absorbent pad is placed on the scanner bed beneath the patient to catch any spills during the injection process. An alcohol wipe is available for sanitizing the injection site. The injection is kept in a shielded syringe guard and lead box to reduce radiation exposure. *Courtesy of the Department of Nuclear Medicine, The Christie NHS Foundation Trust, Manchester.*

To prevent any radiopharmaceutical spills, an absorbent cover should be placed beneath the injection site to catch any potential drops during or after radiopharmaceutical administration. After needle removal, a cotton ball or gauze should be applied to the injection site to absorb any remaining radiopharmaceutical and prevent skin contact. If a spillage occurs contaminating the skin, it must be cleaned immediately to avoid confusion with SLN. The absorbent cover should be safely discarded, and a new one should be securely taped in place before the scan [23].

IMAGING PROTOCOL & IMAGE PROCESSING

The imaging protocol for cancer types such as vulval, endometrial, and ovarian cancers involves a peritumoural injection of a radiopharmaceutical, followed by imaging procedures. For vulval cancer, the procedure begins with the injection, after which a gamma camera captures a dynamic study, planar images, and/or single-photon emission computed tomography/computed tomography (SPECT/CT) images. The gamma camera is equipped with a low-energy, high-resolution collimator (LEHR) and is set to an energy window of 15 ± 5% around the 140-keV photopeak of Tc^{99m}. The patient remains in the same position for both imaging modalities, allowing for seamless fusion of the images [11]. To ensure high-quality imaging results, patients are advised to wear a surgical gown and to remove any metallic objects from their bodies whenever possible.

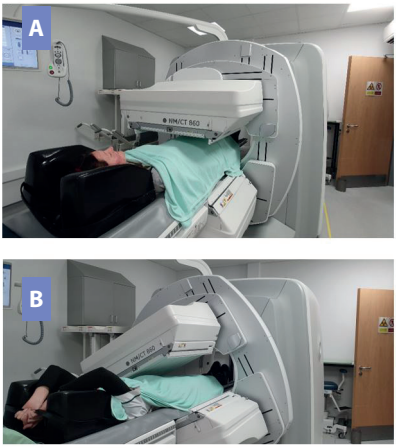

Figure 3: Patient positioning for sentinel lymph node imaging with arms by their sides (A) for planar imaging and with arms raised over the head (B) for SPECT/CT imaging. *Courtesy of the Department of Nuclear Medicine, The Christie NHS Foundation Trust, Manchester.*

For planar imaging, they are positioned supine on the scanner table with their arms at their sides, as in Figure 3A. Planar images are typically acquired for 3–5 minutes in both anterior and lateral views, utilising a matrix size of 256 × 256 or 128 × 128 with a zoom level of 1, although specific protocols may vary from centre to centre. Additionally, a ^{57}Co or Tc^{99m} flood source may be employed to enhance the delineation of the patient's body contours, which can also be manually drawn

using a sealed point source or simply a small volume of activity in a syringe needle guard. Suspected SLNs are usually located on the skin with a point source, then marked up with indelible ink from a surgical marker pen [11].

For SPECT/CT imaging, patients are positioned with their arms raised overhead to minimise truncation and beam-hardening artefacts in the pelvic region, see Figure 3B. SPECT/CT is generally performed immediately after planar imaging, although there is no standardised acquisition protocol, leading to variability among centres. Accepted parameters typically include 120 projections (60 for each detector) with 3° angular increments and 15–25 seconds per projection, along with a matrix size of 128 × 128 and a zoom level of 1. CT parameters will differ based on the specific CT device used [11]. Adequate immobilisation is provided using foam wedges to stabilise the arms, shoulders and knees, enhancing patient comfort and reducing motion artefacts.

Planar images do not require specific processing, but truncating high activity areas, such as the injection site, can enhance the visualisation of the SLN. Using a logarithmic scale to display low-count regions is advisable. For SPECT imaging, it is essential to consider the various types of gamma cameras and available software, and to select appropriate processing parameters to optimise image quality. Iterative reconstruction with a low-pass post-filter often yields better results than filtered back projection, with the ordered subsets expectation maximisation (OSEM) algorithm being ideal, using two to five iterations and 8 to 20 subsets. Attenuation and scatter corrections should be applied, and the SPECT images must be fused with CT images for two- or three-dimensional orthogonal reslicing, ensuring they are accessible in the surgical room for consultation [11].

IMAGE INTERPRETATION

Within the pelvis lymph nodes are found clustered into groups that follow the course of the major blood vessels. Lymphatic fluid drains along channels that follow these blood vessels proximally to eventually converge upon the lumbar/para-aortic lymph nodes stations. Since vulvar tumours are superficially located, drainage typically initiates via the superficial or deep inguinal nodes, hence SLNs frequently localise to nodes in one or both groins (Figure 4). Their superficial location means that nodes can often be readily surgically located with the help of skin surface marking and planar imaging for depth estimation, however SPECT/CT imaging can increase confidence, particularly when obesity complicates surface marking and results in increased node depth.

Cervical and endometrial tumours are located centrally within the pelvis, hence their SLNs typically localise to the deep nodal stations (Figure 4). They are frequently situated within one of the iliac stations, but may also localise to sacral nodes or even the lumbar/para-aortic stations if drainage occurs along the course of the ovarian vessels. Due to the

greater difficulty in localising and surgically accessing nodes in these deep locations, SPECT/CT imaging is strongly recommended for patients in this group.

When viewing images, it is important to use appropriate window settings to allow visualisation of low count areas. The SLN is frequently that which is both most intense and closest to the injection site, however since this is not always the case it is important to review dynamic imaging to establish the route of lymphatic drainage towards the visualised nodes. This is also important when deciding if later appearing nodes are separate SLNs or second echelon nodes receiving channels from earlier identified nodes. Where SPECT/CT is not performed it is crucial that imaging is performed in at least two orthogonal planes to avoid misinterpretation of skin contamination as nodal uptake. Figures 5 and 6 show a patient with vulval cancer who underwent planar imaging and SPECT/CT.

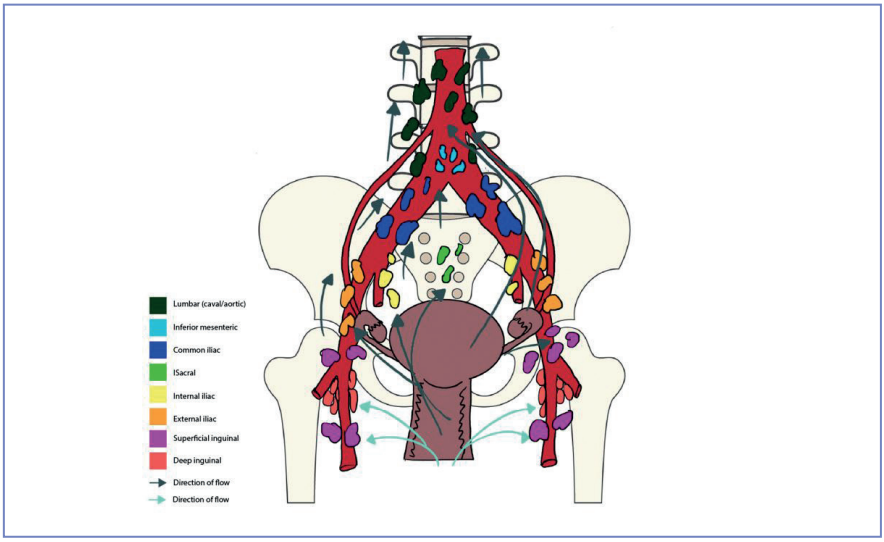

Figure 4: Diagrammatic representation of the pelvis including the distribution of lymph node stations relative to the gynaecological structures and major arteries. The typical direction of flow of lymphatic fluid from vulvar tumours is shown by the light green arrows, while the various routs of drainage typically seen with cervical and endometrial tumours is demonstrated by the grey arrows. Note that this flow preferentially towards deeper nodal stations than with vulvar tumours, hence SPECT-CT is important for nodal localisation with these tumours. *Courtesy of The Christie PET/CT Academy, Manchester.*

Since surgery is usually scheduled soon after the imaging procedure, it is important that reporting takes place sufficiently quickly for the report to be available to the operating team. The report will usually include the radiopharmaceutical used, details of the injection technique and the images acquired at each time point. SNLs are described including their intensity and depth from the skin surface and any skin markings used. It may also be helpful to describe non-SLNs.

IMPACT ON CLINICAL PATHWAY

Although SLN mapping has been extensively performed for breast cancer, melanoma, and head and neck tumours, there are challenges in accurately localising SLNs in gynaecological tumours, particularly cervical and uterine cancers, due to deep drainage patterns. The limited detail provided by flat-plane images—primarily anterior and lateral views of the pelvis—highlights the necessity for cross-sectional SPECT/CT slices to improve accurate anatomical localisation.

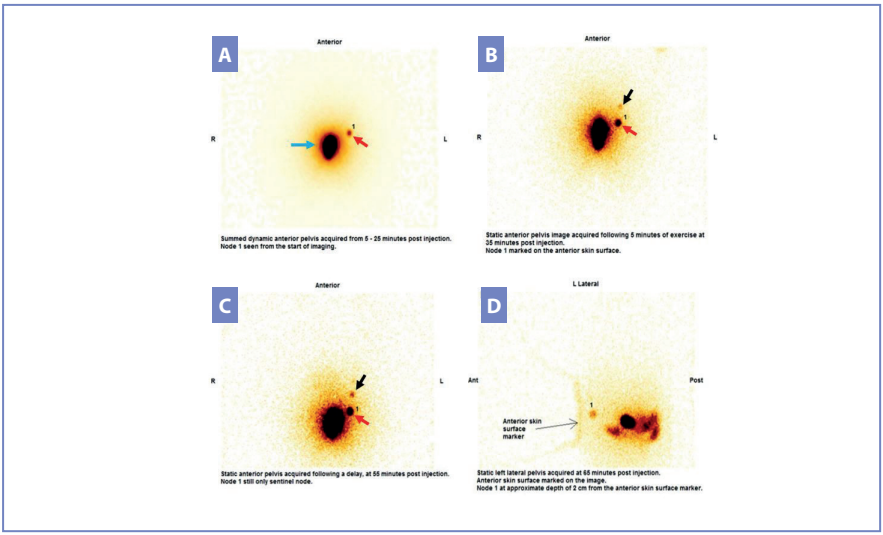

Figure 5: Planar images acquired during SLN mapping of a vulvar cancer patient. (A) Summed dynamic anterior view of the pelvis, with injection site indicated by a blue arrow. (B) Static anterior pelvic image acquired after the dynamic study. Static images of the anterior (C) and left lateral (D) views of the pelvis were acquired following a delay. A single SLN (marked as 1 with a red arrow) is demonstrated throughout imaging, the node proximal to this representing a second echelon node receiving lymphatic drainage from the SLN (black arrow). *Courtesy of the Department of Nuclear Medicine, The Christie NHS Foundation Trust, Manchester.*

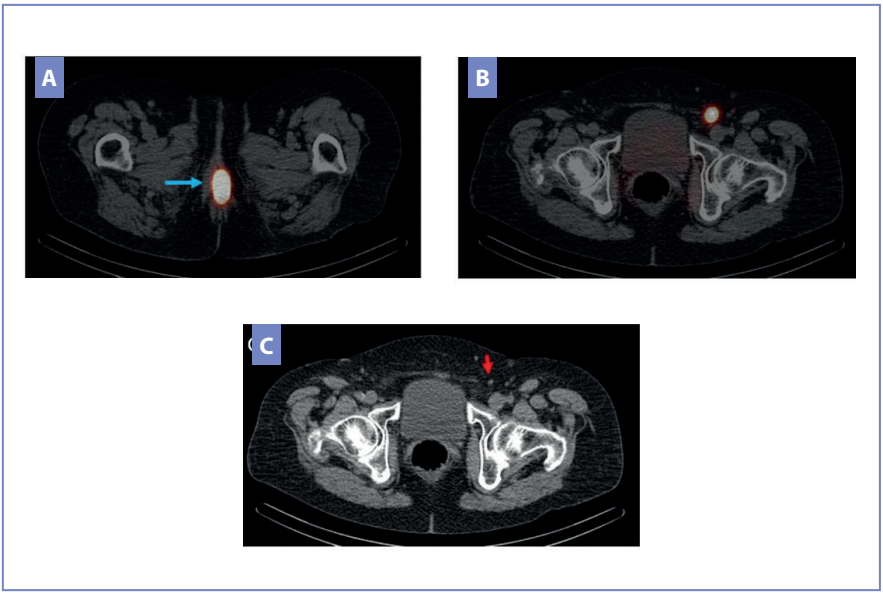

Figure 6: SPECT/CT image A) demonstrates intense activity at the vulvar injection site, blue arrow. Image B) shows discrete uptake in a left superficial inguinal SLN, which localises to a tiny left inguinal node on the CT component (red arrow, image C). *Courtesy of the Department of Nuclear Medicine, The Christie NHS Foundation Trust, Manchester.*

Nuclear medicine imaging, such as SPECT/CT scanning, significantly enhances the accuracy of SLN detection compared to traditional imaging methods and palpation. Studies have demonstrated that these advanced imaging modalities offer higher sensitivity and specificity in identifying lymph node metastases, particularly in cervical and endometrial cancers. For instance, a systematic review showed that SLN detection via radioactive tracers achieved sensitivity rates exceeding 90%, whereas conventional methods often fall short. This improved diagnostic accuracy aids in identifying patients at risk for metastatic spread [24,25].

In cervical cancer cases, SPECT/CT imaging is especially effective in identifying parametrial SLNs and nodes located in atypical positions. Studies show that SPECT/CT can achieve a higher SLN detection rate compared to blue tracer and handheld probe detection methods, demonstrating improvements ranging from 70% to 100% [26,27].

For endometrial cancer, the unique drainage pattern and deep location of the uterine corpus make correlating findings

from planar lymphoscintigraphy with surgical observations less reliable than with other tumour types. In these situations, the three-dimensional data provided by SPECT/CT proves instrumental for surgical planning and may reduce operative time. Pandit-Taskar et al. [28] reported a study involving 40 patients which indicated a higher detection rate with SPECT/CT (100%) compared to planar lymphoscintigraphy and other methods (75%, 93%, and 83%, respectively).

SPECT/CT is utilised less frequently for vulval cancers, as these tumours typically exhibit less deep drainage compared to others. While SPECT/CT can be beneficial for the three-dimensional localisation of SLNs, its impact on overall surgical management or the total number of nodes identified is minimal. Limited reports suggest an increase in detection rates in specific cases, such as vulvovaginal melanoma [11].

SLN mapping is essential for staging gynaecological cancers accurately, directly influencing prognosis and treatment decisions. The detection of micro-metastases or isolated tumour cells in SLNs can alter the initial staging from early to advanced disease, encouraging more aggressive treatment approaches and close monitoring. Evidence indicates that patients with detected micro-metastases have different prognostic outcomes, necessitating personalised management strategies tailored to their specific disease stage [29].

SLN detection imaging provides crucial information that guides surgical planning. For example, when it indicates involvement of the SLNs, surgeons may opt for complete lymphadenectomy. Conversely, a negative SLN result may allow for a more limited surgical approach, minimising patient morbidity. Moreover, this targeted approach reduces the likelihood of unnecessary surgeries, diminishing both physical and psychological burdens associated with extensive surgical interventions [30].

Accurate SLN detection through nuclear medicine techniques has been associated with improved patient outcomes. Increasingly, studies suggest correlations between successful SLN assessments and enhanced survival rates, reduced recurrence rates, and improved quality of life. Further, patients benefiting from less invasive surgical approaches experience shorter hospital stays and decreased complication rates, ultimately fostering a better overall healthcare experience [31].

The results of SLN scans enable healthcare providers to develop personalised treatment regimens. For example, patients with negative SLN findings may avoid aggressive adjuvant chemotherapy or radiation, guiding their treatment plan towards more conservative measures. This not only aligns with current precision medicine initiatives but also helps mitigate the side effects commonly experienced with more invasive therapies [32].

From an economic standpoint, integrating nuclear medicine SLN mapping into clinical pathways can yield cost savings by diminishing the number of unnecessary surgical procedures and their associated complications. Economic analyses highlight that the initial investment in advanced imaging technologies is offset by reductions in healthcare expenditures related to complications from overtreatment, underscoring the potential for more efficient resource allocation [33].

The incorporation of nuclear medicine SLN techniques has led to updates in clinical guidelines and treatment protocols for gynaecological cancers. As a result of this integration, many treatment centres are now adopting multidisciplinary team approaches, fostering collaboration among oncologists, surgeons, and nuclear medicine specialists to optimise patient management and outcomes [34,35].

Patient perspectives on nuclear medicine scans are generally positive, with many recognising the value of advanced imaging in their treatment journey. Reducing surgical burdens via SLN mapping often translates to better experiences, as patients appreciate the less invasive nature of procedures warranted by accurate imaging. Improved communication around the purpose and safety of these scans can further enhance patient acceptance and overall satisfaction with care.

Innovative advances in nuclear medicine hold promise for future SLN assessments. Research into novel radiotracers and imaging modalities may enhance the sensitivity and specificity of SLN detection. Additionally, ongoing clinical trials testing new applications and technologies could redefine best practices and protocols in managing gynaecological cancers, ultimately paving the way for breakthrough approaches that improve patient outcomes [36].

CONCLUSION

In conclusion, SLN mapping has become a pivotal tool in the staging and management of gynaecological cancers, offering precise diagnostic insights and therapeutic advantages. By utilising advanced imaging techniques such as SPECT/CT and radiopharmaceuticals like ^{99m}Tc-labelled colloids, SLN mapping allows for more targeted and less invasive surgical interventions, reducing patient morbidity and enhancing outcomes. The technique's ability to accurately identify lymphatic involvement, particularly in early-stage cancers, ensures better prognosis, more personalised treatment plans, and cost-effective care. As a result, SLN mapping is increasingly being integrated into clinical practice, promoting multidisciplinary collaboration and improving the overall patient experience.

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2.3 DXA/ OSTEODENSITOMETRY

by Daniela Teixeira Maçarico

Rios Centro Dentário, Mondim de Basto, Portugal

EXECUTIVE SUMMARY

Osteoporosis is a metabolic condition characterised by loss of bone mass structure, which makes the bones more prone to fractures. There is a high prevalence of the condition across the globe, and it is more common in women owing to several factors, including genetics, hormonal status and increased life expectancy.

Dual Energy X-Ray Absorptiometry (DXA/DEXA) is the gold standard method for measurement of bone density (BD), where the technologist plays a crucial role in accurate diagnosis and monitoring the effect of treatment.

INTRODUCTION

The skeleton has multiple functions, including support, movement, protection, reservoir for mineral and fat, as well as production of blood cells [1].

The skeleton is continuously renewed by the action of osteoclasts, which reabsorb bone, and osteoblasts, which produce collagen for formation of new bone. This process is called bone remodelling (Figure 1[2]) and in healthy bones there is a balance between mineralisation, or bone formation, and resorption, or bone destruction [3]. This phenomenon occurs throughout the full lifespan of an individual, although there are phases in which it is more intense [3, 4]. When this equilibrium is disrupted, bone loss occurs. Later in life there is a natural reduction in osteoblastic activity with net loss of bone, with hormonal factors like menopause also contributing to this natural phenomenon [5].

Keywords:
Bone Densitometry, Bone Mineral Density, Bone Health, DXA, Fragility Fractures, Osteoporosis

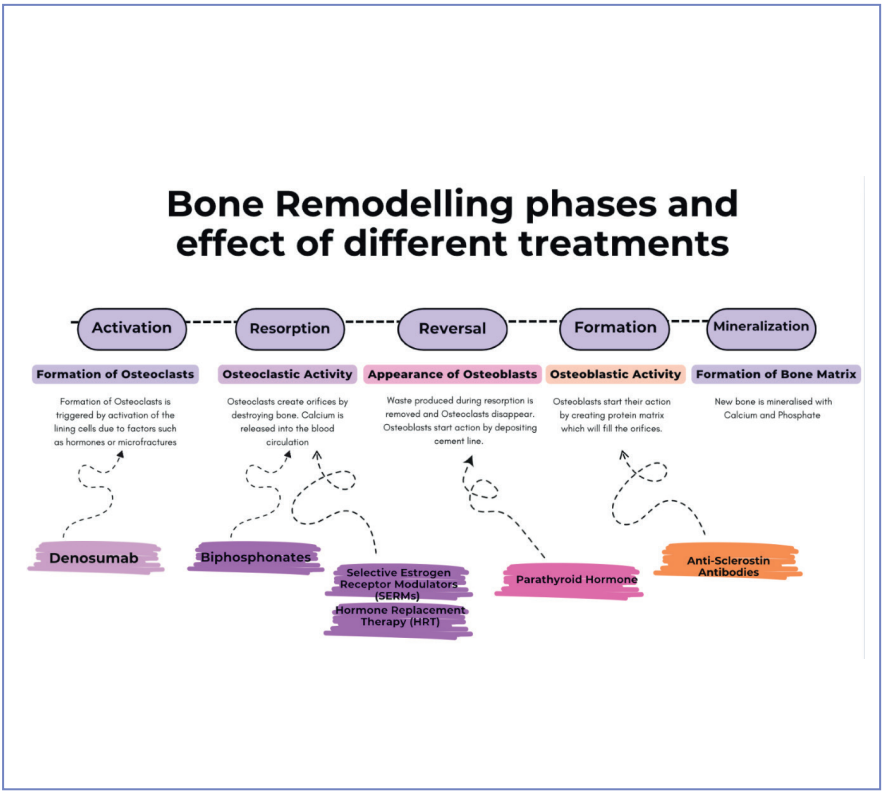

Figure 1. Bone remodelling phases and how different treatments interact in each of the phases to increase bone mineral density [1–5]

Osteoporosis is a systemic metabolic disease [5, 6] caused by an imbalance during bone remodelling, where mineralisation does not occur [3]. Consequently, there is low bone mineral density (BMD) and decreased bone strength [5], so the bone gets weaker and porous [7] and thus fractures more easily [5, 8].

According to Lu et. al, osteoporosis can be classified as primary (type I), which is a consequence of aging, or secondary (type II), which is caused either by medication, disease or is idiopathic [9, 10]. There are several factors that contribute to bone loss and/or fractures (Table 1):

Factors That Contribute to Bone Loss and/or Fractures		
Lifestyle factors	• Alcohol over 2 units/day • Low body mass index • Falls	• Immobilisation • Smoking • Low calcium intake
Hypogonadal states	• Hypogonadism • Low testosterone • Premature menopause	
Endocrine conditions	• Obesity • Cushing's syndrome	• Diabetes • Hyperparathyroidism
Gastrointestinal disorders	• Coeliac disease • Gastric bypass	• Malabsorption syndromes • Pancreatic disease
Haematological disorders	• Leukaemia • Lymphoma	• Monoclonal gammopathies • Multiple myeloma
Rheumatological/ Autoimmune conditions	• Rheumatoid arthritis • Ankylosing spondylitis • Sarcoidosis	• Amyloidosis • Musculoskeletal diseases
Neurological conditions	• Stroke • Parkinson's disease	
Miscellaneous conditions	• Chronic obstructive lung disease	• Depression • Renal disease
Medications	• Antacids containing aluminium • Anticoagulants (unfractionated heparin) • Anticonvulsants • Aromatase inhibitors • Cancer chemotherapeutics • Cyclosporine and tacrolimus	• Glucocorticoids (> 5mg/day of prednisone or equivalent for > 3 months) • Methotrexate • Parenteral nutrition • Proton pump inhibitors • Selective serotonin reuptake inhibitors • Thiazolidinediones

Table 1. Factors that contribute to bone loss and/or fractures [5]

There is a high prevalence of the condition across the globe, which has increased over the years, and it is more common in women (Figure 2) [5, 9, 11]. Females are at higher risk for several reasons, with hormonal factors playing a key role. Oestrogen inhibits bone resorption, therefore protecting the bones. Oestrogen levels drop during menopause, however, thus accelerating bone loss. Additionally, the peak of bone mass is lower in women than in men, as is the muscle mass [9, 12].

Women have higher life expectancy, which increases the prevalence of the condition in this group of patients since they experience bone loss for longer [9, 12].

During pregnancy and breastfeeding, there is an increased need for calcium: if not met through food intake, this might affect the bones, also reducing their density.

Furthermore, there are certain conditions (e.g hyperthyroidism, breast cancer, hyperparathyroidism, auto-immune conditions) and associated medications (e.g glucocorticoids) that are more common in women than men and which are associated with increased risk of osteoporosis [9, 12].

The most common fragility fractures are at vertebral, neck of femur and forearm sites [7, 8]. The consequences of fractures are numerous, including pain, morbidity and reduced quality of life [8]. 55% of people over the age of 90 who sustain a hip fracture are unable to retain autonomy and need nursing and/or family care. It is the most common cause of death after a fall as well as the most common cause of admission for emergency surgery, with an average hospital stay of 20 days, which translates into half a million bed occupations per year in the United Kingdom (UK) alone [11].

Even though osteoporosis is a well-known pathology with high prevalence, the most common type of fracture — vertebral — is still frequently missed, and the symptoms are not taken sufficiently seriously. It is important and recommended to implement robust screening programmes to diagnose the condition as early as possible, as well as differential diagnosis for people presenting with complaints of back pain and/or with obvious signs of kyphosis (Table 2) [11].

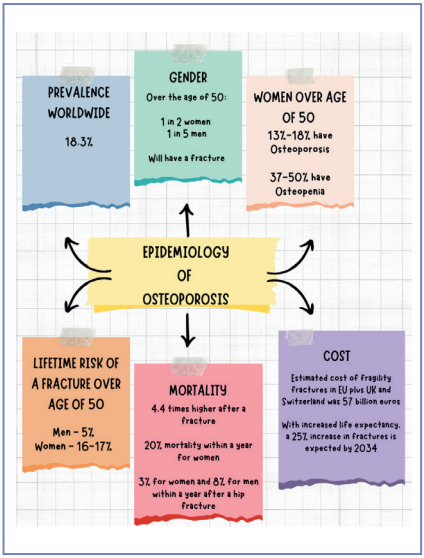

Figure 2. Epidemiology of osteoporosis [5,9,11]

DXA Scan Should Be Considered For:	VFA Should Be Considered For:
Women of age ≥ 65 years and men over age of 70 years.	Patients of age ≥ 50 years with specific risk factors
Patients of age ≥ 50 years and risk factors for osteoporosis	Patients over age of 50 years and T-score < -1.0
Premenopausal women and men under the age of 50 years with certain conditions or therapies that can increase the risk of developing the condition	Height loss of 4cm or more
	Suspicion of undocumented vertebral fracture
	Long-term glucocorticoid therapy

Table 2. Patient inclusion criteria for DXA Scan and VFA assessment in osteoporosis screening programmes [6]

DIAGNOSING OSTEOPOROSIS

The World Health Organization (WHO) endorses the diagnosis of osteoporosis based on the BMD measurement obtained with dual energy x-ray absorptiometry (DXA/DEXA). This method allows a better estimation of the risk of fracture, since for every standard deviation (SD) reduction in the BMD, the risk of osteoporotic fracture doubles [13, 14].

Patient management should be informed by the use of BMD measurements together with risk probability calculators such as QFracture (Figure 3) and/or FRAX (Figure 4), which not only help to select patients eligible for DXA scan but also aid decision-making regarding the treatment pathway going forward [3, 5, 8, 11, 13, 15, 16].

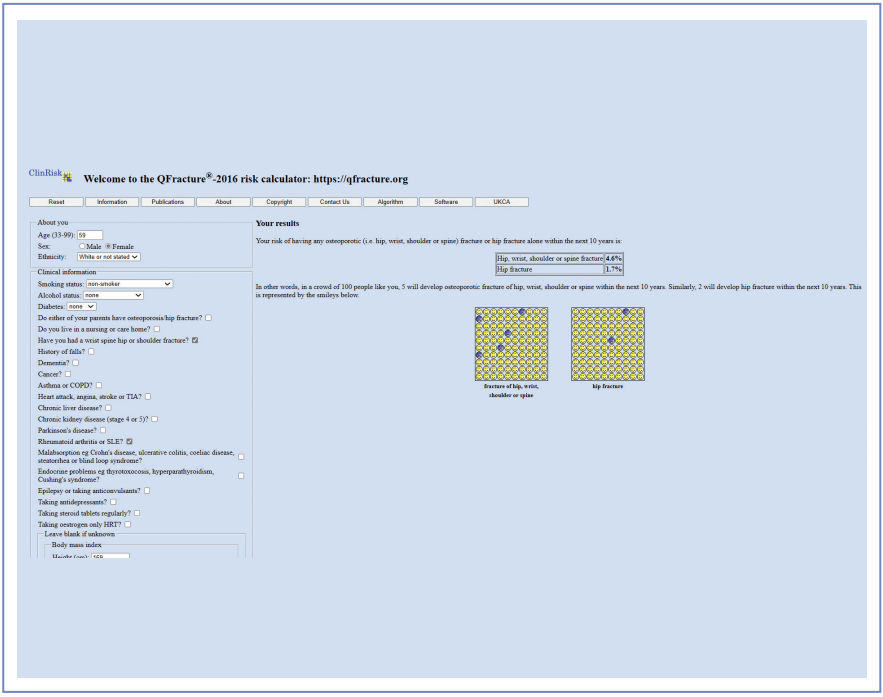

Figure 3 - QFracture tool to calculate the risk of osteoporotic fracture. It takes into consideration the patient's height, weight, age, ethnicity, and clinical risk and lifestyle factors such as smoking, alcohol use, and previous history of fracture, amongst others. This tool can be used by virtually any healthcare provider to aid patient management, including referral for a DXA scan, specialist follow-up, starting treatment or just general lifestyle advice.

Figure 4. FRAX tool to calculate risk of fracture (A) and help decide patient pathway. It takes into consideration the patient's height, weight, age, gender and some risk factors. It also incorporates femoral neck BMD and gives clear advice regarding the patient's follow-up (B).

BMD measurements are obtained using a two-compartment model, where the bone mineral is one compartment, and the soft tissue is another. By measuring absorption using high and low x-ray energies and using the attenuation properties of the soft tissue and bone mineral at the energies provided, the quantity of bone mineral present can be calculated. These profiles are then scaled appropriately and bone mineral content (BMC) calculated by subtracting the low-energy (bone) from the high-energy profiles (bone and soft tissue). This is done pixel by pixel of the area of interest (limited by an edge detection algorithm), and an average of those pixels is then calculated , which will give the BMC in grammes (g) [17].

BMD is obtained by multiplying the ***BMC x Area of Interest***. The projected area of bone is measured in cm^2 and is found by adding up the pixels in the area of interest [17].

The evaluation of bone density (BD) is calculated by dividing the given BMD differences by the SD from a normal distribution in a reference population. The Z-score is calculated based on an age-matched population — expressing the risk in comparison to peers (Equation 1) — and the T-score based on a young healthy population — expressing the risk in comparison to peak bone mass (Equation 2). The reference population also takes into account ethnicity and gender [17].

$$Z - Score = \frac{Measured\ BMD - Mean\ Age\ Matched\ BMD}{Standard\ Deviation\ of\ Sample\ Population}$$

Equation 1 - Z-score formula

$$T - Score = \frac{Measured\ BMD - Mean\ Young\ Healthy\ BMD}{Standard\ Deviation\ of\ Sample\ Population}$$

Equation 2 - T-score formula

T-Score	Diagnosis
≥ -1 SD	Normal
< -1 SD, > -2.5 SD	Osteopenia / Low Bone Mass
≤ -2.5 SD	Osteoporosis
≤ -2.5 SD plus fragility fracture	Established Osteoporosis

Table 3. WHO criteria for diagnosis of osteoporosis

The WHO criteria for osteoporosis can be can be found in table 3. These are applicable to postmenopausal women, men over the age of 50 and the anatomical regions spine, proximal femur and forearm only [13].

Z-Score	Comment
> 0 SD	Above average for age
≤ 0 SD, ≥ -2 SD	Below average for age
< -2 SD	Low for age

Table 4. Z-score interpretation

Z-scores (Table 4) can be used for everyone but should be the only value reported for younger patients [13]. They express the risk of fracture in comparison with a population of the same age [13, 14].

THE DXA SCAN

Standard Techniques and Patient Preparation

To guarantee the consistency and accuracy of the DXA measurements, a few checks and questionnaires must be performed prior to exposure, alongside patient preparation – for example, removal of objects/tight clothing from the scanning area and asking about previous iodate contrast, amongst others (Figure 5) [6, 13].

Patient Preparation and Checks Prior to Exposure	
✓	Clinical indications
✓	Authorisation and justification
✓	Height and weight recorded
✓	For follow-up scans, retrieve previous images in order to replicate same scanning conditions for positioning, acquisition parameters, regions and analysis
✓	Removal of any metal, plastic buttons or tight clothing since it causes artefacts and/or changes in BMD
✓	Exposure to iodinated or barium contrast, radioisotope scan or therapy are contra-indications
✓	History of previous fractures, prothesis and primary hyperparathyroidism
✓	Pregnancy status
✓	Lifestyle questionnaire
✓	Scanner quality assurance

Figure 5. Checks to be performed prior to DXA scan to collect important information for diagnosis, as well as selecting the best image protocol for the patient's clinical history and condition and identifying situations where there is a need to delay the scan.

Quality control is essential to maintain precision and accuracy of the scans. Precision depends on several factors including stability of scanner, patient positioning by the operator and accurate scan analysis [6, 18].

Since DXA follow-up scans are used to measure very small changes in the patient's BMD to assess the evolution of the condition, it is important to optimise all parameters that could interfere with precision, including the precision error of the operators performing the scans. Consequently, every centre should routinely evaluate this parameter and take it into consideration during the scan report by calculating the Least Significant Change (LSC). In order to achieve this, for each anatomical area scanned in the department, duplicate or triplicate scans should be acquired of a group of 30 or 15 patients, respectively, per operator, and LSC calculated *as a 95% level of confidence of 2.77 x precision* error [6, 18].

Additionally, scanner factors should also be perfected, including quality assurance, maintenance of the scanner and cross-calibration of equipment when scanners are replaced or to validate results between machines [6, 13, 18]. As far as it is feasible, an effort should be made to scan the patients in the same scanner and under the same conditions, so as to minimise error in the results [13, 18].

Radiation Protection

The effective dose in DXA is considerably lower than in other modalities, with values between 1–15 μSv for spine and proximal femur, depending on the equipment [19]. For VFA, the dose reported can range between 0.002 – 0.05 mSv, while for peripheral areas, such as forearm, it can be lower than 0.01 mSv [20].

Generally, exposure among technologists performing DXA scans is also low, though this depends on the equipment and technology used. The scatter dose at 1m from the source of radiation can have a range of up to 5μSv/h; therefore, with a workload of 20 patients per day, the staff exposure can be 0.1 to 1.5mSv per year [21].

The most important factor to ensure radiation safety of staff performing DXA scans is the design of the room [21]. The acquisition station should be positioned 1 m, 2 m or even 3.5 m from the source of radiation, depending on the equipment (pencil beam, fan-beam or older systems). Alternatively, fixed or mobile shielded screens can ensure operator safety. As with other modalities, the use of dosimeters may also be recommended, although this depends on the legislation in the respective country [20, 21].

Standard Techniques for Positioning and Analysis

The most common anatomical sites for assessing BMD are at the lumbar spine, total hip, femoral neck and at 1/3 of the radius (Table 5), which are validated and suitable to use the WHO criteria for diagnosis of osteoporosis. A lateral view of the spine is also commonly used for assessment of vertebral fractures [6].

Anatomical Area	Scanning Technique[6]
AP Spine	• Patient supine, centred on the bed (Figure 6). • A block underneath the knees creating a 60° to 90° angle of the femur to flatten the spine, reducing magnification and creating better separation of the vertebrae. • Scan to be acquired with spine centred on the field of view (FOV) from the vertebral body of L5 to T12, with iliac crest and the first rib evident. To ensure this, the technologist should locate the anterior superior iliac spine (ASIS) by feeling the top of the crest, and position the laser around 5cm above it and in line with the middle of the sternum. • For follow-up scans, ensure that positioning and scanning mode are the same. It might be necessary, in some situations, to acquire two scans for comparison and as new baseline (*e.g.* if weight change is significant and the scanning mode changes between scans). • Patient instructed to remain still and breathe normally.
Proximal Femur	• Patient supine and centred on the bed, feet to bottom and arms alongside the body (Figure 8). • Non-dominant proximal femur, unless contra-indicated, should be used for measurement. • Patient's non-dominant leg (unless contra-indicated) straight, parallel to the bed and abducted from the midline (around 15°), to create separation between ischium and lesser trochanter. • Rotation of the leg internally by around 25° to move greater and lesser trochanter and allow clear visualisation and measurement of the neck of the femur. • Patient's foot rested against a foot brace positioned in alignment with the centre of the bed to help maintain the positioning and avoid over-rotation of the femur, which can result in over-estimation of BMD. Sand bags can be used alongside the foot to help patient to maintain position. • FOV starts from below ischial ramus and above the greater trochanter, with little or no lesser trochanter evident. To ensure this, laser needs to be positioned 7–8 cm below greater trochanter, which is also in line with pubic symphysis. • Patient instructed to remain still, and positioning should match previous examination for follow-up scans to ensure consistency. It might be necessary, in some situations, to acquire two scans for comparison and as new baseline.

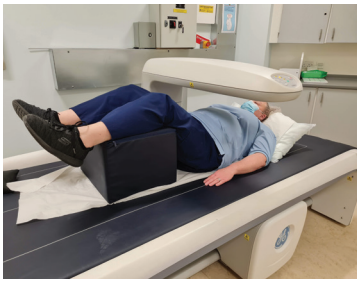

Figure 6 - AP spine positioning

Figure 8 - Proximal femur positioning

Table 5. Scanning and analysis techniques for AP Spine, Proximal Femur, Forearm and Vertebral Fracture Assessment in DXA scans

Analysis Technique[6]

• Vertebrae correctly identified from L1-L4 with the intervertebral markers positioned between the vertebral bodies, equidistant from adjacent vertebrae, on the point of lower BD as indicated on the bone profile (Figure 7).

• Bone map should be checked and adjusted for obvious errors when around 25% or more of the vertebrae are missing.

• Artefacts on the soft tissue should be removed physically, if possible. Some scanners will allow them to be marked as such and excluded from analysis, while for others the adjacent vertebra will need to be excluded.

• Consider vertebral exclusion, if necessary, for focal abnormality (e.g. fracture, degenerative changes), artefacts or over 1SD of difference from adjacent vertebrae and visual sclerotic changes in the spine. Note that two vertebral levels are needed for diagnosis and exclusion will make the results less statistically reliable.

• Adequate annotations should be made to inform the reporting practitioner of important factors that could interfere with the report/results.

• For follow-up scans, ensure the regions are positioned at the same levels.

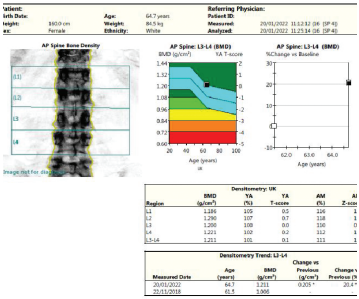

Figure 7 - AP spine scan analysis

• Bone map should be checked and adjusted, if necessary and possible, to ensure it truly reflects the bone.

• Femoral box should be positioned according to manufacturer's instructions (Figure 9).

• Ensure no ischium or greater trochanter are included in the analysis boxes.

• Adequate annotations should be made to inform the reporting practitioner of important factors that could interfere with the report/results.

• For follow-up scans, ensure the regions are positioned at the same levels and include the same anatomical areas.

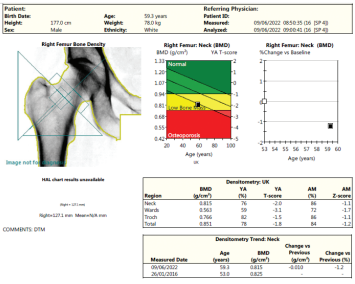

Figure 9 - Proximal femur scan analysis

Anatomical Area	Scanning Technique[6]
Forearm	• Depending on the scanner, patient might be able to lie supine for the image acquisition or in a seated position parallel to the scanner (Figure 10). • Non-dominant forearm (unless contra-indicated) should be positioned straight, aligned, at a 90° angle to the elbow, hand in a loose fist and palm down to reduce magnification. • Some manufacturers might have a board to aid positioning, which should be used according to manufacturer's instructions. • Image should contain the 1st line of carpal bones, radius and ulna centred and straight in the FOV.
Lateral Spine	• Vertebral Fracture Assessment (VFA) is performed, depending on the scanner, with the patient in lateral decubitus, with the spine straight against a board positioned behind the patient (Figure 12), or with the patient supine, with the DXA arm rotating into the desired position. • FOV starts at L5 level and finishes at T4. The laser should be positioned midway between ASIS and iliac crest, around 4–5 cm below top of iliac crest.

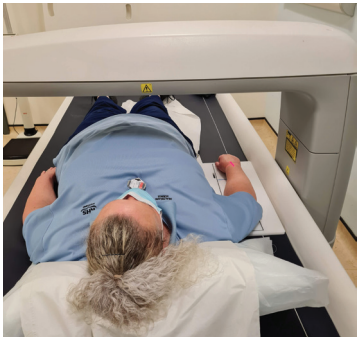

Figure 10 - Example of possible positioning for forearm acquisitions

Figure 12 - Possible positioning for VFA acquisitions

Table 5. Scanning and analysis techniques for AP Spine, Proximal Femur, Forearm and Vertebral Fracture Assessment in DXA scans

Analysis Technique[6]

• Reference line is located at the distal tip of ulnar styloid and the ultra-distal line immediately inferior to the radial end plate, so it contains the latter (Figure 11).

• 33% ROIs between radius and ulna in accordance with reference line.

• Adequate annotations should be made to inform the reporting practitioner of important factors that could interfere with the report/results.

• For follow-up scans, ensure the regions are positioned at the same levels and include the same anatomical areas.

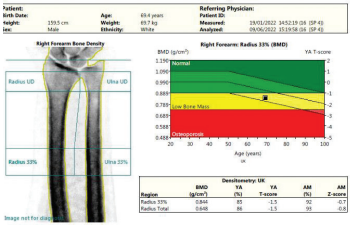

Figure 11 - 1/3 of radius scan analysis

• The posterior elements should appear in the image and 2–3 cm of soft tissue on the anterior side of the vertebrae (Figure 13).

• Visual assessment and possible fractures are identified if there is a deformity of over 20%.

• This image can be used to assist in the analysis of AP spine (*e.g.* identification of vertebral levels, fractures, aorta calcifications, osteophytes), particularly for vertebral exclusions.

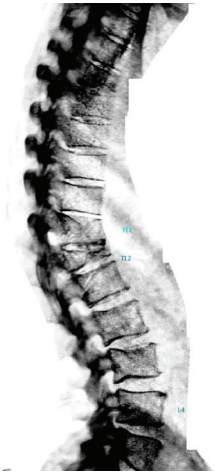

Figure 13 - VFA scan

Data Interpretation and Reporting on DXA Scans

The results of the scans are based on the T-scores and Z-scores obtained at the lowest level. Diagnosis using the distal forearm can be used if neither hip nor spine is reliable (e.g dual hip replacement and vertebral fractures) and for patients with primary hyperparathyroidism. However, these should be carefully considered since there are limitations to using the BMD at this site, namely for follow-up scans [6, 13].

Both the DXA operator and the reporting practitioner are responsible for the accuracy and reliability of the results, and need to pay particular attention to errors and pitfalls that might falsely increase the BMD, resulting in over-medication of patients (Table 6) [6, 13].

Other Applications of DXA

There are other utilities of DXA imaging, namely identification of aortic calcifications during VFA analysis. These can be scored and used to predict cardiovascular risk [6].

Trabecular Bone Score (TBS) is an algorithm to evaluate variations in the pixels of lumbar spine images acquired by DXA. It can therefore provide information regarding microarchitecture of the bone, identifying good and poor connectivity of the trabecular bone [22]. TBS can be useful in predicting fragility fractures, especially because it can be incorporated into FRAX and facilitate treatment decisions for patients with borderline results [6, 22]. Additionally, therapy response monitoring is more robust using BMD combined with TBS for anabolic and denosumab treatment [6].

Atypical femur fractures (AFF) can also be identified using extended femur DXA imaging. By opportunistically performing this scan, it is possible to detect *focal periosteal or endosteal thickening of the lateral femoral* cortex prior to complete fracture, giving the opportunity for early and preventive medical action. AFF are rare, but more common in patients on bisphosphonates [6].

Whole-body composition (WBC) is another modality acquired with DXA technology which allows the measurement of BMC, BMD, and lean and fat mass [6]. Clinical indications for WBC imaging include assessment of patients who have lost over 10% of weight as part of obesity treatment, quantification of lean body mass in patients with muscle weakness or at risk of sarcopenia, as well as to assess body fat in those treated with antiretroviral drugs as part of human immunodeficiency virus (HIV) therapy [23, 24]. Although there is evidence of the usefulness of WBC, it is still not used routinely in clinical practice [6].

Reasons for falsely increased BMD in DXA scans	
• Osteoarthritis of spine	• Aortic calcification
• Vertebral fractures	• Hip osteoarthritis
• Surgical material/Implants	• Arthroplasty
• Ankylosing spondylitis	• Gluteal implants
• Radio-opaque contrast	• Hip dysplasia
• Undissolved calcium tablets	• Paget's disease
• Bone metastases	• Incorrect ROI positioning
• Diffuse idiopathic skeletal hyperostosis	• Incorrect rotation of femur
• Splenomegaly due to glycogen storage disease	

Table 6. Reasons for falsely increased BMD in DXA scans

OSTEOPOROSIS TREATMENT

There are several approved treatments to improve BD and consequently the patients' quality of life. Alongside pharmacological treatment (Table 7), there are some non-pharmacological recommendations such as [5, 11]:

- Healthy balanced diet.
- Increase calcium intake.
- Increase intake of vitamin D.
- Weight bearing and muscle strengthening exercises.
- Smoking cessation.
- Reduce alcohol intake to 2 or less units per day.
- Falls assessment and prevention.

FINAL CONSIDERATIONS

Osteoporosis is a common condition that is known worldwide, and even though it affects both genders, women are at much higher risk than men. This condition is more evident post-menopause, though it can affect women of any age. Although rarely, it can occur during pregnancy, which has debilitating consequences not only for the women, but also for the dynamics of the new parents. Mental health is very frequently affected by the loss of autonomy and by the pain suffered by these patients. Some people's performance status deteriorates, causing them to adjust or stop their normal routines and avoid leaving their homes since they fear further fractures.

Osteoporosis Pharmacologic Treatment					
Type of treatment	Anti-Resorptive	Anabolic	Selective Oestrogen Receptor Modulators	Other Mechanisms	Adjunctive
Mechanism of Action	Inhibition of osteoclasts reducing bone resorption	Increase bone formation by targeting the osteoblasts	Selective oestrogen receptors with agonist/antagonist activity		Used additionally to other treatments
Drugs	✓Bisphosphonates ✓Denosumab	✓Parathyroid hormone supplement	✓Raloxifene	✓Strontium ✓Romosozumab	✓Calcium ✓Vitamin D
Side Effects	• Gastro-intestinal (GI) symptoms • Acute phase • Iritis • Atrial fibrillation • Atypical femur fracture • Osteonecrosis of jaw	• Anaemia • Chest pain • GI symptoms • Hypotension	• Hot flushes • Pulmonary embolism (PE)	• Strontium changes the mineral content of the bones. Last choice of treatment and patient mustn't have history of cardiovascular disease. • Romosozumab has anabolic and anti-resorptive effect	
Administration	Oral bisphosphonates – Weekly tablet on an empty stomach, patient in vertical position with a full cup of tap water. Eat 30 min post-administration and must stay in an erect position until then. Denosumab – Subcutaneous injection every 6 months	Daily injections for 24 months	Daily tablet	• **Strontium** daily solution • **Romosozumab** monthly injections	Daily tablets
Notes	1st line of treatment. Denosumab doesn't cause GI side effects but once the drug is stopped there is a pronounced drop in BMD, therefore additional treatment is needed.	BMD of the hip drops in the first 6 months and improves afterwards. Reduces vertebral fractures by 70%.	Reduction of vertebral fractures by 30%.	**Romosozumab** reduces vertebral fractures by 73% but it is not approved worldwide.	

Table 7. Pharmacological treatment for osteoporosis [11, 25–28]

DXA is the gold standard method for diagnosing this pathology, and nuclear medicine technologists have an important role in patient care. This technique is very different from other scans in the area, not only because of the type of radiation and scanner used, but also due to how these images are analysed, which calls for optimal validation of the camera system. Considering that the scan measures very small changes in patients' BMD to assess the success of the treatment, DXA operators must be highly trained, confident and have an active critical mind to ensure the results reported are accurate and of clinical significance, therefore improving the quality of life of millions of patients around the globe.

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2.4

[^{18}F]FDG PET/CT IN WOMEN'S HEALTH

by Louise Campbell[1],[2] and Peter Garcia[1]

[1]R1Department of Nuclear Medicine, Royal Brisbane and Women's Hospital
[2]Australian and New Zealand Society of Nuclear Medicine

EXECUTIVE SUMMARY

[18F]FDG PET/CT is a key imaging modality in diagnosing, staging, and managing cancers affecting women, such as breast and gynaecological cancers. It aids in diagnosing malignancies, assessing treatment response, and detecting recurrences. A standardised protocol ensures reliable results, incorporating essential elements of patient preparation such as fasting and blood sugar monitoring, and reducing factors like brown adipose tissue uptake.

Breast Cancer

2-[18F]fluoro-2-deoxy-D-glucose [18F]FDG positron emission tomography/computed tomography (PET/CT) has been established as a crucial tool for staging, identifying suitable biopsy sites and occult distant metastases, and monitoring treatment.

Uptake patterns are known to vary with tumour grade, histology, hormone receptor status and phenotype; therefore it is important to specify these details in the request form.

While [18F]FDG PET/CT excels in detecting advanced and high-grade malignancy, it is less effective for small, low-grade tumours (9, 10, 12–15).

Gynaecological Cancers

[18F]FDG PET/CT improves staging accuracy and recurrence detection, thus significantly influencing treatment. In terms of technical features, respiratory gating and contrast-enhanced imaging refine the detection and precise location of metastases, particularly in ovarian cancer (26–29).

Pregnancy and Breastfeeding Considerations

Pregnancy: [18F]FDG PET/CT is safe in pregnancy with activity adjustments and informed consent, balancing maternal benefits against foetal risks. A physician with a valid licence for administration of radiopharmaceuticals should advise on the justification for the procedure.

Breastfeeding: Interruption is not necessary; precautions which aid in reducing infant exposure are detailed below.

Keywords:
[18F]FDG PET/CT; Breast cancer; Breastfeeding; Gynaecological cancer; Pregnancy

INTRODUCTION

Globally, approximately 9.1 million women were diagnosed with cancer in 2022. Over 3.7 million were cancer types that are specific to patients of the female sex, including breast cancer, cervical cancer, uterine cancer, ovarian cancer, vaginal cancer and vulval cancer. Global Cancer Observatory data (GLOBOCAN) reports that these cancer types combined resulted in a worldwide mortality of over 1.3 million women in 2020, see Figure 1 below.

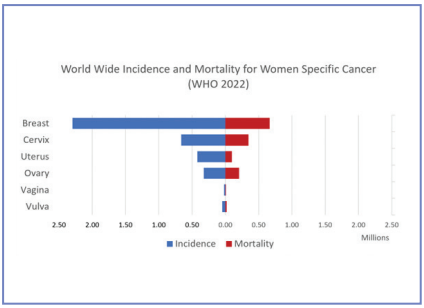

Figure 1. GLOBOCAN 2022: Estimated cancer incidence, mortality, and prevalence worldwide in 2020.

Fluorodeoxyglucose positron emission tomography/computed tomography ([18F]FDG PET/CT) has emerged as a pivotal imaging modality in the field of women's health, particularly in oncology. [18F]FDG PET plays a crucial role in the diagnosis, staging, and management of various cancers, including those that predominantly affect women, such as breast, ovarian, cervical and other gynaecological cancers.

For women, the significant health challenges caused by cancer highlight the need for accurate diagnostic tools. [18F]FDG PET has become one of the primary imaging modalities for the management of the various stages of cancer in women:

Diagnosis: To differentiate malignant from benign lesions, especially in complex cases where other imaging modalities may be inconclusive.

Staging: Accurate staging is essential for determining prognosis and tailoring treatment options. [18F]FDG PET provides comprehensive information on the extent of disease, including lymph node involvement, nodal and distant metastases.

Treatment Monitoring: By assessing metabolic response to therapy, [18F]FDG PET can guide adjustments to treatment plans, allowing for more personalised care.

Recurrence Detection: [18F]FDG PET is valuable in monitoring for recurrence and complements conventional morphological imaging, excelling at detection of distant metastasis. PET/CT is effective even in the presence of normal tumour markers (12).

ROUTINE ONCOLOGY [18F]FDG PET/CT PROTOCOL

[18F]FDG uptake in oncology is primarily mediated by glucose transporters (GLUTs), which facilitate the entry of [18F]FDG into cells. [18F]FDG is a glucose analogue, and once inside the cell, it is phosphorylated by hexokinase to form [18F]FDG-

6-phosphate. However, unlike glucose, [18F]FDG-6-phosphate cannot undergo further metabolism due to the absence of a 6-phosphatase enzyme, causing it to accumulate inside the cell. Tumour cells, which have higher metabolic rates and often exhibit upregulated GLUT expression, tend to accumulate [18F]FDG to a greater extent compared to normal tissues, making [18F]FDG PET imaging useful for detecting malignancies, assessing tumour staging, and monitoring treatment response.

A standardised protocol for [18F]FDG PET/CT imaging is crucial for ensuring accurate and reproducible results and quantification using standardised uptake values (SUV) (2,3), allowing comparison of information from sequential exams and from scans performed in different facilities. The following is an overview of a typical routine [18F]FDG PET/CT protocol.

Consent

Consent is an important part of any medical procedure, and in particular procedures that involve exposure to ionising radiation. Informed consent must be obtained prior to commencement of any stage of the PET scan. Special consideration is required when obtaining consent from people with childbearing capacity (4). A patient interview to assess the likelihood of pregnancy is required, with discretion used to ascertain the possibility of pregnancy in adolescents and transgender people (7).

Medical History

Due to the effect on [18F]FDG uptake and the consequent impact on image interpretation, it is important to record recent surgery including biopsy, medications (especially corticosteroids, growth factor etc.), chemotherapy, immunotherapy and radiotherapy, and confirm if there has been enough time between therapies and scans to avoid misleading findings due to treatment-related effects: for example, use of endocrine agents and chemotherapy may cause a flare effect. The FDG PET/CT: EANM Procedure Guidelines for Tumour Imaging: Version 2.0 suggest that an interval of at least 10 days between chemotherapy and [18F]FDG imaging is adequate, an interval of more than two weeks is warranted for patients receiving treatments with growth factors, and that waiting two to three months post radiation therapy would be appropriate prior to performing [18F]FDG PET (3).

The technologist should also document recent vaccinations and site of administration. Vaccinations, especially COVID-19 vaccination, can cause increased nodal uptake in the ipsilateral adjacent nodes (6).

Patient Preparation

Pregnancy Status: Confirm pregnancy status, following institution's policy regarding pregnancy testing.

Breastfeeding: Lactation status should also be established and documented; lactation can cause a false positive appearance due to diffuse increased physiological breast uptake.

Fasting: Patients should fast for at least 4–6 h prior to the scan to optimise glucose levels and ensure low insulinaemia, as circulating insulin in the blood impacts the uptake of glucose by non-tumour cells. Parenteral nutrition and intravenous fluids containing glucose should be discontinued for 4 h(3).

Blood Sugar Check: Blood glucose levels should be measured; ideally, they should be below 200 mg/dL (BSL < 11.1 mmol/L) (3).

Hydration: Patients should be advised to hydrate adequately with plain water before the scan, unless contraindicated.

Avoid Strenuous Exercise: Patients must avoid exercise prior to the scan, preferably for 24 h, to avoid [18F]FDG muscular uptake.

The technologist should also assess the patient's ability to adhere to procedure requirements, e.g. during the rest period, and with regard to positioning during the scan and understanding of the need to follow social contact restrictions afterwards.

Administration of [18F]FDG

Radiopharmaceutical Activity: 7 MBq x patient weight / time per bed (for PET systems that have FOV overlap of greater than 30%) or 14 MBq x patient weight / time per bed (for PET systems that have FOV overlap of less than 30%) administered intravenously, followed by a saline flush of at least 10 ml. (3)

Uptake: Patients should rest in a quiet, warm environment (to limit physiological brown adipose tissue (BAT) uptake) during the uptake and should remain relatively still to prevent muscle uptake of [18F]FDG. Allow 60–90 m for uptake (3).

Positioning: Prior to scanning the patient is asked to empty the bladder. Patients are typically positioned supine on the scanner bed, with arms above the head or down by their side depending on the clinical indication to minimise attenuation artefacts in the region of interest (3).

Comfort: The technologist should ensure that the patient is comfortable, explaining the procedure in advance to alleviate anxiety. If necessary, show the patient the scanner before administration.

Image Acquisition

Scanning: Typically, scan range including skull base to the proximal femur is suitable for most patients, although scanning ranges may vary depending on clinical indications and institutional protocols.

Scanner Settings: Appropriate scan parameters should be set for the institution's PET/CT scanner. Time per bed is typically from 2 to 5 min. Select suitable slice number and reconstruction algorithms to optimise images for review (2,3).

Normal Distribution of [18F]FDG

FDG scan, Figure 2, shows high uptake in the brain, heart, and muscles due to their metabolic activity, moderate uptake in the liver, kidneys, and spleen, and low uptake in the lungs and thyroid. The bladder appears bright due to renal [18F]FDG excretion, and bone marrow shows mild uptake in active

areas. The gastrointestinal tract may have variable uptake. Factors including fasting time and muscle activity can influence distribution, and it is important to distinguish normal physiological uptake from abnormalities.

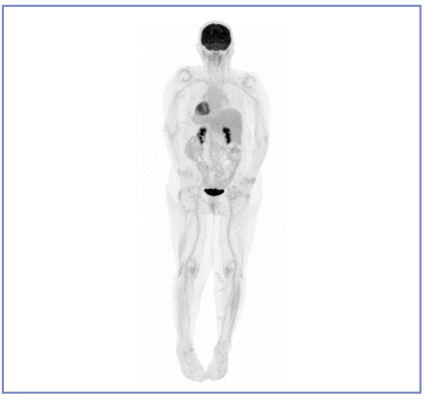

Figure 2. 71-year-old female showing normal biodistribution of 279 MBq of [18F]FDG, injected 56 minutes prior to scan. The patient had been fasting for 12 hours prior to injection and recorded a BSL of 5.9 mmol/L at time of injection. Source: The Department of Nuclear Medicine, Royal Brisbane and Women's Hospital, Australia.

Use of Propranolol for Reduction of Brown Adipose Tissue Uptake

Brown adipose tissue uptake is a common physiological finding in younger women. Propranolol is effective in preventing 2-[18F]FDG uptake in BAT during PET scans, which can confound cancer imaging (Figure 3). BAT activation is influenced by the sympathetic nervous system and cold exposure, and leads to altered 2-[18F]FDG distribution, impacting diagnostic accuracy and therapeutic response assessment (5). Propranolol, a beta-blocker, mitigates BAT uptake by reducing catecholamine activity, though it carries risks such as bradycardia, hypotension, and hypoglycaemia, particularly in patients with contraindications like asthma, certain heart conditions, or pheochromocytoma. In adults, a 20–40 mg dose is recommended an hour before the 2-[18F]FDG injection (5).

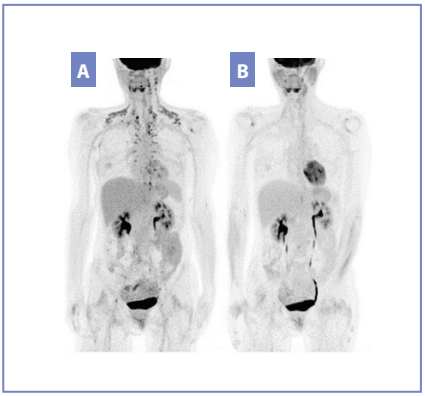

Figure 3. [18F]FDG scans of a 48-year-old female, scanned 6 months apart without propranolol pre-treatment (image A) compared with propranolol pre-treatment (image B). Image A demonstrates intense [18F]FDG uptake in the brown fat, mimicking possible lymphadenopathy. Post-propranolol image B demonstrates elimination of brown fat physiological [18F]FDG uptake for this patient. Source: The Department of Nuclear Medicine, Royal Brisbane and Women's Hospital, Australia.

[18F]FDG PET/CT IN BREAST CANCER

Breast cancer is the most common cancer in women, causing 670,000 deaths globally in 2022 (8). The treatment for breast cancer depends on the biological characteristics of the cancer and precise knowledge of the distribution of the cancer/metastases. Treatment often combines surgery, radiotherapy and systemic therapies, including chemotherapy and hormone therapies. To determine the optimal treatment for a patient, [18F]FDG PET/CT is core to the diagnostic imaging algorithm, in addition to MRI, CT, US and mammogram, to stage and restage women with breast cancer.

[18F]FDG PET/CT for Staging of Breast Cancer

[18F]FDG PET/CT has gained increasing importance in the staging of breast cancer and has shown high accuracy in detecting extra axillary lymph nodes and distant metastatic spread.

It is important to consider the appropriate use of [18F]FDG PET in breast cancer staging and assessment for recurrence. In particular, awareness of the potential for false negatives or false positives is essential to ensure that healthcare costs and radiation exposure are minimised.

According to Groheux et al. (9), factors affecting tumour uptake in breast cancer are:

1. Tumour grade – low-grade tumours (grade 1–2) show lower uptake than grade 3.
2. Histological subtype – lobular and ductal carcinoma in situ (DCIS) show lower [18F]FDG PET uptake when compared with invasive carcinomas.
3. Proliferation index (Ki67 index) – lower uptake in tumours with lower proliferative activity.
4. p53 mutation status – [18F]FDG PET uptake is higher in tumours with p53 mutation.
5. Hormone receptor status – [18F]FDG PET uptake is lower in oestrogen receptor (ER)- positive and progesterone receptor (PR)-positive tumours and higher in ER-negative and PR-negative tumours. This relates to how well-differentiated the tumours are.
6. Tumour phenotype – triple negative breast cancer which is ER- and PR-negative and has no overexpression of HER2 will show high uptake when compared with other tumours.
7. [18F]FDG PET uptake is lower in luminal A tumours than in luminal B tumours.

No special type (NST) breast cancer (BC) corresponds to invasive breast cancers and other special types of breast cancers. A joint guideline for the role of [18F]FDG PET/CT in NST BC published by EANM-SNMMI recommended [18F]FDG PET/CT as being extremely useful in breast cancer management (10).

It should be noted that [18F]FDG PET/CT is not a screening tool for breast cancer. Rather, its primary role should be for staging of tumours with known tumour histology and grade, to inform the presence and extent of

metastasis, to best guide treatment options, to assess for neoadjuvant systemic treatment response and for restaging after therapy to achieve optimal patient outcomes. Further, due to its limited spatial resolution, [18F]FDG PET/CT is not recommended for small volume loco-regional spread and should not replace sentinel node biopsy for assessment of axillary nodes (11). Groheux et al. (12) conclude that [18F]FDG PET/CT becomes useful for initial staging in breast cancer patients from clinical stage IIB and above, and is not recommended for staging of patients with clinical stage I breast cancer. In this setting, MRI or US are appropriate alternatives.

The diagnostic strength of [18F]FDG PET/CT in the setting of both locally advanced and distant metastasis is the ability to perform a "whole-body" scan to assess for both loco-regional and distant metastasis in a single examination (Figure 4). Furthermore, PET/CT enables the contemporaneous acquisition of contrast-enhanced diagnostic CT in a single visit for further assessment or completion of diagnostic imaging for accurate staging.

[18F]FDG PET/CT False Negatives and Positives in Breast Cancer

False negatives for [18F]FDG PET/CT are a result of sub-centimetre ≤10 mm (or 4–5 mm in digital PET scanners) and low-grade tumours and certain histological subtypes that reduce the sensitivity of [18F]FDG PET/CT (10).

False positives can be a result of benign processes that can show intense [18F] FDG uptake, such as e.g. fibroadenomas, infection and physiological causes, which also reduces the specificity (9). False positives can also be a result of metabolic flare due to endocrine treatments, which occurs 7–10 days after commencement or secondary to immunotherapy. The authors' institutional practice is to perform [18F]FDG PET/CT 3 weeks after chemotherapy and 3 months after radiotherapy, where appropriate.

[18F]FDG PET/CT is proven to be effective in detecting distant metastases, both in skeletal and soft tissue, with the exception of brain metastasis (9). This is due to the normal high physiological uptake of FDG in the brain, reducing the target-to-background ratio; MRI is considered to have improved sensitivity for this reason. Importantly, [18F]FDG PET/CT reliably upstages and downstages patients, leading to changes in management. In a study by Vogsen et al. (15) [18F]FDG PET/CT led to stage migration in 40% of women, which resulted in changes to treatment intent. Vogsen et al (15) concluded that [18F]FDG PET/CT should be considered for primary staging of high-risk primary breast cancer.

Quantitative [18F]FDG PET/CT

Quantitative [18F]FDG PET/CT is used for response assessment and prognosis — this includes the use of SUV using either SUV_{bw} or lean body mass (SUL), maximum standardised uptake value (SUV_{max}), metabolically active tumour volume (MATV or MTV), and total lesion glycolysis (TLG). Response assessments should be performed according to either the European Organisation for Research and Treatment in

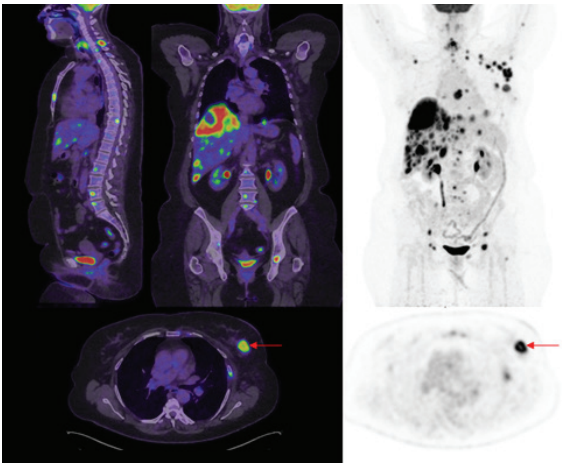

Figure 4 56-year-old female referred for staging, with new diagnosis of left breast cancer with axillary node involvement. Histology was invasive, no special type, triple negative breast cancer. Staging PET demonstrated extensive distant metastasis. Red arrow indicates primary tumour.
Source: The Department of Nuclear Medicine, Royal Brisbane and Women's Hospital, Australia.

Cancer (EORTC) PET response criteria or the PET Response Criteria in Solid Tumors (PERCIST) (10).

There are challenges associated with the use of [18F]FDG PET/CT for response assessment, including cost due to the large patient group, radiation dose, and access to PET/CT. Data are needed to measure the cost effectiveness of response assessment using [18F]FDG PET/CT. Further consideration should therefore be given to the development of quantitative analysis and data collection methods to allow modelling. Such data would enable the development of AI to support imaging specialists, and would be highly valuable.

For the future, access to digital PET/CT and whole-body PET/CT scanners will allow significant activity reduction, deliver improved resolution for lesion detection and, when combined with rigorous response assessment measures such as PERCIST, be a vital tool for management of aggressive breast cancers (10,14).

[18F]FDG PET/CT in Breast Cancer Recurrence

[18F]FDG PET/CT has been shown to be highly effective in detecting recurrence. Recurrence may be suspected upon clinical review, radiological review, or increase in the

tumour markers cancer antigen 15-3 (CA 15-3) or carcinoembryonic antigen (CEA) (12). [18F]FDG PET/CT has a significant role in evaluating recurrence, which in turn has a major impact on patient management.

Hildebrandt et al. (13) evaluated the diagnostic accuracy of [18F]FDG PET/CT with contrast CT and bone scintigraphy in patients with suspected recurrence and found that [18F]FDG PET/CT was more accurate in diagnosing recurrence and allowed for distant metastasis evaluation when compared to conventional imaging.

In conclusion, [18F]FDG PET/CT provides better prognostic information for the management of patients with breast cancer recurrence by identifying if recurrence is local or if there are distant metastases. Early detection of progression may allow discontinuation of current therapies which are ineffective and consideration of alternative treatment options. Within the setting of personalised medicine, [18F]FDG PET/CT is important for accurate and timely evaluation of treatment efficacy. Early identification of non-responding tumours permits a shift in lines of treatment which will benefit the patient and prove more cost effective.

As technology improves towards digital PET/CT and whole-body digital PET/CT, the ability to offer low-dose [18F]FDG PET/CT for early, frequent and reliable response assessments is essential. For this reason, [18F]FDG PET/CT will remain a vital tool for treatment response evaluation.

[18F]FDG PET IN GYNAECOLOGICAL CANCERS

Globally, gynaecological cancers, which include cervical, ovarian, endometrial, vaginal, and vulvar cancers, represent a significant burden on women's health and quality of life. In 2020, these cancers accounted for over 14% of all cancers diagnosed in women. Cervical cancer remains the most common, with an estimated 604,000 new cases and 342,000 deaths in 2020, predominantly in low- and middle-income countries due to disparities in screening and vaccination programmes.

Ovarian cancer, while less common, is highly fatal due to commonly being diagnosed in advanced stages. It thus causes a higher proportion of deaths among women globally, with a mortality rate of 63% reported by the World Health Organisation (WHO) in 2022.

Accurate staging at the time of diagnosis is considered to be the most important prognostic factor for gynaecological cancers (19), with 5-year survival rates shown in the table below (20–24):

The initial role of [18F]FDG PET/CT in most gynaecological cancers has been to provide accurate pre-treatment staging, often leading to upstaging due to its superior detection of distant metastases compared to other imaging modalities. However, arguably the most significant impact of [18F]FDG PET in gynaecological cancers is in the role of detecting early recurrence of the disease in patients.

5-Year Survival Rates for Common Gynaecological Cancers			
	Localized Stage	**Regional Stage**	**Distant Stage**
Ovarian	93%	75%	31%
Cervical	91%	60%	19%
Endometrial	95%	70%	18%
Vaginal	69%	57%	26%
Vulvar	86%	53%	19%

Table 1: 5-Year Survival Rates for Common Gynaecological Cancers; derived from American Cancer Society database (20–24).

Imaging Techniques for Gynaecological Cancer

In both initial staging and recurrence identification, accurate disease detection is crucially important to appropriate patient management. There are some key techniques that should be considered by the nuclear medicine technologists when performing [^{18}F]FDG PET/CT scans, namely:

Imaging Direction:

When imaging any pelvic pathology, it is advised that the PET be acquired from pelvis to head. This will capture the bladder almost immediately after voiding and reduce any misregistration caused by the filling of the bladder between the CT acquisition and the PET acquisition (25).

Respiratory Gating:

Respiratory-gated PET is available on most modern commercial systems, with a variety of different methodologies used to achieve respiratory-gated PET images. Respiratory-gated PET images offer the ability to reduce PET artefacts caused by respiratory motion during the PET acquisition. Respiratory gating can be applied to any PET acquisition where respiratory motion may lead to artefacts. In the authors' experience, applying respiratory gating to gynaecological imaging has been particularly beneficial.

Circulation of peritoneal fluid throughout the abdomen and pelvis often results in diaphragmatic metastases of ovarian cancer

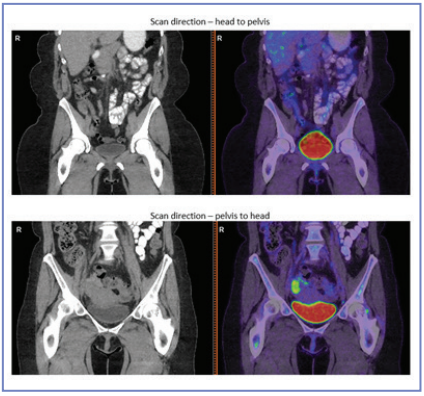

Figure 5. Two [18F]FDG PET scans performed on women with ovarian cancer.

Top Row: PET acquisition direction from head to pelvis, resulting in misalignment of pelvic structures around the bladder between PET and CT.

Bottom Row: PET acquisition direction from pelvis to head, showing appropriate alignment of bladder and pelvic structures.

Source: The Department of Nuclear Medicine, Royal Brisbane and Women's Hospital, Australia.

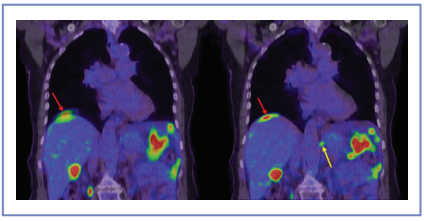

Figure 6. Free-breathing [18F]FDG acquisition (left) vs respiratory-gated acquisition (right). Red arrows show resolution of diaphragmatic motion artefact on the respiratory-gated image. Yellow arrow shows para-aortic [18F]FDG avid node only visualised on respiratory-gated acquisition.

Source: The Department of Nuclear Medicine, Royal Brisbane and Women's Hospital, Australia.

(26). Due to peritoneal-pleural communication through the diaphragm, metastatic spread into the thoracic compartment is common and often goes undiagnosed at the time of initial staging (27). With ovarian cancer, as there is a likelihood that metastases could occur in the diaphragmatic and thoracic compartments, performing a respiratory-gated PET scan should be considered to help improve lesion detection. A modern PET/CT system can provide a combination of deviceless gating and reconstruction algorithms, making respiratory gating simple to acquire without the need for a longer acquisition time.

IV and Oral Contrast-Enhanced PET/CT:

The use of contrast-enhanced CT as part of [18F]FDG PET/CT imaging has increasingly become standard across multiple pathology types. The typical benefits of using both oral and IV contrast in PET imaging for gynaecological cancers include better delineation of anatomic structures, better visualisation of the urinary tract, and better visualisation of hepatic structures and metastases (28). These benefits need to be weighed against the risks of using contrast media, including the risk of anaphylactic reactions to CT contrast.

A number of studies have investigated the use of contrast-enhanced PET/CT (cePET/CT) with specific reference to ovarian cancer. For ovarian cancer staging (28), cePET/CT was more effective than contrast-enhanced CT alone, with higher sensitivity, specificity, and accuracy (96%, 92%, and 95% for cePET/CT compared to 84%, 59%, and 76% for ceCT).

cePET/CT also performed better in cases of ovarian cancer recurrence (29), with higher sensitivity, specificity, and accuracy (86.9%, 95.9%, and 92.5%) compared to PET/CT alone. It was particularly useful for detecting smaller lesions, leading to changes in treatment for 39% of patients.

[18F]FDG PET/CT IN PREGNANCY AND BREASTFEEDING

[18F]FDG PET/CT in Pregnancy

[18F]FDG PET/CT imaging during pregnancy should only be performed when clinically urgent and when delaying the scan until after childbirth is neither feasible nor safe for the patient. The decision to perform imaging assessments during pregnancy should always involve weighing the clinical benefits to the mother against the possible harm to the foetus (3).

The most common pregnancy-associated cancers are melanoma, breast and cervical cancers (18). The presence of cancer during pregnancy requires accurate staging (or restaging) so that the oncological and obstetric care can be customised for the respective gestational age.

When [18F]FDG PET/CT examination is being considered for a pregnant patient, specific multidisciplinary counselling should be given about the need for PET, taking into consideration risks for the gestational age of the foetus, and

informed consent obtained. The gestational phase from conception to 12 weeks (first trimester) is a critical development stage. As such, it is generally considered acceptable to postpone [18F]FDG PET/CT until after 12 weeks of gestation where justified considering maternal risk from delay, although data to support this is not yet available (17).

During the second and third trimesters, the estimated total absorbed dose is less than in the first trimester (Table 2). Since [18F]FDG crosses the placental barrier, the currently adopted standard dosimetry for foetal exposure is as follows (16):

Whilst there is a lack of data, modelling suggests that the threshold for deterministic effects in humans is approximately 100 mGy and above (17). The period between weeks 4–15 of gestation is the most sensitive for irreversible growth, mental retardation and microencephaly, which occur with doses higher than 200 mGy (18). The use of both PET and CT delivers no more than 15–20 mGy when using standard administered activities and CT parameters, so any stochastic effects are small when compared to other risks of pregnancy (18).

The risk of mis-staged cancer diagnosis is considered greater than the foetal risk of an optimised low-dose [18F]FDG PET/CT scan (17). Appropriate protocol modification should be implemented when PET/CT is required, using reduced administered activities and longer imaging times. These factors will reduce the absorbed dose to the foetus. Furthermore, substantially reducing the mAs when acquiring the CT for attenuation correction will still provide a suitable scan for the purpose of attenuation correction while significantly minimising foetal dose. Figures 7 and 8 represent PET scans performed by the authors which demonstrate the utilisation of digital PET technology and reduced mAs for the CT attenuation scan. In Figure 8 the scan was performed with the patient's arms down, resulting in a significant beam- hardening artefact affecting the scan quality. When using ultra-low-dose CT imaging parameters, it is advised that the acquisition be acquired with the patient's arms above their head. For the pregnant patients in Figures 7 and 8 the same administered activity [18F]FDG was given and the same mAs was delivered for the CT. Note that there was a difference in foetal dose, which was 3 mGy for the 16-weeks-pregnant patient and 2 mGy for the 25-weeks-pregnant patient, despite the same administered activity and CT dose. This difference is due

mGy/MBq [18F]FDG	Gestation
2.5E–02	early first trimester (0–10 wk)
1.3E–02	late first trimester (11–13 wk)
8.5E–03	second trimester (14–26 wk)
5.1E–03	third trimester (after 27 wk)

Table 2. Dosimetry for foetal exposure using Olinda 2 (human data)

predominantly to the change in foetal volume and geometry, among other factors (18).

The introduction of digital PET/CT scanners has allowed for a significant reduction in administered activity, with only moderate acquisition time compensation required to provide optimal scan quality. The highest photon dose to the foetus comes from the maternal bladder. To reduce foetal irradiation, increased maternal hydration and frequent voiding is therefore encouraged prior to and following administration of [18F]FDG. Where available, [18F]FDG PET/MR could be used instead to avoid the radiation exposure delivered by CT (18).

[18F]FDG PET/CT IN BREASTFEEDING

Breastfeeding interruption is not necessary (3). The lactating breast accumulates [18F]FDG, however very little is excreted into the breast milk. The main source of potential radiation is related to the proximity of the infant to the mother rather than to the ingestion of milk.

Appropriate patient counselling is required to discuss radiation exposure and dose reduction strategies for the infant. It is recommended to minimise close prolonged contact for 4 hours when standard activities are administered (3). Where an infant can be bottle-fed by a third person, this can be employed to minimise radiation exposure to the infant. Technologists should be knowledgeable

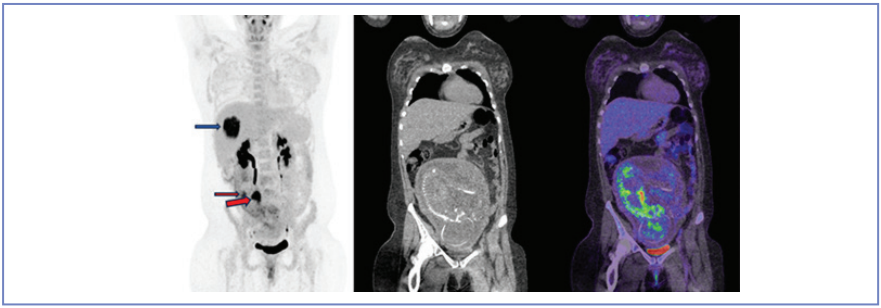

Figure 7. 27-year-old female (63 kg), 25 weeks pregnant. Referred for assessment of new liver lesion on background of colorectal cancer. Patient received radiation counselling for potential foetal risk and written consent was obtained. 116 MBq [18F]FDG was administered, CT for attenuation correction was acquired using parameters 100 kVp and 20 mAs. Estimated foetal dose was calculated to be approximately 2 mGy. Due to reduced administered [18F]FDG activity, image acquisition time was increased by a factor of 2. Increased hydration and voiding were recommended. Blue arrow represents solitary segment VII liver lesion, SUV max 12.7. Thin red arrow represents foetal kidney and thick red arrow represents foetal heart. Images acquired using Siemens Biograph Vision 600 Edge digital PET/CT scanner.

Source: The Department of Nuclear Medicine, Royal Brisbane and Women's Hospital, Australia.

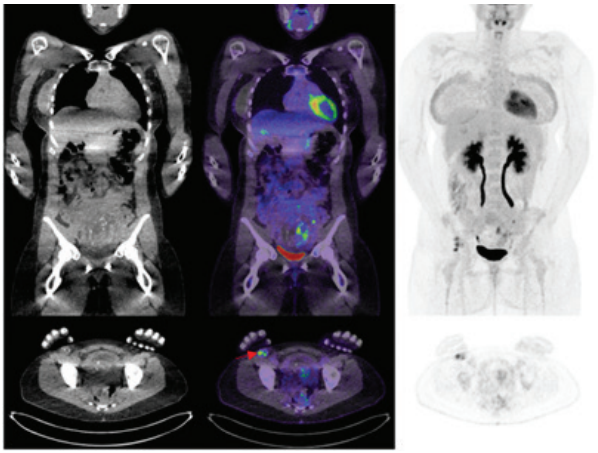

Figure 8. 33-year-old female (73kg), 16 weeks pregnant. Referred for assessment of recurrence of melanoma presenting with new enlarged inguinal lymph node (red arrow) on a background of resected stage IIIa BRAF mutant melanoma. Patient received radiation counselling for potential foetal risk and written consent was obtained. 116 MBq [18F]FDG was administered, CT for attenuation correction was acquired using parameters 100 kVp and 20 mAs. Estimated foetal dose was calculated to be approximately 3 mGy. Due to reduced administered [18F]FDG activity, FDG PET image acquisition time was increased by factor 2. Increased hydration and voiding were recommended. Note beam-hardening artefact due to arms positioned down. Images acquired using Siemens Biograph Vision 600 Edge digital PET/CT scanner.

Source: The Department of Nuclear Medicine, Royal Brisbane and Women's Hospital, Australia.

about the advice to be provided and know when to seek additional medical input in complex scenarios.

Where maternal [18F]FDG PET/CT scan is required during the early neonate stage, and breast feeding is still being established, the authors have successfully used low-activity [18F]FDG administration and commensurate increase in imaging time using digital PET/CT to minimise radiation exposure (Figure 9). In this case example, following multidisciplinary counselling, a 2- hour interruption of breastfeeding was recommended following administration of 120 MBq [18F]FDG. Given

the very low administered activity, this approach allayed maternal concerns related to breastfeeding interruption during breastfeeding establishment phase with neonate.

In conclusion, [18F]FDG PET/CT is not contraindicated during pregnancy and breastfeeding. However, all efforts should be made to appropriately modify the protocol to achieve the lowest dose to the infant yielding an adequate diagnostic study. Patient counselling on dosimetry involving a multidisciplinary team is required for informed consent when imaging the pregnant or breastfeeding patient.

CONCLUSION

[18F]FDG PET/CT has established itself as a cornerstone imaging modality in women's health, especially in the diagnosis, staging, treatment response monitoring, and recurrence detection of cancers affecting women. Its ability to provide comprehensive whole-body imaging and accurate metabolic data significantly enhances the management of breast and gynaecological cancers. Innovations like digital PET/CT and respiratory gating continue to improve its diagnostic efficacy and safety. As personalised medicine evolves, [18F]FDG PET/CT remains an indispensable tool in optimising patient care and oncology outcomes for women.

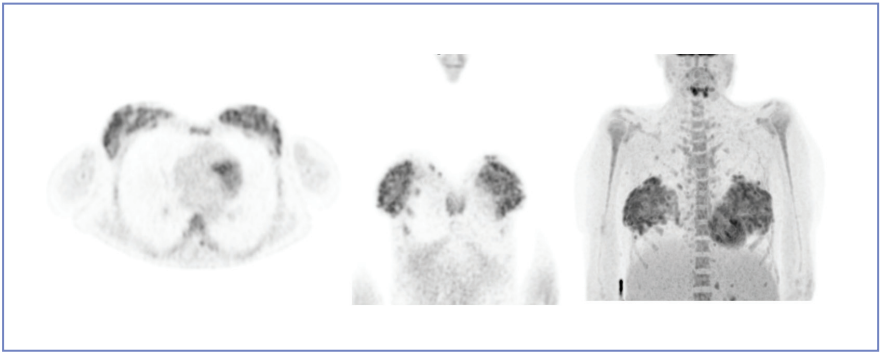

Figure 9. 34-year-old breastfeeding female (66kg), 6 weeks post-partum, referred for fever of unknown origin. 120 MBq [18F]FDG administered IV (50% [18F]FDG reduction and imaging time increased by factor of 2). Scan demonstrates intense [18F]FDG activity in bilateral breast fibroglandular tissue, in keeping with current lactation. Due to reduced administered [18F]FDG activity, the patient-specific radiation counselling advised avoidance of prolonged contact for breastfeeding for 2 hours post injection and increased hydration and voiding. Written informed consent was obtained. Images acquired using Siemens Biograph Vision 600 Edge digital PET/CT scanner.

Source: The Department of Nuclear Medicine, Royal Brisbane and Women's Hospital, Australia.

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2.5 CARDIOVASCULAR DISEASE IN WOMEN

by Nouzha Ben Raïs

Department of Nuclear Medicine
Mohammed VI International University Hospital Rabat
Mohammed VI Faculty of Medicine Rabat
Mohammed VI University of Sciences and Health Morocco

EXECUTIVE SUMMARY

Cardiovascular disease (CVD) is the leading cause of death from non-communicable diseases, killing 17.9 million people each year, followed by cancer, respiratory diseases and diabetes. More than 275 million women worldwide are affected by CVD, which accounts for 35% of deaths in women each year (about one third of all female deaths worldwide), more than deaths from all cancers combined, including breast cancer.

In addition to anatomy and pathophysiology, women's cardiovascular health is affected by hormonal changes throughout life, including those associated with menstruation, pregnancy, and menopause.

Women often present with atypical symptoms that differ from the classic signs of myocardial infarction, such as chest pain. In patients with non-obstructive coronary artery disease, coronary microvascular disease and/or coronary spasm has been reported in about half of cases. Women are more likely to suffer from non-obstructive CVD and microvascular dysfunction, which can lead to underdiagnosis and undertreatment.

The most advanced non-invasive techniques are coronary computed tomography angiography, cardiac magnetic resonance imaging and nuclear cardiac imaging. The latter plays a key role thanks to advances in hybrid imaging, solid-state semiconductor cameras and appropriate tracer selection, improving the accuracy and safety of cardiac imaging in women and enabling better outcomes and more personalised care. Historically, CV research has focused more on men, resulting in a lack of knowledge about how heart disease manifests and progresses in women. Despite efforts to raise awareness and research and advances in the diagnosis and treatment of CVD, women continue to be seriously under-recognised, under-diagnosed and undertreated. Although awareness has improved, better education, targeted screening, targeted prevention and more gender-specific research are essential to reduce the global burden of CVD in women.

Keywords:
Women, CVD, CMVD, NOCAD, SPECT/CT, PET/CT

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death from non-communicable diseases, claiming 17.9 million lives each year and affecting more than 275 million women. It accounts for 35% of female deaths worldwide, more than deaths from all cancers combined, including breast cancer [1,2]. Women often present with atypical symptoms and are more prone to coronary microvascular disease (CMVD) and coronary spasm than their male counterparts, which can lead to under-diagnosis and under-treatment [1, 2]. Increased awareness of these differences may lead to faster and more accurate diagnoses and improved outcomes for women with CVD [2–4].

Hybrid nuclear imaging for the diagnosis and monitoring of CVD in women presents unique challenges due to anatomical, physiological and technical factors, highlighting the need for gender-specific approaches in clinical practice [5, 6].

The incidence and outcomes of CVD vary considerably between regions and populations, noting that certain epidemiological factors uniquely affect women [7]. Coronary heart disease (CHD) is the most common form of CVD in women, with significant disparities in incidence, particularly in low- and middle-income countries (LMICs), where women face higher mortality rates and poorer health outcomes due to limited access to healthcare. Women in LMICs account for about 80% of all CVD deaths and typically present with CVD 7 to 10 years later than men [8, 9].

CVD also has a significant impact on pregnant women, affecting up to 4% of all pregnancies, and is the leading cause of maternal morbidity, contributing to a third of pregnancy-related maternal deaths [9–12]. The incidence of peripartum cardiomyopathy (PPCM) ranges from 1 in 1000 to 1 in 4000 live births in Western countries and is influenced by factors such as age, ethnicity and pre-existing medical conditions [13].

This chapter will cover female-specific characteristics in detection and diagnosis of cardiac disease, the challenges associated with diagnosis and possible imaging artefacts related to female anatomy, followed by how nuclear diagnostic modalities (SPECT and PET) can impact on real-life clinical pathways. New positron emission tomography (PET) tracers offer specific advantages for cardiac imaging in women, providing better image quality, lower susceptibility to artefacts and absolute quantification of myocardial perfusion (MP), i.e. myocardial blood flow (MBF) and coronary flow reserve (CFR), which are key elements of CMVD. Ongoing research will continue to highlight the role of advanced nuclear imaging in providing personalised, gender-sensitive cardiovascular (CV) care [6, 14, 15].

In addition, CVD is a major health risk for cancer survivors, affecting one in three women, particularly those who have survived breast or cervical cancer, and placing them at higher risk of cardiac problems [16]. Assessment of post-therapy cardiotoxicity

will thus also be discussed. Women also have a higher lifetime risk of stroke due to longer life expectancy and higher incidence of hypertension and atrial fibrillation, making stroke a leading cause of disability and death in women [17]. Furthermore, the prevalence of peripheral arterial disease (PAD) is particularly high in older women, but they often present with atypical symptoms, leading to under-diagnosis [18]. The chapter will conclude with promising tracers and what's next for emerging technology and research in this field.

Characteristics of Women's CVD and Risk Factors

The following are specific risk factors for CVD in women:

Anatomy: Women tend to have smaller hearts and smaller coronary arteries than men, and the muscular walls of women's hearts are thinner, which can affect how heart disease manifests and progresses. A woman's heart tends to have a smaller left ventricle (LV), which can affect haemodynamic responses during exercise [19]. Women have different coronary anatomy, including smaller-diameter arteries and a higher prevalence of MVD [20].

Hormonal: Sex differences are due to gene expression from sex chromosomes and the resulting differences in sex hormones. Hormonal changes affect women's CV health throughout life, including during periods, pregnancy and menopause [21].

Oestrogens have cardioprotective effects, influencing the structure and function of the CV system, protecting blood vessels, promoting vasodilation and maintaining endothelial health, which affects vascular tone and blood flow (BF) [22, 23]. Studies show that hormonal dysfunction increases the risk of atherosclerosis and CHD events [23].

Polycystic ovary syndrome (PCOS), pregnancy and menopause are linked to changes in sex hormones. PCOS, in particular, is marked by high androgen production leading to ovarian dysfunction, and is often linked to insulin resistance. Post-menopausal women with PCOS have more risk factors for CHD and a higher rate of adverse coronary events [24].

Hormonal, vascular, genetic and pathophysiological hypotheses have been proposed to account for the development of PPCM, but the exact underlying causes remain debated, as does the complexity of the contributing multifactorial causes [13].

- **Pregnancy:** Pregnancy-related factors such as pre-eclampsia, gestational diabetes, and preterm birth are now recognised as major risk factors that significantly increase a woman's lifetime risk of CVD. Women with such a history should be continuously monitored and treated appropriately. Spontaneous coronary artery dissection (SCAD) is a major cause of myocardial infarction (MI), particularly in young and middle-aged women and during pregnancy [12, 25, 26]. Adaptive physiological changes in the CV system occur during pregnancy due to increases in left ventricular end-diastolic

volume, left ventricular mass, and cardiac output. Pregnancy is also associated with tachycardia, which can be a technical limitation for ECG gating. The most common cardiac complications during pregnancy are primarily PPCM and CMVD. PPCM is defined as symptomatic LV systolic dysfunction with LV ejection fraction (LVEF) <45% [2, 13, 26].

SCAD is particularly common in the first week after delivery [12, 27].

Pregnant women are advised to use non-ionising imaging techniques such as echocardiography or non-contrast cardiac MRI, while magnetic resonance imaging (MRI) with a field strength greater than 1.5 Tesla should be avoided due to concerns about heating effects, particularly in the first trimester [28].

In cases of uncertainty, more aggressive techniques such as invasive coronary angiography (ICA), optical coherence tomography (OCT) and intravascular ultrasound (IVUS) can be used to guide revascularisation [29].

- **Menopause:** The incidence of CVD often rises sharply after menopause due to decreased levels of protective oestrogens that previously provided vascular protection. Menopause contributes to changes in lipid profiles and increases the risk of atherosclerosis. As we age, sex hormones affect inflammation and immune function [11].

During menopause, the protective role of oestrogen in reducing immune cell activation disappears, resulting in a decrease in CD4+ and CD8+ T cells and natural killer cell activity, and an increase in pro-inflammatory cytokines, tumour necrosis factor (TNF), and C-reactive protein (CRP). At the same time, levels of auto-antibodies and immune complexes increase due to persistently low oestrogen levels. CRP is a marker of inflammation and a harbinger of CVD [30, 31].

Psychosocial and Socioeconomic Factors: Exposure to stress, limited access to healthcare, and uncontrolled risk factors further increase the risk of CVD in women, particularly in LIMICs. In addition, women are more susceptible to autoimmune diseases, which are associated with chronic inflammation and a higher risk of CVD [32, 33].

Mental health conditions such as depression and anxiety are more commonly reported in women and may play a greater role in women's risk of diabetes and contribute to the development and progression of CVD [34].

Diabetes: Women with diabetes have a sixfold increased risk of heart disease, which is associated with poorer lipid profiles and higher rates of obesity. Worldwide, there are 17.7 million more men than women with diabetes. However, women appear to have more risk factors at diagnosis, particularly obesity [35].

Pathophysiology of Female CVD

Atherosclerosis is probably the deadliest disease in the world. The pathogenesis of atherosclerosis leading to MI and myocardial ischaemia results from vascular inflammation, lipid accumulation, intimal thickening and fibrosis, remodelling, and plaque rupture or erosion. Women may have a different pathophysiology of atherosclerosis and often develop more diffuse plaques than obstructive lesions[30]. Atherosclerosis progresses faster in patients receiving alkylating agents, fluoropyrimidines and platinum compounds, increasing the risk of arterial thrombosis and vasospasm [36].

Plaque characteristics in women

Women with CHD are more likely to have soft fatty plaques rather than the more calcified plaques commonly seen in men. These fatty plaques are more likely to be diffuse, forming thin layers along vessel walls, rather than large, localised blockages, making them harder to detect with traditional imaging techniques. They are also softer and more fragile, although smaller and less obstructive [36, 37].

Women are more likely to have high levels of inflammatory cells, which contribute to plaque instability and increase the risk of rupture. This potentially leads to acute coronary syndrome (ACS) or heart attack. This variation in plaque composition has consequences for both disease progression and imaging [37].

Non-calcified plaques are less visible on standard computed tomography (CT) imaging, which relies on the detection of calcium deposits. This may result in an underestimation of the severity of CVD in women. However, advancements in imaging techniques and the incorporation of anti-inflammatory therapies have emerged as promising solutions, aiming to enhance detection and outcomes [38].

Symptom variability and atypical presentation

Common symptoms in women with coronary artery disease (CAD) may include:

- unexplained fatigue and weakness
- shortness of breath or difficulty breathing
- nausea, indigestion or heartburn-like symptoms
- pain in areas other than the chest, such as the jaw, neck, back or upper abdomen, and dizziness or light-headedness [39, 40].

Atypical symptoms in women can lead to delays in diagnosis and treatment, with serious implications for outcomes [40].

Traditional diagnostic tests designed to detect major obstructions may not detect NOCAD or MVD in women. This difference can lead to misdiagnosis or inappropriate treatment [41].

Coronary microvascular disease (MVD)

MVD and endothelial dysfunction in women can lead to ischaemia or infarction without causing significant coronary artery obstruction visible on conventional angiography [41].

MI with non-obstructive coronary arteries (MINOCA) is an acute infarction without coronary artery obstruction on the ICA and without a specific differential diagnosis to exclude myocarditis and broken heart syndrome, also known as stress-induced cardiomyopathy [42, 43].

Broken heart syndrome

Scientifically known as takotsubo cardiomyopathy (TTC), it is predominantly a disease of post-menopausal women, accounting for 90% of cases, 80% of which are diagnosed after the age of 50. TTC highlights the impact of emotional stress on heart health and classically mimics ACS with ST elevation and elevated troponin, making TTC a differential diagnosis of MINOCA. TTC can also present as acute heart failure or, less commonly, be asymptomatic [43, 44].

Heart failure

Women are more likely than to develop heart failure (HF) with preserved ejection fraction (HFpEF), which can be associated with ageing, obesity, hypertension and diabetes. This condition is more difficult to treat and is more common in older women. The pathophysiology of HFpEF involves complex interactions between obesity, systemic inflammation and changes in cardiac structure [45].

DIAGNOSTIC MODALITIES AND HYBRID NUCLEAR IMAGING

In women with suspected CAD, advanced non-invasive cardiac imaging plays an important role:

Coronary computed tomography angiography (CCTA)

In women with risk factors, the CT coronary calcium score ("CT calcium score") (CCTA) can detect calcified atherosclerotic plaque well before the onset of symptoms and is the best predictor of future cardiac events. CT with SPECT also allows quantification of intrathoracic fat and coronary artery calcium score, which provide incremental prognostic value for MACE in women [46].

CCTA can sometimes detect non-calcified plaques using contrast agents, although it is typically less sensitive for these types of plaques than for calcified plaques. CCTA can detect and assess the severity of coronary stenosis, with obstructive CAD defined as stenosis ≥ 70%, or ≥ 50% when ischaemia is documented. The sensitivity and specificity of CCTA are slightly lower in women than in men, despite an overall high diagnostic accuracy for detecting stable CAD. Women with moderate or severe ischaemia are more likely than men to have non-obstructive coronary artery disease (NOCAD) (i.e.<50% stenosis in all vessels) on CCTA [46, 47].

Functional myocardial perfusion imaging (MPI)

MPI techniques such as stress echocardiography, cardiac MRI and nuclear MPI can assess BF to the myocardium and are particularly helpful in detecting MVD and diffuse plaque. This is beneficial in CMVD, where small vessel dysfunction leads to poor perfusion [48, 49].

Combining stress testing with MPI using a pharmacological agent or treadmill exercise may improve sensitivity in women by highlighting areas of ischaemia that might otherwise go undetected, especially in the MVD or diffuse plaque [50].

Nuclear MPI is diverse and includes single-photon emission computed tomography (SPECT) with ^{99m}Tc-agents or ^{201}Tl (Thallium), and PET using Rubidium ions ($^{82}Rb^{+}$), [^{13}N] Ammonia ([^{13}N]NH_3), or [^{15}O]H_2O [50, 51, 52].

Equilibrium radionuclide angiography (ERNA), also known as multi-gated acquisition (MUGA), is a well-validated non-invasive test to accurately determine cardiac function [53].

A cardiac MRI is used when CAD is suspected. It doesn't use ionising radiation, so is indicated in pregnancy and is more sensitive than SPECT for stable coronary disease [54].

Nuclear imaging modalities in coronary syndromes in women[1]

Nuclear imaging provides insight into female-specific cardiac conditions, including MVD and NOCAD.

SPECT/CT

^{99m}Tc-agents, such as [^{99m}Tc]Tc-sestamibi or [^{99m}Tc]Tc-tetrofosmin:

» Provide better resolution and are less affected by breast tissue attenuation compared to ^{201}Tl.

» High-quality images with clear delineation of perfusion defects, making them useful for identifying small ischaemic areas [5, 6, 50, 51].

Thallium-201

» Behaves similarly to potassium and is taken up by myocardial cells in response to BF, providing an indication of MP and viability.

» Redistributes after initial uptake, which makes it useful for viability studies, especially in areas of previous MI.

» Has a relatively long half-life (73 h) and emits low-energy gamma rays.

» Primarily used for viability studies, less commonly for routine MPI due to higher radiation exposure and susceptibility to artefacts [5, 6, 52, 53].

By comparing images taken during stress (exercise or pharmacological testing with dobutamine, adenosine or regadenoson) and at rest, it can assess BF and identify areas of reversible ischaemia. SPECT can help determine myocardial viability by showing whether areas with reduced BF can still benefit from revascularisation. In addition, if stress imaging is normal, skipping resting acquisitions can reduce the total radiation dose [52, 53].

[1]This chapter does not provide in-depth information about each radiopharmaceutical or imaging modality; its focus is on the specific role the latter play in imaging cardiac disease in women, as compared to the remaining population. Please refer to guidelines for details about each imaging modality.

SPECT has been extensively studied and validated, with decades of clinical data supporting its use in the diagnosis of CAD. SPECT is also widely available and is less expensive than PET [55]. This makes SPECT the most common functional imaging technique for ischemia detection and risk stratification of women with stable CAD.

CZT camera

Solid-state digital SPECT cameras, such as the cadmium zinc telluride (CZT) camera, have highly sensitive detectors that allow the injection of less radiotracer, thus optimising radiation safety while improving diagnostic accuracy in women with a low to moderate likelihood of CAD.

In addition, CZT-based detectors reduce the percentage of artefactual perfusion defects. Clinical applications and other benefits include speed of results, image quality, simultaneous multi-isotope imaging and patient compliance [56, 57].

Disadvantages

Despite the overall high diagnostic accuracy in women, the detection of small areas of ischaemia by SPECT-MPI may be limited in post-menopausal women. The latter have a smaller LV volume, which, combined with the limited spatial resolution of SPECT, leads to image blurring. In addition, SPECT-MPI cannot rule out CMVD as its low resolution does not enable absolute quantification of MBF. A major drawback of SPECT-MPI in young women is the estimated radiation exposure of 2–8mSv. Due to its lower radiation exposure, ^{99m}TcTc should therefore be given preference over ^{201}Tl [54, 55].

PET/CT

PET/CT is particularly useful for quantitative assessment of BF, offering higher sensitivity, better spatial resolution and lower radiation exposure than SPECT and reducing the rate of false-negative results in women related to smaller LV size.

Radiopharmaceuticals used in cardiac PET/CT include 2-[^{18}F]FDG, Na[^{18}F]F, Rubidium ions (^{82}Rb^{+}), [^{13}N]Ammonia ([^{13}N]NH_3), and [^{15}O]H_2O [58, 59].

^{82}Rb^{+}:

» Potassium analogue that is taken up by the myocardium as a function of BF.

» ^{82}Rb has a high sensitivity in quantifying MBF and PI, improving the detection and assessment of MVD, multivessel CAD and diffuse ischaemia, which are more common in women.

» Very short half-life of 75 seconds, resulting in minimal radiation exposure, which is beneficial for women, especially those of childbearing age.

» Less susceptible to attenuation artefacts from breast tissue, improving diagnostic accuracy in women.

» However, ^{82}Rb requires an on-site generator due to its short half-life, which can limit accessibility and increase cost [60–62].

[^{13}N]NH_3 :

» [^{13}N]$NH_3$is incorporated into the myocardium, providing a highly accurate assessment of MBF and viability.

» Consists of quantitative MP and BF imaging, often in high-risk or complex cases where detailed flow information is required.

» Advantages for female imaging are high resolution and quantitative capabilities: $[^{13}N]NH_3$ is therefore excellent for detecting MVD, which may be more common in female patients with NOCAD.

» ^{13}N has a longer half-life than ^{82}Rb, i.e. approximately 10 minutes, but still provides relatively low radiation exposure, allowing for repeated examinations if necessary.

» Provides reliable BF quantification, allowing detailed analysis of CFR, a valuable metric in the assessment of CMVD.

» However, it requires an on-site cyclotron due to its short half-life, which limits availability [58, 63].

$[^{15}O]H_2O$:

A short-lived inert tracer that diffuses easily across barriers and achieves rapid equilibrium between tissue and blood concentrations. Its use is limited in clinical practice due to resolution challenges and difficulties in separating blood from myocardial images.

2-[^{18}F]fluoro-2-deoxy-D-glucose or 2-[^{18}F]FDG:

Glucose analogue that is taken up by viable heart cells.

Many uses and was first described as a marker of vascular inflammation associated with atherosclerosis over 20 years ago.

Can distinguish viable but hibernating myocardium from scar tissue.

Particularly useful for assessing myocardial viability and determining whether dysfunctional myocardium can regain function after revascularisation.

Allows viability studies and metabolic imaging, especially in patients with ischaemic cardiomyopathy or cardiotoxicity due to cancer treatment [64, 65].

PET/MRI

PET/MRI combines the high sensitivity of PET tracers with excellent spatial resolution and has enormous potential for CV imaging, such as assessment of CAD, cardiomyopathy, viability and inflammation.The only barriers remain its limited availability and high cost [66].

In summary

Choosing the right radiopharmaceutical for cardiac SPECT/CT, PET/CT and PET/MRI in women involves balancing diagnostic needs against concerns about radiation exposure and susceptibility to artefacts:

» SPECT with ^{99m}Tc-agents is generally preferred to ^{201}Tl due to their lower radiation and fewer artefacts.

» PET with $^{82}Rb^+$ and $[^{13}N]NH_3$ offers high sensitivity, better quantitative capabilities, minimal artefact interference and lower radiation exposure than SPECT [47, 65, 66].

» PET using either $[^{13}N]NH_3$, $^{82}Rb^+$, or $[^{15}O]H_2O$ enables absolute quantification of MP, i.e. MBF and CFR, which are key elements of CMVD. It should be noted that MBF values at rest are higher and CFR values lower in

women than in men, and the predictive value of PET-derived MBF and CFR for major adverse cardiovascular events (MACE) is lower in women than in men. On the other hand, a blunted heart rate response after pharmacological stress for [^{13}N]NH_3-PET is a predictor of reduced CFR in women with suspected myocardial ischaemia, but not in men [63, 64, 65].

Disadvantages

PET has limited availability, higher cost, and requires specific tracers that are not universally available [63, 64, 65].

Imaging Assessment of Cardiac Function and Volumes in Heart Failure

Echocardiography is the first-line exam to assess cardiac function, though it may be technically limited in women because of a smaller acoustic window related to breast.

Cardiac MRI is considered the reference standard to measure right and left chamber volumes and mass, to assess both systolic and diastolic functions, determine HF aetiology, and look for complications in HFrEF as well as in HFpEF [67, 68].

MUGA with ECG-gated SPECT or SPECT only has the ability to calculate left and right ventricular EF, assess ventricular motion (multiple view) and wall thickening, and provide estimates of LV volumes, which are important in assessing overall cardiac function and the impact of heart failure on the heart's structure [53].

ERNA-PET can accurately determine EF and other functional parameters and provide precise measurements of LV volumes and mass, which are essential for assessing the severity of heart failure and guiding therapeutic interventions [69, 70].

Nuclear Imaging Assessment of Myocardial Sympathetic Innervation

[^{123}I]mIBG or *meta*-[^{123}I]-iodobenzylguanidine:

- Primary SPECT radiotracer used to image myocardial sympathetic innervation. Similar to norepinephrine and can therefore be taken up by nerve endings in the myocardium.
- It allows for the assessment of sympathetic activity by measuring the heart-to-mediastinum (H/M) ratio and washout rate, which may reflect the degree of sympathetic function or dysfunction in the heart. Women with HF, particularly HFpEF, may have unique autonomic profiles.
- Valuable tool for assessing autonomic dysregulation, providing personalised treatment information. It can assess autonomic function in women undergoing chemotherapy.
- Can help identify patients at risk of arrhythmia or sudden cardiac death, which is critical for female patients.
- Used to assess the risk of adverse events in patients with HF by evaluating the degree of sympathetic loss.
- Carries a radiation dose that should be carefully considered in women, particularly younger patients [71].

Research is ongoing to develop ^{99m}Tc-labelled radiotracers for imaging sympathetic innervation, as ^{99}mTc has favourable properties and widespread availability. Some investigational ^{99m}Tc-tracers have shown potential but are not yet available for routine clinical use. These include:

- [^{99m}Tc]Tc-EPH (epinephrine), used in research settings to study sympathetic nerve endings [79-81];
- [^{99m}Tc]Tc-DAA (dopamine analogues), used in experimental settings to study dopaminergic pathways and sympathetic innervation [72, 73].

Nuclear Imaging in Cardiac ATTR Amyloidosis and Sarcoidosis

SPECT/CT

SPECT/CT has an important role in the diagnosis of cardiac transthyretin amyloidosis (ATTR), using bone SPECT tracers such as [^{99m}Tc]Tc-pyrophosphate (PYP), [^{99m}Tc]Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) or [^{99m}Tc]Tc –hydromethylene diphosphanate (HMDP) to identify the presence and extent of cardiac uptake. Bone tracer cardiac scintigraphy has high sensitivity and specificity for cardiac amyloidosis compared with tissue biopsy [74, 75].

PET/CT

2-[^{18}F]FDG can provide information on cell metabolism and viability. It can also avoid biopsy, which is important in patients with suspected HF. [^{18}F]FDG-PET can differentiate active reversible lesions from irreversible fibrotic sarcoid lesions, which is highly important in determining optimal treatment [76].

Na[^{18}F]F uptake is low compared with conventional bone scintigraphy, and it may be effective in localising amyloid deposition and monitoring disease in patients with ATTR amyloïdosis.In addition, assessment of inflammation and ATTR amyloid deposition affecting the myocardium can be detected with 2-[^{18}F]FDG and Na[^{18}F]F respectively [77, 78].

New PET tracers which target amyloid fibrils, such as ^{11}C-labelled Pittsburgh compound B ([^{11}C]PiB), [^{18}F]florbetaben, [^{18}F]florbetapir and [^{18}F]flutemetamol, have also been proposed for imaging of cardiac amyloidosis [79].

Nuclear Imaging of Cardiotoxicity

Nuclear imaging modalities are crucial for assessing cardiotoxicity in patients undergoing potentially harmful therapies like chemotherapy, immunotherapy, and radiotherapy. Women with left-sided breast cancer receiving radiotherapy face a higher risk of CAD due to fibrous stenosis and plaque progression [69, 80–83]. The cardiotoxicity and autoimmune effects of immune checkpoint inhibitors pose a public health threat [84].

SPECT, PET and MUGA scans are vital for diagnosing and monitoring CVD [69, 70, 82, 83].

Early detection and monitoring are of paramount importance:

» Cardiotoxicity can manifest as reduced LVEF, HF, myocardial ischaemia and arrhythmias [80, 81].

» Early detection is critical as cardiotoxic effects may be irreversible if not detected and treated promptly [69, 70, 80, 85].

» Monitoring allows clinicians to assess early functional changes in the myocardium, guiding treatment adjustments such as switching to less cardiotoxic agents, adding cardioprotective drugs such as beta-blockers or angiotensin-converting enzyme inhibitors, or avoiding highly cardiotoxic drugs [69, 70, 81, 82, 85].

Nuclear imaging can be used to establish baseline cardiac function prior to treatment and to monitor early changes. Periodic imaging (e.g.every 3–6 months or between treatment cycles) can be used to detect subclinical changes that may indicate early cardiotoxicity [70, 81]:

» MUGA/ERNA-SPECT and ERNA-PET enable accurate and reproducible measurement of LVEF, making them a standard tool for monitoring changes during cardiotoxic treatment [53, 69, 70].

» SPECT MPI assesses MP to detect ischaemia that may result from MVD associated with some cancer therapies [64, 70, 80].

» PET with 2-[^{18}F]FDG can assess myocardial viability, which is helpful in understanding whether the myocardium is metabolically active or irreversibly damaged [65, 85].

» 2-[^{18}F]FDG PET can detect inflammatory changes that may be early signs of cardiotoxicity and can measure MBF and CFR, helping to identify MVD and other early signs of cardiotoxicity that may not be apparent on standard perfusion imaging [85, 86].

Tracers such as [^{123}I]mIBG may play a role in cardio-oncology, where early detection of autonomic dysfunction may predict or monitor chemotherapy-induced cardiotoxicity [71, 85].

Patients with significant imaging changes may require long-term cardiac follow-up, even after cancer therapy has been completed [87].

Combining nuclear imaging with other modalities, such as echocardiography or cardiac MRI, provides a comprehensive view of cardiac function and structure, further refining risk assessment and management strategies [29, 54, 69, 79].

New research and tracers in cardiotoxicity

Radiolabelled PET tracers for specific cardiotoxicity markers are being investigated to specifically identify early markers of cardiotoxicity, such as myocardial apoptosis, inflammation and fibrosis. This may allow even earlier intervention and more precise treatment modifications [86].

Ongoing research is evaluating the long-term effects of cardiotoxic treatments and the potential of nuclear imaging to predict which patients may develop late-onset cardiac complications [87, 88].

Nuclear Diagnostic Challenges and Potential Imaging Artefacts

Women generally have a lower body weight and different body fat distribution than men, which can affect tracer distribution in nuclear imaging. Good patient preparation is important, particularly to prevent over-projection of abdominal activity over the heart region. The false-positive rate dramatically increases with the number of artefacts, which shows the importance of having a robust quality control [89].

It is of great importance that the technologists performing these scans do so in a knowledgeable, consistent manner, being mindful of the parameters leading to artefacts and tackling them with correct positioning and precise processing techniques [90].

The most common artefacts are:

» **Patient movement** and/or positioning of the heart (stress, rest or both) in the region of interest (ROI), which is dramatically increased in overweight and obese patients;

» **Breast attenuation** artefacts can mimic perfusion defects, particularly in the anterior wall of the heart. This can lead to false positives, where ischaemia is suspected when none is present;

» **Soft tissue** from the diaphragm and abdomen can attenuate signals, particularly in images of the inferior wall of the heart. This is a concern for all patients, but can be more pronounced in women, especially those with smaller body sizes [90–92].

Several techniques help to reduce attenuation artefacts, including:

» Image acquisition in prone position, dual-position imaging (supine and prone). The prone position has the advantage of less movement of the patient and can reduce artefacts and minimise interference between the breast and the chest wall [91];

» Use of a breast bandage or similar breast support garment is recommended [92];

» SPECT/CT and PET/CT can correct for attenuation artefacts by using CT to map and compensate for soft tissue interferences [93, 94];

» The use of ECG-gated imaging and breath-hold techniques, particularly in PET, can reduce the effect of respiratory motion and improve image accuracy [53, 69, 70, 94];

» Modern SPECT/CT and PET/CT systems often have diaphragm attenuation correction algorithms [95];

» Advanced image reconstruction techniques can also help reduce the effect of breast attenuation on SPECT images [93, 95];

» Tracers that are less susceptible to attenuation, such as ^{99m}Tc agents for SPECT and $^{82}Rb^{+}$ for PET, are advantageous in female patients [50, 52, 61, 62];

» A dedicated cardiac SPECT camera offers a number of advantages specific to cardiac imaging, providing better resolution and greater sensitivity for detecting cardiac pathology than general-purpose gamma cameras [57].

Promising New Tracers

The early detection of atherogenesis with 2-[^{18}F]-FDG and [^{18}F]fluoride represents an exciting development within cardiac PET [96, 97].

Other tracers are being investigated for cardiac imaging, offering new ways to assess MP, metabolism and inflammation. Some promising tracers include:

[^{18}F]Flurpiridaz

» [^{18}F]-Flurpiridaz is promising in cardiac PET imaging, especially for women, as it overcomes current tracer limitations and improves accuracy.

» Better than other PET tracers at detecting CAD and MVD, which are hard to diagnose accurately, especially in female patients. This tracer provides accurate quantitative assessments of coronary BF and CFR, enabling the identification of both obstructive CAD and MVD, which can be difficult to detect with SPECT or traditional PET tracers.

» Represents a promising tracer for assessing MBF, has high myocardial retention, provides high-quality perfusion imaging and allows more accurate defect detection [60, 63].

» Improves image resolution and reduces noise, providing high-quality images of small coronary vessels, which are more common in women and often difficult to visualise with other tracers.

» Less affected by soft tissue attenuation, making it particularly promising for women.

» May be useful in monitoring cardiotoxic effects in women undergoing cancer treatment [63, 98, 99].

[^{18}F]Flubrobenguane

» Also known as [^{18}F]F-LMI1195, is an ^{18}F-labelled NE transporter ligand that shows promise for assessing sympathetic function by targeting cardiac sympathetic innervation.

» May help to assess HF and arrhythmias, side effects of cancer therapies.

» Provides insight into the autonomic regulation of the heart, which may be valuable in women with HFpEF.

» [^{18}F]Flubrobenguane uptake mimics the physiological NE uptake mechanism, allowing assessment of cardiac neuronal integrity and function [100].

Na[^{18}F]F (Sodium Fluoride)

» The early detection of atherogenesis with Na[^{18}F]F is an exciting development within cardiac PET.

» Potential for imaging vascular microcalcification, which is a component of atheroma progression [96, 97].

» Detects microcalcifications and is useful for risk assessment and identification of vulnerable plaques that may lead to acute coronary events [97].

» May provide insight into the early progression of CAD in women, who may experience atherosclerosis differently from men [101].

[^{68}Ga]Ga-FAPI (Fibroblast Activation Protein Inhibitor)

May have potential for visualising the pathophysiology of ICI-associated myocarditis beyond inflammation.

Active myocardial FAPI expression is followed by myocardial remodelling and fibrosis, so may be used to detect active myocardial fibrosis [102].

[^{18}F]F-DOPA

» Also known as 6-[^{18F}]fluoro-L-3,4-dihydroxyphenylalanine, primarily used in neuroendocrine tumours but has applications in imaging of myocardial sympathetic innervation.

» May be useful in assessing conditions such as HF with autonomic involvement, which may present differently in female patients [103].

What's Next

Recently, machine learning techniques based on artificial intelligence (AI) have emerged as a promising tool in the imaging field, opening up unprecedented possibilities in CV imaging. AI algorithms can improve image quality through advanced reconstruction techniques, reducing artefacts and noise in imaging studies. This improvement results in clearer images, which can facilitate diagnosis and treatment planning [104].

Given the impact of sex hormones on CVH, the development and use of PET probes targeting sex hormone receptors in women represents a potentially exciting research tool in the field of gender-specific medicine. PET probes targeting sex hormone receptors in women could significantly advance our understanding of CVH and provide valuable insights into the complex interplay between hormones and CVH, ultimately leading to improved prevention and treatment strategies for cardiovascular diseases in women [105].

CONCLUSION

Many countries have developed screening programmes targeting high-risk groups, such as diabetics and pregnant women with a history of hypertension. It is essential to expand access to these programmes, especially in LMICs. Global campaigns aim to increase women's awareness of CVD and promote early detection, especially among

high-risk groups. Despite these efforts, there is still a lack of recognition of the risk of CVD in women [106].

There is a growing call for more gender-specific research and data to better understand and treat CVD in women. Understanding the biological and social determinants that affect CVD in women will enable the development of appropriate interventions [107].

Increased awareness of ischaemia with NOCAD among physicians is urgently needed to enable accurate diagnosis, individualised treatment and patient-centred management [108].

CLINICAL CASES

First Case: A 64-year-old female former smoker was referred to PET/CT for evaluation of atypical chest pain (Fig. 1 and Table 1). She did not have any other coronary risk factors, and this patient also underwent CCTA fused with PET images (Fig 2. a, b) [109].

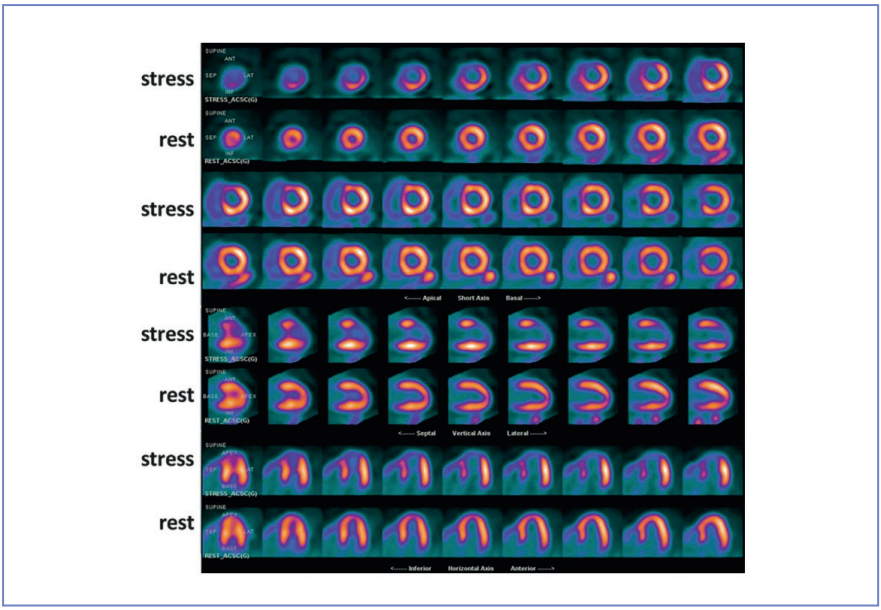

Figure 1. Summed rest and vasodilator-stress myocardial perfusion PET images obtained with 82Rb show a medium-sized perfusion defect of severe intensity involving the mid anteroseptal wall, the apical LV segments, and the LV apex with complete reversibility [109].

Findings

The PET images demonstrate normal LV size and a medium-sized perfusion defect of severe intensity involving the mid anteroseptal wall, the apical LV segments, and the LV apex with complete reversibility.

The quantitative BF data (Table1) demonstrate high MBF at rest with good augmentation during stress, albeit lower in the LAD territory. The MFR is reduced in the LAD territory but preserved in the LCX and RCA territories.

The coronary CTA shows subtotal occlusion of the mid LAD coronary artery which seems to also involve the take-off of a first diagonal branch.

Differential Diagnosis: Obstructive CAD.

Correlative Imaging: Invasive coronary angiography (Fig.3).

Management: The patient underwent successful percutaneous coronary intervention (PCI) of LAD/diagonal arteries.

Teaching Points: This case example illustrates the complementary value of quantitative stress MBF and FR information in diagnosis and management. In this example, the normal stress MBF and MFR in the LCX and RCA territories helped exclude the presence of multivessel CAD.

Second Case: A 52-year-old obese female, body mass index (BMI: 35) with a history of hypertension, referred for evaluation for atypical angina and dyspnoea. She underwent a rest and Regadenoson-stress [13N]-Ammonia myocardial perfusion PET/CT study (Fig. 4 and Table 2) and Coronary Artery Calcium Score (CACS) assessment (Fig. 5) [110].

	Rest (mL/min/g)	Stress (mL/min/g)	MFR
LAD	1.30	2.05	1.58
LCX	1.39	3.05	2.19
RCA	1.19	2.35	2.09
Global LV	1.30	2.39	1.97

Table 1. Summary of the quantitative BF data demonstrating high MBF at rest with good augmentation during stress, albeit lower in the left anterior descending (LAD) territory. The MFR is reduced in the LAD territory but preserved in the left circumflex artery (LCX) and right coronary artery (RCA) territories [109].

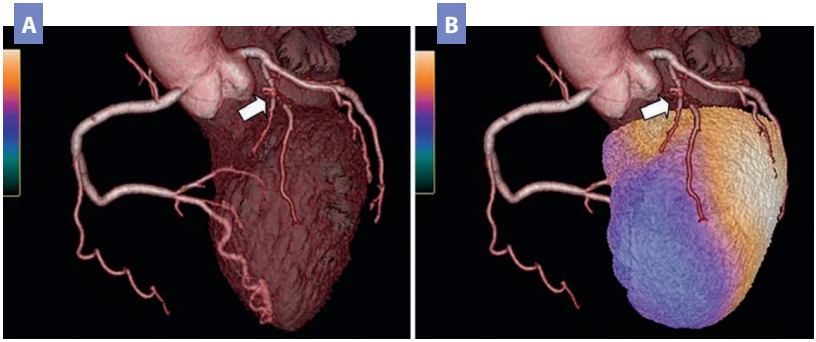

Figure 2. The fused myocardial perfusion PET/CCTA demonstrates severe stenosis of the mid LAD coronary artery panels a) and b) involving the proximal first diagonal branch (arrows). 3D rendering of PET study (b) shows hypoperfusion involving the antero-septal wall [109].

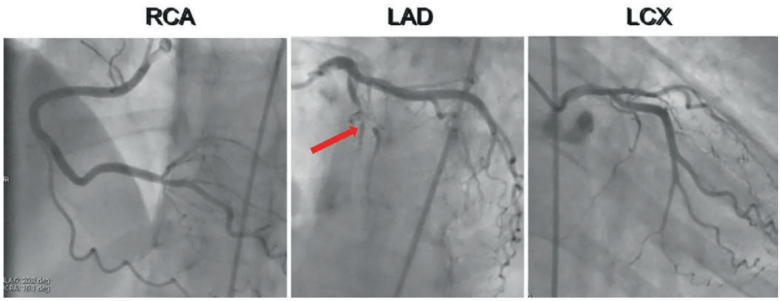

Figure 3 Selective views from coronary angiography demonstrating a complex critical stenosis of the mid LAD and diagonal coronary arteries (red arrow) [109].

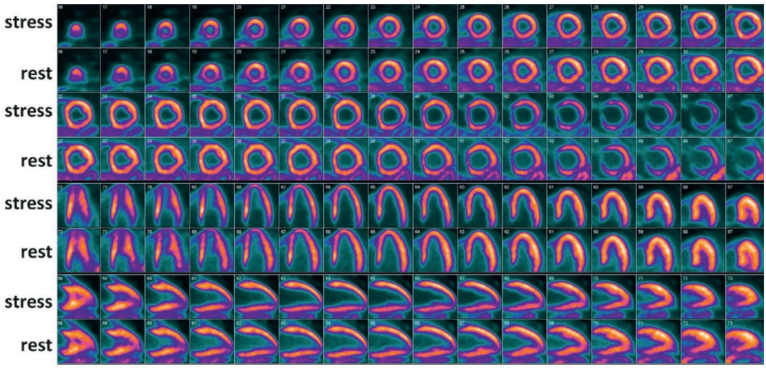

Figure 4. Rest and Regadenoson-stress [^{13}N]NH_3myocardial perfusion PET/CT images demonstrate normal myocardial perfusion both at rest and during stress [110].

	Rest (mL/min/g)	Stress (mL/min/g)	MFR
LAD	1.51	1.96	1.70
LCX	1.27	2.04	1.61
RCA	1.17	2.00	1.71
Global LV	1.19	2.00	1.68

Table 2. Summary of the quantitative BF data demonstrating preserved stress MBF (normal value >1.8 mL/min/g) but reduced MFR (normal value >2.0) in all coronary artery territories and globally [110].

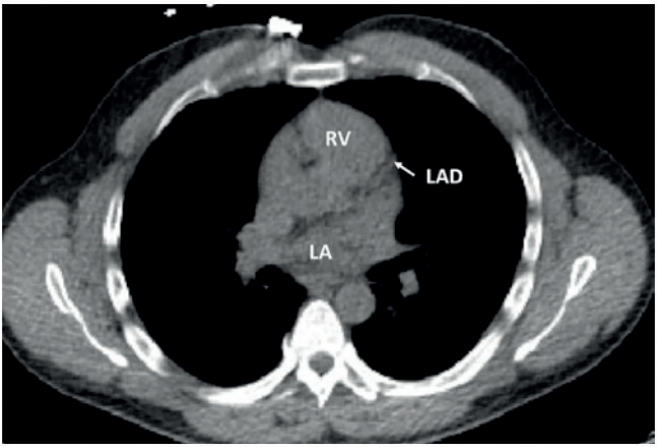

Figure 5 Cross-sectional transaxial chest CT image demonstrating no evidence of coronary artery calcifications [110].

Findings

The images demonstrate normal LV size. There is normal regional myocardial perfusion on both the stress and rest images.

The ECG-gated images demonstrated a rest LV ejection fraction of 63%, which increased to 66% post stress with normal LV volumes. There was normal regional wall motion and thickening.

The transmission CT scan demonstrated no evidence of coronary artery calcification.

The maximal stress MBF is relatively normal (>1.8 mL/min/g) in all coronary territories and globally, but the MFR is reduced due to an increase in her resting flows.

The CT transmission scan demonstrates no evidence of coronary artery calcifications.

Differential Diagnosis: NOCAD, coronary MVD.

Correlative Imaging: None.

Management: Management of hypertension and weight reduction.

Teaching Points: The normal myocardial perfusion PET images associated with the absence of coronary calcifications and normal stress myocardial blood flow are consistent with a low likelihood of flow-limiting CAD or non-obstructive atherosclerosis.

However, the presence of increased rest MBF and a mild reduction in MFR places her at an intermediate clinical risk (1–3% cardiac death rate/year). This phenotype is common among women, who typically have a low prevalence of obstructive atherosclerosis, and has been linked to MVD, which may be the source of her symptoms.

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3.1

[^{99m}Tc]Tc-MARACICLATIDE IN ENDOMETRIOSIS

by Célia Fernandes[1] and Gracinda Costa[2]

[1]Departamento de Engenharia e Ciências Nucleares, Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Universidade de Lisboa, Bobadela, Portugal
[2]Serviço de Medicina Nuclear, Unidade Local de Saúde de Coimbra, Coimbra, Portugal

EXECUTIVE SUMMARY

[99mTc]Tc-Maraciclatide is an investigational radiolabelled small peptide which has shown promising preliminary results in non-invasive imaging of cellular expression of integrins $\alpha_V\beta_3$ and, especially, $\alpha_V\beta_5$. It is widely recognised that integrins play an important role in the establishment and growth of endometriotic lesions.

It is important to emphasise that, at the time of publication, this tracer is not yet approved by the US Food and Drug Administration (FDA) and European regulatory authorities, and therefore that its use is limited to investigational purposes only. As a result, clinical experience with this radiopharmaceutical is still scarce and the total number of publications in *PubMed* is low (twenty-six papers had been published up until March 2025, when search terms "NC100692" or "maraciclatide" were used).

Despite the clinical immaturity of this radiopharmaceutical, the promising results of this non-invasive diagnostic tool in changing the diagnostic journey of endometriosis justifies the inclusion of [99mTc]Tc-Maraciclatide in this women's health guide.

Keywords:
[99mTc]Tc-Maraciclatide; maraciclatide; Arg-Gly-Asp peptide; Endometriosis; SPECT/CT;

INTRODUCTION

[99mTc]Tc-Maraciclatide is an investigational radiolabelled small peptide which has shown promising preliminary results in non-invasive imaging of cellular expression of integrins $\alpha_V\beta_3$ and, especially, $\alpha_V\beta_5$ (1).

The first references to disorders related to endometriosis date back to ancient Egypt in 1500 BC (2). It's incredible, but in the 21st century, endometriosis remains an enigmatic, incurable, chronic, dysfunctional, debilitating and very common gynaecological disease. It is characterised by the presence of functional oestrogen-dependent ectopic endometrium-like epithelium and/or stroma outside the endometrium and myometrium, usually with an associated inflammatory process (3). It most commonly affects the pelvic structures, including the fallopian tubes, ovaries, intestines, urinary bladder and peritoneum (2).

Endometriosis is often categorised, according to the type and location of lesions, as (2,4):

- Deep Infiltrating Endometriosis;
- Ovarian Endometriosis;
- Superficial Peritoneal Endometriosis — the most common subtype of endometriosis (present in up to 80% of women affected by the disease and representing the only clinical finding in 30% of laparoscopically confirmed endometriosis cases), characterised by the presence of ectopic endometrium-like tissue outside the uterus, extending up to 5 mm under the peritoneal pelvic surface and/or the serosa of the pelvic viscera (3).

Despite being a benign condition, endometriosis can considerably compromise the patient's well-being as well as their work and social activities. Women with endometriosis may be asymptomatic or may suffer from chronic and recurrent pain, often associated with the menstrual cycle, and about half are considered infertile.

The pathogenesis of endometriosis is complex, multifactorial and is not fully understood, an aspect that only increases the mystery surrounding this female pathology. However, "retrograde menstruation", a common phenomenon where menstrual blood flows backward into the pelvic cavity, seems to be a key mechanism in the development of this disease (5).

In the words of the *World Health Organization*, endometriosis affects approximately 10% of reproductive-aged women worldwide, impacting the lives of 190 million people (6). However, with so many challenges related to correct diagnosis, it's realistic to assume that the number of women affected could be considerably higher. The global impact on society is also very significant, with the economic burden of endometriosis being estimated to be as high as 78–119 billion USD per year in the US alone (7).

PATIENT PATHWAY DURING ENDOMETRIOSIS DIAGNOSIS AND TREATMENT

Unfortunately, the diagnosis of endometriosis presents a significant challenge, because of its variable clinical presentation, unspecific symptoms that often overlap with other conditions, and the poor sensitivity of non-invasive diagnostic tools (transvaginal ultrasound and even MRI). Due to its flat plaque-like conformation and the generally small size of the lesions, *superficial peritoneal endometriosis* (the most frequent subtype of endometriosis) is particularly difficult to diagnose using conventional imaging techniques (ultrasound or MRI) (8). Invasive procedures based on laparoscopic or surgical identification of lesions and histological confirmation of endometrial-like cells are the *gold standard* for diagnosis of endometriosis (9).

Medical treatment aims to reduce inflammation, suppress ovarian cycles and inhibit oestrogen activity. Surgery may involve the excision of lesions or even the removal of organs (10).

Late diagnosis, ranging from 4–12 years, is a big problem in endometriosis due to the inevitable delay in beginning the treatment (11). Not uncommonly, undertreatment can result in more aggressive disease that can lead to irreversible organ damage (such as loss of kidney function), social isolation and depression (9). There is thus an unmet clinical need to develop not only effective therapeutic options but also new non-

invasive tools for early and accurate diagnosis of endometriosis (10,11). The expectation is that nuclear medicine imaging with [99mTc]Tc-Maraciclatide will be able to fill this unmet need, potentially improving diagnosis and the outcome of this serious condition.

[99mTc]Tc-Maraciclatide Molecular Target: $\alpha_v\beta_3$ Integrin

[99mTc]Tc-Maraciclatide is a synthetic molecule that specifically binds via the arginine-glycine-aspartic (RGD) amino-acid motif to $\alpha_v\beta_{3/5}$ integrin receptors (Fig. 1) (1). In this way, it allows for the non-invasive in vivo identification of lesions whose cells express this specific target.

Integrins are from the transmembrane protein family of cell adhesion molecules that are a key player in communication between cells and their microenvironment. They facilitate cell adhesion to components of the extracellular matrix and adjacent cells. The complex and diverse structure, composed of alpha and beta heterodimers, allows integrins to recognise and bind to a variety of ligands (12). To date, 24 different integrin heterodimers have been identified in mammals. The $\alpha_v\beta_3$ integrin is upregulated in activated proliferating endothelial cells, associated with neoangiogenesis (formation of new blood vessels from pre-existing ones), and is also expressed in invasive tumour cells, macrophages, activated leukocytes and osteoclasts (12), whereas expression is weak

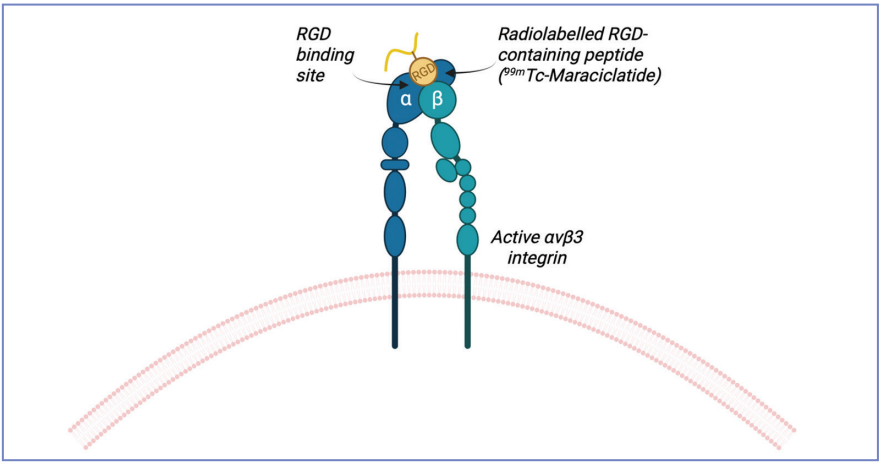

Figure 1. Diagram of $\alpha_v\beta_3$ integrin in active conformation, bound to [99mTc]Tc-Maraciclatide via the RGD component (created on Biorender) (1). Used under the Creative Commons Attribution License 4.0 (CCBY).

or absent on resting quiescent endothelial cells and most normal tissues (1).

The potential role of [99mTc]Tc-Maraciclatide in endometriosis is based on the increased expression of integrins in this disease. Neoangiogenic processes in endometriosis share common phenotypic features with tumour neoangiogenesis processes, and overexpression of $\alpha_v\beta_3$ integrin is found in endothelial cells (13) and in ectopic endometrial stromal cells from endometriosis patients (14).

History of [99mTc]Tc-Maraciclatide Development

The first RGD-based peptide tracers for imaging integrins, radiolabelled with iodine-125, were described in 1999 for three different tumour models. Since that time, many improvements in tracer design have been introduced, allowing *positron emission tomography* (PET) and *single photon emission computed tomography* (SPECT) imaging and expansion of its clinical use (15). Published studies have demonstrated the usefulness of [99mTc]Tc-Maraciclatide in inflammatory arthritis, endometriosis, neoplasia and cardiovascular diseases.

One of the most effective SPECT tracers targeting the $\alpha_v\beta_3$ integrin molecule is [99mTc]Tc-Maraciclatide, previously known as [99mTc]Tc-NC100692 (16). It was developed for detection of primary breast cancer lesions and metastatic lesions in patients with lung or breast cancer (15,16). In 2018, *Serac Healthcare Limited* acquired this imaging agent from GE Healthcare (17). A new cycle has thus begun for this tracer, with clinical studies being promoted to generate evidence of efficacy and safety.

A recent Phase 1, randomised, placebo-controlled study assessed the safety, biodistribution and radiation dosimetry of [99mTc]Tc-Maraciclatide in healthy volunteers. Biodistribution was assessed by acquiring scintigraphic images at time points up to 24 h after a bolus injection of the radiotracer. The authors concluded that [99mTc]Tc-Maraciclatide was safe and well tolerated, with no serious adverse events reported (1).

The DETECT (Detecting Endometriosis inTEgrins using teChneTium-99m) Phase 2 imaging study will be completed this year (18). This prospective study aimed to assess the correlation between locations of [99mTc]Tc-Maraciclatide uptake identified on SPECT/CT and the locations of endometriotic lesions detected during laparoscopy. Preliminary data demonstrated that [99mTc]Tc-Maraciclatide correctly identified superficial peritoneal endometriosis in those patients who went on to have this early-stage endometriosis confirmed by laparoscopy and could have the potential to be the first non-invasive imaging test for superficial peritoneal endometriosis (8).

Based on those promising results, the FDA has granted fast track designation to [99mTc]Tc-Maraciclatide as a diagnostic SPECT/CT agent for the visualisation and diagnosis of superficial peritoneal endometriosis in women of 16 years and older (fast track is a process designed to facilitate the

development and expedite the review of drugs to treat or diagnose serious conditions and fill an unmet medical need) (19).

A Phase 3 clinical trial is being planned in the context of detecting endometriotic lesions with [99mTc]Tc-Maraciclatide. This study will provide robust data on the diagnostic power of this molecular tracer.

Radiopharmaceutical Production

As stated earlier, [99mTc]Tc-Maraciclatide is a small peptide with high affinity for integrin receptors that are upregulated and expressed preferentially on proliferating endothelial cells. In the case of endometriosis, these receptors are indeed overexpressed, which means they are likely to be viable for imaging using this radiopharmaceutical.

Maraciclatide (Fig. 2) is a small cyclic peptide that contains an RGD tripeptide sequence held in a specific conformation by a disulphide bridge and one thioether bridge. A bifunctional chelator was also conjugated to the cyclic RGD sequence to allow radiolabelling with technetium ^{99m}Tc. The C-terminal end of the peptide sequence is modified with a short polyethylene glycol (PEG) unit.

[99mTc]Tc-Maraciclatide is prepared from freeze-dried kits that should be stored at -20 °C. Each vial contains 44 nmol of maraciclatide (molecular weight 1697 Da) and the reducing agent Sn(II), among other excipients (1,16). The radiolabelling with ^{99m}Tc is performed by reconstitution of the kit with 3 ml of sodium [99mTc]pertechnetate in saline solution and incubation at room temperature for 20 minutes, and the radiopharmaceutical can be used for up to 3 h post-preparation — this may be a relevant consideration for scheduling of patients in the future.

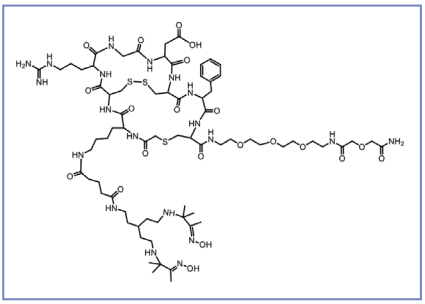

Figure 2. Chemical structure of Maraciclatide

Radiochemical purity (RCP) testing of [99mTc]Tc-Maraciclatide is performed by silica gel instant thin-layer chromatography (ITLC-SG) and high performance liquid chromatography (HPLC). The amount of reduced hydrolysed technetium [99mTc] (RHT) in the preparation is determined by ITLC-SG using a mixture of saline and acetonitrile (70/30) as eluent. In this chromatographic system, the hydrolysed [99mTc] species remain in the application point while all the other radiochemical species migrate with the solvent front. The HPLC analysis allows the detection and separation of [99mTc]Tc-Maraciclatide from all the radiochemical impurities potentially present in the preparation. Two studies followed this protocol, reporting a RCP higher than 90% 20 min post-reconstitution (1; 16). Moreover, stability studies indicate that

the [99mTc]Tc-Maraciclatide maintains stable radiochemical purity above 85% for over 4 h after preparation, allowing the establishment of the safe post-preparation timeframe of 3 h before administration mentioned above.

Imaging Acquisition

[99mTc]Tc-Maraciclatide is intravenously administered as a single injection followed by a saline flush. In most clinical imaging studies, an activity ranging from 740–1100 MBq (20.0–29.7 mCi) was administered (1). The available literature does not indicate the need for any specific preparation for this scintigraphic study.

The best imaging acquisition protocol, including optimal imaging time-point, has not yet been established. In the last available updated results of a Phase 2 study focussing on the use of [99mTc]Tc-Maraciclatide in endometriosis, SPECT/CT imaging performed 10 minutes post-injection was identified as the optimal time-point, allowing sufficient clearance of the agent from the blood pool and minimising bladder activity (8).

The imaging acquisition method includes anterior and posterior whole-body planar images, SPECT and SPECT/CT (Figure 3). The latter seems particularly appropriate, as fused images are particularly useful for anatomical localisation and for evaluating the extent of endometriotic lesions. This information is important in clinical management and can be of great value in surgery planning (20).

Despite the scarcity of published data, considering the activity administered and the radiopharmaceutical pharmacokinetics, it is reasonable to think that radiological protection precautions include hydration, frequent urination and limiting contact with children and pregnant women.

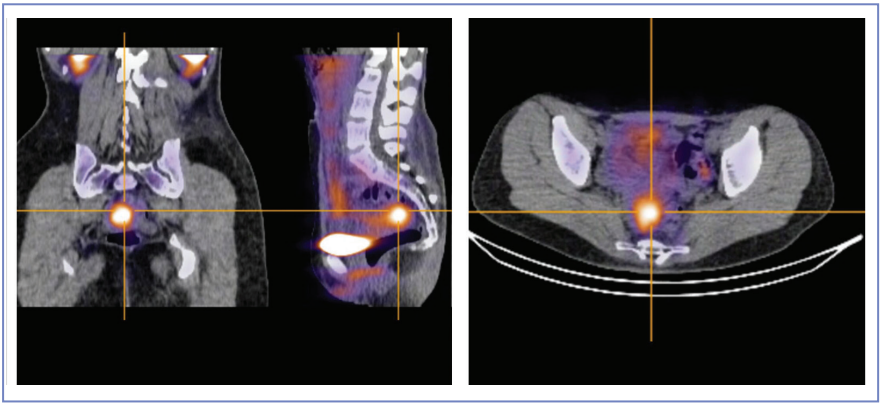

Figure 3. Images courtesy of Prof C Becker, University of Oxford, and Dr T Garrood, Guy's Hospital (21)

Image Interpretation

After intravenous injection, the resulting image represents the expression of the target: $\alpha_v\beta_{3/5}$ integrin receptors in the lesions. Just like other radioligands, it should be emphasised that this agent is not disease-specific, but rather molecule target-specific. Therefore, image interpretation must also consider clinical data and the results of other diagnostic procedures.

[99mTc]Tc-Maraciclatide administered in healthy volunteers demonstrated uptake of the agent in the liver and intestines and excretion through the kidneys (Figure 4). Only minimal amounts of background activity (1,22).

If the diagnostic value of this technique in endometriosis is confirmed, advanced SPECT/CT image processing software could play an important role in complementary evaluation of these studies, for example in the quantification of disease burden.

Radiation Exposure

Following intravenous bolus administration, initial [99mTc]Tc-Maraciclatide uptake was rapid, with excretion predominantly via the urinary pathway and gastrointestinal tract (1).

In the Phase 1 study, the mean effective dose per unit injected activity was 7.8 ± 0.8 µSv/MBq, a value comparable to other scintigraphic agents (1).

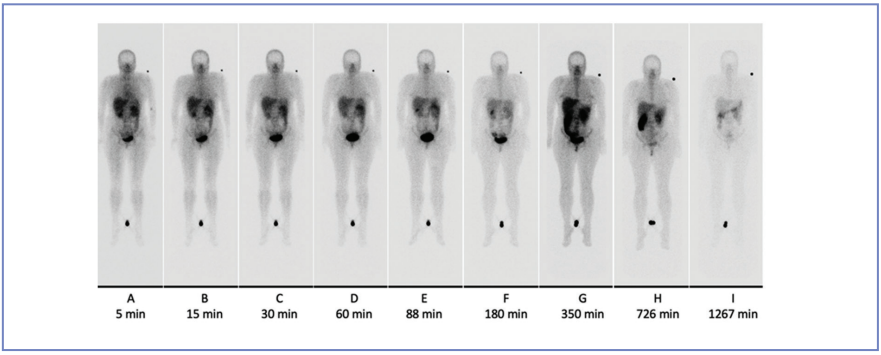

Figure 4. Whole-body geometric mean emission images from one female participant at multiple time points post-injection. The images were acquired for 6 min per scan at 5, 15, 30 min, 1 h, 1.5 h, and 3 h post-injection. Due to decay, the image acquisition was increased to 25 min per scan at 6 h and 35 min per scan at 12 and 24 h. Hence, the unadjusted images show differences in intensity across the timeline. These images were taken on a healthy volunteer, so there were no [99mTc]Tc-Maraciclatide-positive lesions. The images obtained made it possible to study the pharmacokinetics of the radiopharmaceutical and assess dosimetry (source with known activity placed next to the volunteer's feet for dosimetric assessment) (1). Used under the Creative Commons Attribution License 4.0 (CCBY).

The five organs or tissues with the highest absorbed doses per MBq were the urinary bladder wall (36.2 ± 7.0 µGy/MBq), kidneys (16.5 ± 9.5 µGy/MBq), spleen (16.1 ± 8.5 µGy/MBq), the wall of the upper large intestine (14.7 ± 4.0 µGy/MBq) and the wall of the lower large intestine (11.7 ± 2.7 µGy/MBq) (1).

CONCLUSION

Endometriosis is responsible for recurrent pain experienced by women, often interpreted as 'normal' or related to psychological conditions. Non-invasive imaging techniques, such as ultrasound and MRI, have low sensitivity, particularly in superficial peritoneal endometriosis, and laparoscopy is the only way to confirm a diagnosis. This leaves many women with incorrect or delayed diagnoses over a period of several years and is the reason why the FDA has placed functional integrin-based imaging with [^{99m}Tc]Tc-Maraciclatide in a fast-track process to facilitate the development of drugs to fill an unmet medical need. Because $\alpha_v\beta_3$ integrin is an attractive target in endometriosis, high-affinity radioligands are also being developed for PET imaging.

Should science confirm the usefulness and the enormous added value of this tracer in imaging of this disease, it will have a significant impact on the lives of millions of women across the world, providing an improved diagnostic view of a major cause of disability and reduced social, physical and workforce functionality.

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3.2

EXPANDED APPLICATIONS OF PSMA – FES - FAPI IN WOMEN'S HEALTH

by Nicole LaBreque and Oliver Ramsay

Dana Farber Cancer Institute, Boston, Massachusetts, United States

EXECUTIVE SUMMARY

The field of nuclear medicine and molecular imaging plays an essential role in detection, diagnosis, staging, and treatment in patients with breast cancer (BC). New advances in positron emission tomography (PET/CT) show a promising future for this patient population. Prostate- specific membrane antigen (PSMA) targeted PET/CT has shown to have potential for anti-angiogenic therapy in BC patients. 16α-[^{18}F]fluoro-17β-estradiol([^{18}F] FES)-PET/CT effectively determines oestrogen receptor (ER) hormone expression in specific tumours. Additionally, PET/CT with fibroblast activation protein inhibitor (FAPI)-targeting radiopharmaceuticals is surpassing 2-[^{18}F] fluoro-2-deoxy-D-glucose([^{18}F]FDG) PET/CT in BC staging.

Keywords:
Fibroblast, Fluoroestradiol, Breast cancer, Gynaecological cancer, PSMA, PET/CT

INTRODUCTION

The field of nuclear medicine and molecular imaging is quickly developing and has the potential to play a pivotal role in the diagnosis and treatment of a multitude of women's health diseases and disorders. The focus of this chapter will be on the potential roles of three developing radiopharmaceuticals in the most prevalent gynaecological cancers and BC. The GLOBOCAN report indicates that breast, cervical, uterine and ovarian cancers are the most prevalent gynaecological cancers [1].

Of the variety of radiopharmaceuticals that are currently in development, there are a select few that are well poised to bring major benefits to the management of women's health concerns. Oestrogen receptor (ER), fibroblast activation protein inhibitor (FAPI), and prostate- specific membrane antigen (PSMA) targeted radiopharmaceuticals have significant potential to change the practices surrounding gynaecological cancers and BC.

While currently only approved for use in prostate cancer imaging, PSMA PET/CT shows promising applications for anti-angiogenic therapy in BC patients. With BC being one of the most prominent types of cancer in women in the United States (as well as in Europe), advances in PET/CT imaging such as the use of [^{18}F]FES-PET/CT and FAPI-targeting PET/CT show a promising future.

PROSTATE-SPECIFIC MEMBRANE ANTIGEN (PSMA) RADIOPHARMACEUTICALS

PSMA stands for prostate-specific membrane antigen, which is known to be expressed on prostate cancer cells [2]. Several PSMA ligands are being utilised for PET/CT imaging. In fact, [^{68}Ga]Ga-PSMA-11 has already received U.S. Food and Drug Administration (FDA) approval, and the use of PSMA PET is currently suggested by several international guidelines for investigating (prostate cancer) in different clinical settings [3]. Additionally, other PET/CT imaging agents such as [^{18}F] DCFPyL ([^{18}F]F-PYL) and [^{18}F]F-rhPSMA-7.3 have been approved and are now used widely for the detection of prostate cancer in men. Some PSMA ligands are based on small urea-based molecules and others on antibodies; some are bound with ^{68}Ga, some with ^{18}F, and some even with other radionuclides. The current guidelines on utilising PSMA radiopharmaceuticals for prostate cancer recommend an activity of 296–370 MBq for ^{18}F-labelled radiopharmaceuticals and 111–259 MBq for ^{68}Ga-labelled radiopharmaceuticals administered slowly over 1 minute and flushed in with at least the same amount of saline (NaCl 0.9%). Patients are not required to fast prior to administration and are encouraged to drink water during the uptake time of 60 minutes [39]. The effective dose to patients from PSMA radiopharmaceuticals ranges from 0.0116 to 0.022 mSv/MBq, with the highest dosage to an organ being to the kidneys [39]. The advances in PSMA imaging since the first in-human applications in 2012 have been exponential and show a promising course for the future of nuclear medicine and molecular imaging.

Multiple studies have even shown that PSMA radiopharmaceuticals have significant uptake in the neovasculature of solid tumour [2,4]. The neovascular network of solid tumours is made up of thousands of new capillaries that the tumour utilises to grow faster than normal tissue, and this growth makes it a widely applicable target for examining a variety of different cancers. These radiopharmaceuticals have the potential to have their use expanded outside of prostate cancer, specifically in gynaecological cancers, as shown by a recent study in which 100% of primary ovarian cancers and primary endometrial cancers showed PSMA expression in tumour vasculature [5]. In the following, the role of PSMA is explored from a different angle, in line with the theme of this Tech Guide.

Expanded Applications of PSMA

Current research indicates that PSMA is related to angiogenesis of many solid tumours, including kidney cancer, colorectal cancer, glioblastoma, pancreatic cancer, lung cancer, and bladder cancer [6]. This shows that PSMA has the potential to become an extremely versatile PET/CT imaging agent that could be of benefit in the management of further cancer types, especially angiogenesis in BC patients. In this case, angiogenesis is

the formation of new blood vessels within a breast tumour. These exciting studies have highlighted important opportunities for better disease management and could indicate that patients would benefit from the use of neovascular-targeting therapeutic agents.

BC is one of the most common types of cancer in women worldwide. The American Cancer Society estimates that in early 2019, there were around 4 million women with a history of BC living in the United States [8]. The first case of a metastatic BC patient imaged using [^{68}Ga]Ga-PSMA-11 PET/CT was reported in a study performed in 2016. The findings showed detection of bone and liver metastatic disease in a similar fashion to [^{18}F] FDG PET/CT. Figure 1 below demonstrates the powerful capacity of [^{68}Ga]Ga-PSMA-11 to image multiple types of BC and identify both lymph node and bone metastases. These results stimulated curiosity and led to further investigation of how [^{68}Ga]Ga-PSMA-11 PET/CT could be utilised in BC patients.

In another study inspired by these initial findings, [^{68}Ga]Ga-PSMA-11 PET imaging was performed in nine "de novo" diagnosed breast carcinoma patients, in five patients presenting with a loco-regional recurrence of breast carcinoma, and in a pre-treatment metastasised setting in another five patients [7]. The patient population consisted of a mix of patients that were progesterone receptor positive and progesterone receptor negative, as well as a group of patients where the progesterone receptor status was unknown. The study utilised up to 240.5 MBq of [^{68}Ga] Ga-PSMA-11 for the study protocol [7]. Tumour lesion data showed an overall detection rate of 84% for [^{68}Ga]Ga-PSMA-11 PET/CT, which is quite impressive considering its historical exclusive use in prostate cancer. Additionally, [^{68}Ga]Ga-PSMA-11 results proved not significantly different from those obtained using [^{18}F]FDG [7]. Overall, there was a strong expression of PSMA by BC lesions and an absence of PSMA on normal vascular tissues. This further explores the potential for utilising PSMA as a target for anti-angiogenic therapy in BC patients. Selective inhibition of angiogenesis in BC has the potential to be vastly beneficial for this patient population.

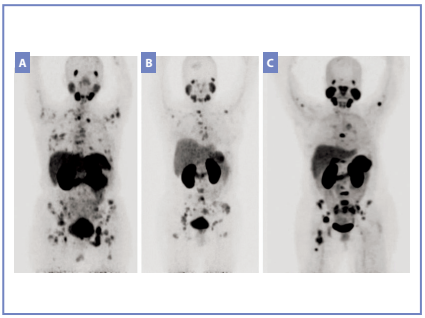

Figure 1. A. Maximal intensity projection (MIP) PET with [^{68}Ga]Ga-PSMA-11 in patient with triple negative (TPN) BC showed normal biodistribution and primary tumour site in right breast, multiple bone and lymph-node metastases. B. MIP in patient with luminal-B HER2 positive BC showed multiple bone metastases with faint uptake in primary site in the left breast. C. MIP in patient with Her-2 overexpression BC showed multiple bone metastases with faint uptake in primary site in the right breast. Image taken from [6].

Barriers to Expanded PSMA Radiopharmaceutical Use

Despite significant opportunities in a multitude of cancers, including gynaecological cancers, there is a substantial amount of work that needs to be completed to effect regulatory change in the use of PSMA radiopharmaceuticals. The main challenges include large-scale clinical trials designed with strategic endpoints, health system approval and coverage of expanded access, and in the distant future the investigation of the potential for utilising alpha- or beta-tagged ligands for radioligand therapy. A common challenge in clinical trials with imaging radiopharmaceuticals is the strategic design of trial endpoints to demonstrate the incredible clinical benefit to treatment as a result of the improved imaging, and the expanded use of PSMA radiopharmaceuticals is no exception. Furthermore, once expanded regulatory indication is achieved there is still the hurdle of health system and insurance cost-benefit analysis and authorisation of widespread use at early stages. Finally, in today's nuclear medicine environment, attention must be paid to the theranostic potential of radiopharmaceuticals, and PSMA radiopharmaceuticals are significant leaders in this sector. With several PSMA radiopharmaceuticals in clinical use and more being developed, there must be careful planning of attempts to expand their use, including production and distribution capacity [3].

[^{18}F]16 ALPHA-FLUOROESTRADIOL ([^{18}F]FES)

Another exciting radiopharmaceutical group that is being investigated for use in gynaecological cancers is oestrogen radiopharmaceuticals. In 2023, the FDA approved [^{18}F]FES for imaging of advanced BC in order to determine oestrogen receptor status of metastases without multiple biopsies. As it stands, the approval helps reduce risk to the patient and obtain oestrogen receptor information from lesions that are too dangerous to biopsy. According to the EMA, 3 trials have been completed with [^{18}F]FES and they have yet to approve it for clinical use.

[^{18}F]FES binds to both oestrogen receptors, A(ERα) and B(ERβ), with more affinity towards ERα. Imaging the density of oestrogen receptors in the body is an incredibly useful tool for the management of women's cancers. While developed for the management of BC, the diagnosis and management of endometrial cancer and other uterine cancers can also be greatly improved using oestrogen radiopharmaceuticals.

Oestrogen Receptor Expression in BC

BC can be broken down and categorised into many different subtypes based on hormone receptor subtype. These subtypes are commonly grouped into four categories based on the immunohistochemical expression of hormone receptors: oestrogen receptor-positive (ER+), progesterone receptor-positive (PR+), human epidermal

growth factor receptor-positive (HER2+), and triple negative (TNBC), which is characterised by the lack of expression of any of the above receptors [9]. Determination of subtype and receptor expression is an essential step in aiding diagnosis, determining treatment strategies, and assessing prognosis. Oestrogen receptor (ER) expression in BC is associated with a more favourable prognosis and is necessary for a response to endocrine therapies [10]. Oestrogen receptor expression is typically and traditionally assessed by invasive biopsy procedures.

[^{18}F]FES-PET/CT

Clinical studies have demonstrated the use of [^{18}F]FES as a method of quantifying *in vivo* ER expression and have explored its potential as a predictive assay and method of assessing *in vivo* pharmacodynamic response to endocrine therapy [10]. There has been an extensive history of developing an oestrogen receptor-targeted radiotracer. Currently, [^{18}F]FES PET is the most widely studied PET/CT imaging agent specific to targeting of oestrogen receptors. [^{18}F]FES PET was approved by the FDA in 2020 for patients with metastatic or recurrent BC. It is widely known

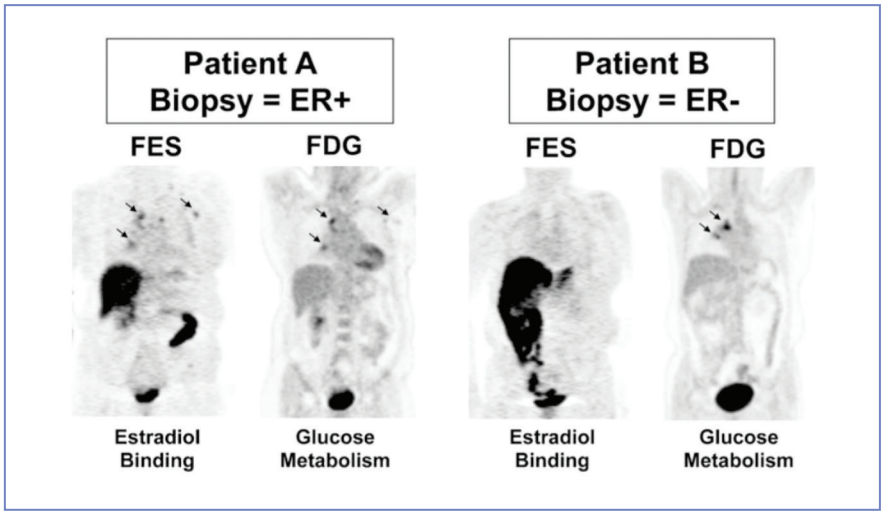

Figure 2. Left panel: Patient A had axillary and mediastinal lesions (arrows) seen on both [^{18}F]FES PET and [^{18}F]FDG PET scans. Core biopsy of the axillary lesion was ER-positive by immunohistochemistry. Right panel: Patient B had mediastinal lesions (arrows) seen only on the [^{18}F]FDG PET scan. Needle biopsy of a vertebral lesion was ER-negative by immunohistochemistry. The dual-tracer imaging approach is important to inform treatment decisions. Image taken from [10].

throughout the United States by its trade name, Cerianna. The package insert states the recommended dosage as 222MBq (6mCi) and specifies that patients should stop oestrogen modulators and other endocrine therapies before their scan [41]. It is also recommended to administer the radiopharmaceutical as a single intravenous injection over one to two minutes. As with any PET/CT imaging tracer, the injection should then be followed by an intravenous flush of 0.9% sodium chloride. PET/CT imaging is then to be performed 20 to 80 minutes following injection time, with no restrictions for patients during the uptake period [41]. The estimated effective dose of [^{18}F]FES PET is 0.022 mSv/MBq, and the organ with the highest dose is the liver [46]. Interestingly, PET/CT imaging with [^{18}F]FES PET can be performed in both premenopausal and postmenopausal women, as the uptake of FES is not influenced by physiological oestrogen.

Many studies have examined the use of [^{18}F]FES PET/CT in order to grade endometrial cancer as well as to differentiate uterine sarcomas and leiomyomas. Overall, these studies found that [^{18}F]FES uptake positively correlated with histochemical levels of ERα and that the level of uptake indicated differentiation of the tumour [11]. In addition, these studies found that performing [^{18}F]FES studies as well as [^{18}F]FDG allowed calculation of the [^{18}F]FDG/[^{18}F]FES ratio, which also correlated with the differentiation of the tumours and correct diagnosis of leiomyomas. The latter are generally considered benign and affect 25%–30% of women. The images in Figure 2 also demonstrate the utility of performing both [^{18}F]FES studies as well as [^{18}F]FDG in order to inform treatment decisions in BC. Another important application of [^{18}F]FES imaging is the pre-therapeutic imaging of ovarian cancer and other ERα-expressing cancers as a method of selecting patients for endocrine therapy [12]. There are many important applications for the use of [^{18}F]FES in gynaecological cancers, but there are several barriers to its expanded use.

Barriers to [^{18}F]FES PET/CT

Currently there are 3 main barriers to expanded [^{18}F]FES use in gynaecological cancers:

- scale of current trial results to effect regulatory change;
- drug interactions;
- radiopharmaceutical supply infrastructure.

Thus far, most of the limited trials investigating expanded use of [^{18}F]FES PET/CT have been small- to moderate-sized case studies that have shown promising results. Large-scale trials need to be undertaken to demonstrate that [^{18}F]FES PET/CT has an important role in managing all of the gynaecological cancers in addition to BC, and that it can be a strong indicator of a patient's response to endocrine therapy. These larger trials with clear benefit-driven endpoints will also be vital to obtaining EMA market approval. In reality, the focus should

be on conducting trials that will indicate the use of FES as a first-step diagnostic tool, because there are significant difficulties in using [^{18}F]FES while patients are undergoing endocrine therapy. If [^{18}F]FES PET/CT were utilised as a first- or second-step diagnostic tool, it would clearly indicate which patients would benefit from the use of hormonal therapy. According to the FES package insert, there are significant drug interactions with systemic endocrine therapies that reduce FES uptake. In order to avoid these interactions, patients cannot take tamoxifen and other oestrogen modulators for 8 weeks and fulvestrant for 28 weeks [41]. Obviously physicians cannot delay the patient's therapy in order to complete an imaging study without significant risk. The clear solution to this barrier would be to strategise for pre-therapy use of [^{18}F] FES PET/CT with the benefit of predicting response to endocrine therapies. Further infrastructure development is also needed to allow more [^{18}F]FES imaging outside of major medical centres. One paper sought to address this issue by illustrating the potential to automate the synthesis of [^{18}F] FES utilising a readily available cassette-type [^{18}F]FDG synthesiser [13].

Fibroblast Activation Protein Inhibitor (FAPI) Radiopharmaceuticals

Fibroblast activation protein (FAP) plays a key role in remodelling of extracellular matrices and in the formation of fibrous tissues [14]. FAP normally plays an important role in healing tissues and tissue repair. In the cancer microenvironment, cancer-associated fibroblasts (CAF) overexpress FAP on their cell surface, creating an exceptional target for fibroblast activation protein inhibitors (FAPI) [14]. FAPI-targeting radiopharmaceuticals image the density of CAF, which are an integral part of the tumour angiogenesis as they make up a significant part of the solid tumour volume. Increased FAPI-targeting radiopharmaceutical uptake is usually linked to a poor prognosis, because the most aggressive angiogenic cancers overexpress FAP. A wide variety of cancers share this tumour physiology, including gynaecological cancers, which creates an incredible opportunity to use FAPI radiopharmaceuticals for diagnosis and even treatment of these cancers. There are a multitude of different FAPI radiopharmaceuticals in development utilising ^{18}F, ^{68}Ga, and ^{99m}Tc for imaging radionuclides. Due to the target and the nature of the physiological process FAPI-targeting radiopharmaceuticals utilise, they have many advantages over the standard of care, [^{18}F]FDG PET/CT.

FAP versus FAPI

FAP is overexpressed in more than 90% of epithelial tumours, including breast and gynaecological tumours [15]. This overexpression is a useful tool in oncology for both the diagnosis and treatment of disease. Though heterogeneous in origin, CAF can be identified by the upregulation of several

surface markers, of which FAP, a membrane-bound type-2 serine protease belonging to the dipeptidyl peptidase 4 family, represents the most specific surface marker [13].

Radiolabelling with different agents, such as antibodies and peptides, has been found to target this molecule. Among the FAP-based radiotracers developed so far, ^{68}Ga-labelled FAPI radiopharmaceuticals provide the most favourable imaging features in terms of high detection rate in a variety of tumours, even in cases considered to be challenging for [^{18}F]FDG PET/CT [13]. The average administered activity for [^{68}Ga]Ga-FAPI PET/CT is 2 MBq/kg, with the highest absorbed dose to an organ being delivered to the bladder wall with a median dose of 0.048 mSv/MBq [37]. Currently, ^{68}Ga-labelled FAPI radiopharmaceuticals are not approved by the U.S. FDA.

Advantages and Limitations of [^{68}Ga] Ga-FAPI PET/CT Imaging

[^{68}Ga]Ga-FAPI PET/CT can be used without any dietary preparation and provides stable tracer uptake 10 minutes to 3 hours after administration [13], compared to [^{18}F]FDG PET/CT imaging where patients must fast for a minimum of 4–6 hours, and blood glucose levels directly correlate with physiological uptake in the body. [^{18}F]FDG demonstrates some well-known limitations, as it is characterised by high physiological uptake in some organs (e.g. the brain), lacking or rather low uptake in some tumour entities, and a lack of specificity, given that glucose metabolism represents a feature in a variety of diseases [15]. In contrast to [^{18}F]FDG PET/CT, [^{68}Ga]Ga-FAPI has drastically less background signal in the brain, liver, oro- and nasopharyngeal mucosa or gastrointestinal tract [13]. This in turn will show an increased tumour-to-background ratio (TBR) compared to [^{18}F]FDG. An improved TBR will cause FAP expression to be more distinct, which can increase tumour detection. As with any imaging agent, however, there are also pitfalls associated with [^{68}Ga]Ga-FAPI PET/CT imaging, such as the short half-life of ^{68}Ga and radionuclide production methods.

FAPI PET/CT Applications for BC

Staging methods for BC use a combination of systemic assessments, such as bone scintigraphy, CT and MRI imaging and [^{18}F]FDG, and local assessments such as ultrasound and mammography. [^{18}F]FDG is essential to disease management, staging, restaging, and even detection of recurrent disease. [^{68}Ga]Ga-FAPI has the potential to contribute important information in the treatment and management of BC.

Although [^{18}F]FDG PET/CT has great value in diagnosing and staging BC, its high physiological background activity in multiple organs and inflamed tissue limits its specificity [14]. This shows how [^{68}Ga]Ga-FAPI can surpass [^{18}F]FDG as a tool in the BC population, as it can provide more accurate staging analysis. The unique role of the tumour stroma and the abundant stromal expression of FAP in primary BC suggest a potential for high

accuracy in FAPI-targeted imaging [16]. This study showed an increased SUVmax level of [^{68}Ga]Ga-FAPI uptake (13.8 +/- 5.1) detected in primary tumoral lesions compared with [^{18}F]FDG uptake (3.9 +/- 3.0). The utilisation of SUVmax is a helpful tool in delivering a more accurate staging and diagnosis assessment.

Invasive lobular carcinoma, also referred to as ILC, is a subtype of BC. Invasive lobular carcinoma (ILC) accounts for about 10% of all invasive BC cases [16]. A study was conducted to compare [^{18}F]FDG PET/CT and [^{68}Ga]Ga-FAPI PET/CT in women with primary ILC of the breast. The patients underwent a standardised preparation regimen prior to [^{18}F]FDG PET/CT imaging, which included a 12-hour fast, and blood glucose levels were to be below 150mg/dL. Patients were injected with 5MBq/kg of [^{18}F]FDG and imaging was initiated 60 minutes later [43]. In contrast, there was no fasting or preparation for the [^{68}Ga]Ga-FAPI PET/CT session. An administered activity of 2–3 MBq/kg was used, and imaging began 45 minutes post-injection. Both [^{18}F]FDG and [^{68}Ga]Ga-FAPI PET/CT imaging was performed from vertex to proximal femur. The study revealed that [^{68}Ga]Ga-FAPI PET/CT exhibited increased tumoral activity retention along with elevated TBR across all lesion locations in comparison to [^{18}F]FDG PET/CT [16]. It was found that [^{68}Ga]Ga-FAPI PET/CT appears to offer 21.8% greater sensitivity than [^{18}F]FDG PET/CT, especially for detecting small lesions or those with low or heterogeneous glucose metabolism.

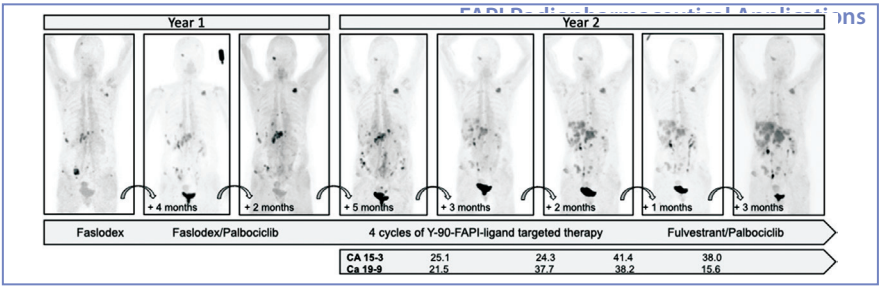

Figure 3. A 79-year-old female with metastasised breast and colon cancer underwent eight [68Ga]Ga-FAPI-PET/CT scans with three different derivatives (FAPI-02, FAPI-04, FAPI-46) within 1.5 years. During that time interval, mainly palbociclib and four cycles of [^{90}Y]Y-FAPI-radioligand therapy were administered. The progression markers CA 15-3 and CA 19-9 were monitored, showing a temporarily stable and even regredient disease, which is in accordance with the [^{68}Ga]Ga-FAPI uptake presented in the PET/CT. However, after a while, the patient possibly developed a resistance to palbociclib or radioligand therapy, presenting with possible progressive disease leading to a change of therapy. Image taken from [17].

in Gynaecological Cancers

FAPI radiopharmaceuticals have significant advantages over [^{18}F]FDG PET/CT, including patient preparation, normal physiological uptake in gynaecological cancers and theranostic potential. [^{68}Ga]Ga-FAPI PET/CT requires no preparation and significantly less uptake time for increased TBR [17]. The drastically different time restrictions for [^{68}Ga]Ga-FAPI PET/CT could contribute to a better patient experience and expanded impact. The normal physiological uptake of FAPI radiopharmaceuticals is also an incredible advantage, especially in gynaecological cancers. [^{18}F]FDG PET/CT has limitations in many gynaecological cancers due to [^{18}F]FDG normal physiological uptake being modulated by the menstrual cycle and increased accumulation in normal ovarian tissue and benign lesions. FAPI radiopharmaceuticals have better TBR in ovarian cancers and cervical cancers and are not affected by the menstrual cycle [14]. The multitude of FAPI radiopharmaceuticals in development presents an adaptable and multi-faceted theranostic approach to the expanded application of this class of radiopharmaceuticals. In Figure 3 alone there are scans completed with 3 derivatives of FAPI radiopharmaceuticals as well as an example of FAPI radioligand therapy being applied and informing treatment decisions. Studies have already been completed with ^{90}Y-labelled FAPI radiopharmaceuticals and have shown promise, despite the short tumour retention time [17]. Investigations into other therapeutic isotopes and pharmaceutical formulations with longer tumour retention times, such as ^{177}Lu and ^{153}Sm, indicate the adaptability of the future theranostic application of FAPI radiopharmaceutical therapy [44,45].

CONCLUSION

BC is now one of the most diagnosed cancers in women worldwide, and gynaecological cancers are complex conditions that deserve better diagnostic imaging. Accurate detection and staging is essential to effective treatment and management of disease. The field of nuclear medicine and molecular imaging plays an essential role in this step, and new advances in PET/CT show a promising future for this patient population. PSMA PET/CT has shown to have potential for anti-angiogenic therapy in BC patients and gynaecological cancers. FES PET/CT has become an essential tool in determining the hormone-receptor status of certain diseases and tumours by effectively determining ER expression. Last but not least, FAPI PET/CT is becoming a useful tool in staging analysis. Overall, the advances in new and emerging PET/CT methods show a promising future for how BC and gynaecological cancers are detected, analysed, and treated across the world.

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Schmalzhofgasse 26, 1060 Vienna, Austria
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