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(Editors)

Rare and Uncommon Gynecological Cancers

A Clinical Guide

Springer

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Part I

General Principles

Introduction

1

Nicholas Reed

1.1 Rationale for the Textbook

Do we need another textbook? Yes – this is an area that has been neglected and we believe we fill a void. It is not easy to find this kind of information in the standard textbooks. Rare conditions generally attract a disproportionate amount of interest compared to their rarity. Perhaps this is because unusual cases generate additional interest and also reflects the fact that for many of us, this presents a distraction from the humdrum of routine care where we are forced to think and seek out information. Rare editions of books, art or music attract collectors, perhaps for the same reasons. Nevertheless it is important when we are dealing with rare and uncommon disorders that we apply the highest standards. Many would argue that because of their rarity these conditions should be looked after by specialist teams. This allows a smaller number of expert teams to develop real expertise in this field. Furthermore, it would seem sensible to propose that there is a degree of centralisation of care for these conditions. Protocols for shared care may be developed in parallel and there are good examples available to follow such as in gestational trophoblastic tumours.

Why is there a need for such a book as this? The main rationale for the book is to provide the reader with some guidance on how best to manage these patients with rare and uncommon cancers. Access to information on these rare cancers can be difficult even in our modern age of rapid electronic communications and electronic repositories of information. Standard textbooks often contain little information apart from descriptive pathology. One can often find a wealth of information on the histopathology as pathologists usually cross-refer to each other and the main centres may develop an expertise in reviewing and reporting these cancers. However, for many of these conditions, modern and constructive management advice is hard to find. Surgeons and oncologists are not so good as pathologists in networking traditionally, although informal networks and "phone-a friend" may be carried out. Modern medical practice is breaking down these barriers. A book like this cannot be too proscriptive as there is often not the information available to allow such an approach, but our expert authors are recognised specialists in their field and have produced authoritative guidance on how to interpret the available literature. We cannot produce specific protocols for most situations but can guide the readers through the published literature and hopefully allow them to draw the right conclusions and apply them to their practice.

Of course the greatest weakness is that virtually from the moment the author completes the chapter, it is in danger of obsolescence as a new paper is published. However, with rare conditions this may be less of a risk and developments tend to occur more slowly as cases are so few, but occasional dramatic breakthroughs are seen such as the treatment of GIST with imatinib.

In this book we aim to review most of the relatively uncommon and rare gynaecological cancers. We cannot cover everything and if we are able to run to a second edition, maybe readers can provide suggestions to include what is missing! It is probably not realistic to include conditions where only a handful of anecdotes have been recorded in the literature. Ironically, it does seem that there are quite a number of these rare conditions in the gynaecological oncology area. Perhaps this reflects the fact that we are dealing with several

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different organs and although many of them are thought to be of Mullerian tract origin they do develop in diverse ways. The major omission from the book is paediatric cancers as these are covered by other texts, but there will be an overlap with some cancers of adolescence which we have hopefully addressed. Maybe this is another chapter we can discuss with the publishers if we run to a second edition. Publishing is evolving very rapidly and electronic communication will predominate in the near future, so a series of e-appendices might be an option to consider.

1.2 Multidisciplinary Team Management

These conditions are best looked after by multidisciplinary teams so that there is the opportunity for surgeons and radiation and medical oncologists working with dedicated and specialist pathologists and radiologists to care for these patients. This will allow the best opportunity for the highest standards of care to be developed. In the United Kingdom we have further reinforced this by using Clinical Networks where agreed protocols and patterns of care are developed. Clinical Networks will bring together all the relevant disciplines in the field to work together and use agreed clinical protocols. In addition, data collection, registration and audit are key components to allow comparison with other networks as well as international comparisons of standards of care and outcome. Comprehensive cancer centres with multidisciplinary teams should be able to offer these same high standards.

1.3 Structure of the Book

We have attempted in this book to start with introductory chapters to cover broad topics. We had a dilemma in the subsequent chapters as to whether we would take each individual rare tumour in each individual organ or whether it would be better to group together the same histological types, and bring together the same pathological groups in one chapter. After much discussion and debate we have opted to use a pathologically oriented approach by putting together similar pathological types. This latter approach was chosen as it seemed to be more comprehensive. There are probably strong similarities between clear cell tumours of the ovary and uterus and it is better to consider them in this way. The chapters will highlight some of the differences that may be apparent.

We have tried not only to emphasise both the clinical and diagnostic issues but also to illustrate, where possible, some of the exciting new translational techniques and molecular pathways that are emerging. Exciting clues that are emerging from these molecular pathways may allow us to establish new treatments. A really exciting feature is the excellent review of imaging, which is as important as pathology. Working in centres which have developed expertise in pathology and imaging is essential to support the practising oncologists.

1.4 Databases, Registries and Tumour Banks

It is essential that we learn more about these tumours. One of the first apparent weaknesses in investigating the topic is the lack of real data. Thus, how rare is rare? Let us not get bogged down in a debate about actual numbers. Some diseases that are uncommon are given "orphan status" and this will apply to many of the tumours described here. Thus, one of the first priorities must be to set up reliable and accurate databases and registries. National cancer databases are often unreliable due to poor and incomplete recording and coding. Regional and national networks are ideally placed to capture and record this data. From this we may build a picture of the real size of the problem. Pathology registers are another valuable resource given that rare cancers do tend to get shown around, but we must be cautious about potential double counting!

Equally important is access to tissue and serum to allow clinical researchers and clinical scientists to expand our knowledge. Whilst tumour banks are immensely valuable resources, the creation of virtual tumour banks with modern IT has made this much easier. Thus, tracking of specimens and tissues can speed up new technological developments and registries should facilitate both of these functions. Our French colleagues have led the game with their "Observatoire National des Tumeurs Malignes Rares de l'Ovaire" (http://ovaire-rare.org/). These initiatives need to be

replicated around the world and then linked up. The Gynaecological cancer InterGroup (GCIG) had tried to do this previously but failed mainly due to concerns over secure transfer of confidential data. By doing it nationally many of these issues should be overcome.

1.5 Clinical Trials

It is extremely challenging to run clinical trials in this setting and it is usually left to local champions to pursue this. The attitude of "why should I bother to go to all the trouble of putting through Ethics/IRB" is understandable when only one or two patients may be seen and their data entered. We need to rethink our approach to clinical trials in rare diseases; it is of course not just an oncology issue. In Europe, the misguided EU Clinical trials directive has backfired by stifling academic research and this particularly applies to rare cancers where pharmaceutical company-sponsored studies are uncommon and investigator-led studies predominate. We need to think creatively by looking at groups of rare tumour studies being submitted and approved together. Thankfully, there are still motivated and committed enthusiasts out there willing to make the effort to develop trials.

1.6 Tumour Sub-Types

It is becoming apparent that tumour sub-types maybe highly relevant. In the Western world clear cell and mucinous ovarian cancers make up around 5% of ovarian cancer cases; however their biology is different and their response to treatment, especially for mucinous tumours, is distinct. New trials are being developed specifically for these tumour types. It is possible that similar developments will occur with uterine cancers. Equally we are recognising that many sarcomas of ovary and uterus are not sarcomas; so, paradoxically, they may be included with epithelial cancers. Once again the role of the specialist pathologist becomes crucial to management.

1.7 Guidelines vs. Protocols

Given this sort of format we cannot produce protocols for clinical use, partly for medico-legal reasons but also because they would be outdated within a year or two. However, we can provide guidelines or simply guidance in the sense that they will help to direct the clinician to sources of references and the kind of approaches needed for management. However, the Cancer Networks and Comprehensive Cancer Centres should be developing their own or network-agreed protocols for care. If we cannot develop clinical trials, then we should try and coordinate care to try and treat rare diseases in a consistent manner and thus allow some useful data that can be used to develop new protocols.

We hope that this book will be useful as a handy reference for teachers, trainers and trainees. We run the risk that the book may become obsolescent fairly quickly but producing it in this format, we hope that it will be suitable to update it and maybe even produce an online edition that can be adapted for changes more readily. We have attempted to be as comprehensive as possible in our coverage; everybody will have their own definition of a rare and uncommon cancer and doubtless we will have omitted somebody's favourite rare tumour. Nevertheless, we hope that with the range of tumour types and histologies that we have covered, we have addressed most of the common issues that will arise. We hope readers will find this a valuable and useful resource, but the editors would also be receptive to feedback from readers so that we can adapt this if we come to a second or subsequent edition.

Epidemiology and Databases

2

Nicholas Reed

There can often be confusion as to what we mean by rare or uncommon and whilst the dictionary may give a definition of what is meant by rare or uncommon, we have to take into account a number of modifying factors. These include the kind of practice that is run, the local geography, the part of the world where we work and local politics and arrangements. For example, clear cell cancers of the ovary are considered to be relatively uncommon in the Western world, accounting for only 3–5% of ovarian cancers, and yet in the Far East they may account for 15–20%. There are other examples where there are variations in the frequency of a condition on a global basis. From a different standpoint, an individual working in a small district cancer hospital seeing only 1,000 or 1,500 new cancers a year will see very few rare conditions, and yet those of us who work in major supra-regional or comprehensive cancer services will see a reasonable number of these so-called uncommon and rare cancers. Thus it is all relative to the kind of practice in which we work. In the introductory chapter we have already made reference to the fact that it may be argued that concentration of the care of these rare and uncommon cancers should be in the hands of a smaller number of regional or supra-regional centres, but of course there can be opportunities for shared care and networking between the smaller district hospital and the regional cancer centre. There is no "one size fits all" and it will be determined by local arrangements.

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It is probably helpful at this point in time to list many of the types of tumours that we are discussing in this book. Firstly we are focusing on tumours of the ovary, uterine corpus, uterine cervix, vagina and vulva. We are concentrating mainly on tumours such as mucinous tumours, clear cell cancers, neuroendocrine tumours, sarcomas and sex cord and stromal tumours. Other less common cancers include serous uterine cancers, squamous cancers arising in ovarian dermoid tumours and melanomas of the vulva and vagina. We also cover uncommon situations like high grade borderline cancers which are worthy of merit not only because of their clinical infrequency but also because of their different biological behaviour. Fallopian tube cancers have not been specifically included as they are considered to be similar to ovarian cancers, and a recent provocative paper has suggested that Fallopian tube cancers may be the "mother of gynaecological epithelial tumours". Given the strong similarity between serous epithelial ovarian and tubal cancers, there is no attempt to distinguish them. The topic of gynaecological cancers arising in pregnancy is also a challenging one and we are fortunate to be able to include a chapter from the team based in Leuven who have been addressing this important topic. We also are pleased to be covering the controversial topic of pseudomyxoma peritonei (PMP). In the UK we have developed a National Service in Basingstoke and the chapter has been written by their team.

What has been omitted? We have not covered some important areas such as gestational trophoblastic tumours and germ cell cancers mainly because the management of these is usually relatively straightforward and there are already well established referral pathways and guidelines for centralisation of care.

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2.1 Rare and Uncommon Gynaecological Cancers

We have already alluded to the difficulties in trying to define a rare or uncommon cancer and one of the challenges is trying to establish just how infrequent these tumours are. Cancer registers are very variable in their quality around the world but often reflect the quality of the data recorded at the time of initial diagnosis, and particularly for rare tumours the subsequent management and review of the case may indicate that we are dealing with a different final diagnosis. This revised diagnosis is unlikely to be routinely picked up by cancer registries. Internationally, there is huge variation in the way that this data is collected and one of the issues that we would like to address is the setting up of formal registries for these rare tumours. The Gynaecological Cancer Intergroup (GCIG) attempted an initiative a few years ago to try and set up a web-based register but unfortunately this faltered, mainly because of issues of how to deal with confidentiality and security. Transferring data globally presents major challenges and many felt that this was not securely achievable at present. However, other initiatives have shown that this can be done at least within a nation. The presentation at ESMO 2007 by Isabel Ray-Coquard on behalf of the French Rare Tumour Registry has shown how this can be done working within one nation and using a defined framework. The reader is referred to their website http://ovaire-rare.org/. Although this was set up partly to provide advice on the management of these rare cancers it has led the way forward in establishing how to collect data on these rare cancers.

The GCIG Rare Tumour Working Group has tried to lead the way in resolving how to overcome the challenges of setting up these databases internationally. One initiative would be to have a series of national registries and databases which could then be linked once the data had been suitably anonymised. However, to do this it would be necessary to have a common dataset. This could be in the format of a core dataset where the basic registration details with some form of unique identifier are kept. We would then have add-on modules in which we would collect specific details for the specific tumour types.

The benefits of this kind of registry are not simply that we would be able to collect data on the frequency of these tumours and establish whether they are truly rare or uncommon, but also that we could have a fantastic valuable resource for clinicians and scientists wanting to develop clinical research or translational studies in these areas. Using virtual tumour and serum banks we do not necessarily need to have tissues and serum flying round the world but can use identifiable tagging processes. We must use every opportunity to take advantage of modern technologies and these kinds of initiatives will hopefully lead the way in developing and progressing care.

We can also see whether, over the course of time, there are changes in patterns of disease. For example, uterine sarcomas were considered to be very uncommon tumours and yet, more recently, carcinosarcomas have become more frequently documented. Is this a genuinely increasing incidence or is this better recognition by pathologists using modern immunocytochemical techniques? For example, is the incidence changing due to exogenous oestrogens and use of tamoxifen for breast cancer? These kinds of issues can be addressed. We have to work together but the modern world is getting smaller and smaller due to the expanding use of electronic technologies. Many of the so-called Third World or low-income countries now have access to technology to match those of us in the Western world and no longer need to be excluded from these initiatives.

2.2 Definition: What is Rare?

There can often be confusion as to what we mean by rare or uncommon and whilst the dictionary may give a definition of what is meant by rare or uncommon we have to take into account a number of factors.

How do we define rare? Is there a simple definition? One definition is “few in number and widely separated from each other (in space or time)” and another is “of a kind, class or description seldom found, met with or occurring: unusual, uncommon, exceptional”. This does not help as no numbers are given and it has already been commented that what is rare in a small centre may be seen more often in a big centre. Recently the National Institute of Health and Clinical Excellence (NICE) in the UK suggested that a cancer with less than 7,000 cases per annum would be proposed as uncommon. This would be considered generous by most standards and many intermediate incidence cancers like renal and oesophagus would be included. A reasonable proposal might to be to suggest fewer than 50 cases per million population but the author has never seen such a figure

proposed and we have to start somewhere! This will include virtually all of the cancers listed below.

What kinds of examples can we consider? Listed below are some of the other rarer cancers.

2.3 Examples of Rare and Uncommon Cancers

- Ophthalmic cancers
- Thyroid cancers
- Neuroendocrine cancers
- Soft Tissue and Bone sarcomas
- Brain and CNS cancers

However, we are looking often at subsets of the more common gynaecological cancers as well as the rarer types; these have been listed below.

- Sub-sets of commoner gynaecological cancers
  - Small cell and neuroendocrine cancers
  - Clear cell cancers
  - Mucinous cancers
  - Serous endometrial cancers
  - Sarcomas/carcinosarcomas
  - Sex cord tumours

Having thus set the scene, it is now time for the reader to review the contents and it is to be hoped that we have done our best to address most of the issues likely to be raised. In the next section of the book we have brought together all the rarer types into sections as listed, but we recognise that there are differences between some of the tumour types. In each section we have attempted to have a template format of epidemiology, diagnosis, imaging and treatment with particular emphasis on the multi-modality and multi-disciplinary treatments. It will be noticed that the chapters and sections vary in their detail, but this reflects the amount of information that is known about a condition and the degree of controversy about their management and care. We have attempted to include not just the clinical aspects but the molecular pathology and the associated biomarkers as appropriate.

Whilst we accept that there are differences between mucinous or clear cell cancers within the ovary, uterus and cervix, it is felt that this commonality of approach is justifiable because there are similarities in their aetiology and in their clinical behaviour. The increasing use of molecular markers to diagnose tumours has indicated that the pathways to cancer development may be similar. This is increasingly being reflected in the use of cell signalling pathway inhibitors as part of the therapeutic armamentarium. It is very likely that by the time the book is published, our knowledge will have leapt further forward, but nevertheless, we hope that this is an accurate reflection of the state of the art at the time of writing.

Rare and Uncommon Gynaecological Cancers: A Clinical Guide

3

W. Glenn McCluggage and David Millan

3.1 Pathology

The female genital tract, comprising the vulva, vagina, uterine cervix and corpus, fallopian tubes and ovaries, as well as the pelvic peritoneum as part of the secondary Mullerian system, is characterised by the occurrence of a greater range of tumour types than any other organ system in the body. This is especially so in the ovary where numerous diverse tumours, benign and malignant, occur. There are three main groups of primary ovarian neoplasm comprising tumours in the surface epithelial-stromal, germ cell and sex cord-stromal categories (Table 3.1) [1]. Within each of these categories, several rare and uncommon tumour types exist. Metastatic tumours are also quite common in the ovary. Clinical correlation is of great importance in the recognition of rare tumour types; for example, the occurrence of hypercalcaemia in a young woman with a small, round blue cell ovarian tumour assists in establishing the diagnosis of a small cell carcinoma of hypercalcaemic type.

It is beyond the scope of this chapter to describe in detail the pathological features of the many individual tumours, but a few general points are made. The first is that generous sampling by the pathologist with the examination of multiple tissue blocks may assist in histologically problematic cases by revealing more diagnostic areas. For example, primary neuroendocrine carcinomas within the ovary may be associated with a component of usual surface epithelial-stromal tumour and generous sampling may reveal such areas, providing strong evidence that the neuroendocrine carcinoma represents a primary ovarian neoplasm rather than a metastasis from elsewhere. Careful sampling may also assist in cases in which a particular tumour is closely mimicked by another neoplasm. For example, some ovarian endometrioid adenocarcinomas may closely mimic a sex cord-stromal tumour, such as a granulosa cell tumour or a Sertoli cell tumour. Generous sampling may reveal areas of more typical endometrioid adenocarcinoma or foci of squamous differentiation or endometriosis, all of these features in this diagnostic dilemma being characteristic of an endometrioid neoplasm. Sampling may also help to identify mixed neoplasms; for example, in the uterus, mixed endometrioid and serous carcinomas are not rare and extensive sampling may reveal a minor component of a particular tumour type. If the minor component constitutes a more aggressive neoplastic type, this may be therapeutically and prognostically important. Sampling is also particularly important in primary ovarian mucinous neoplasms. These are typically extremely large neoplasms with a heterogeneous admixture of benign, borderline and malignant elements. If not adequately sampled, a small area of invasive carcinoma may be potentially missed which may have an adverse effect on the outcome. Additional sampling can be carried out subsequently after the first set of slides have been examined, if these reveal a borderline mucinous tumour at the upper end of the spectrum with intraepithelial carcinoma.

Given the wide range of potential tumours in the female genital tract, some of which are extremely rare such that an individual pathologist may not see a particular neoplasm in his or her lifetime, it may be useful to seek a specialist opinion. This has the added advantage of resulting in accrual of case series of unusual

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Table 3.1 Three main groups of primary ovarian neoplasm

Surface epithelial-stromal
Germ cell
Sex cord-stromal

neoplasms where clinical information and pathological features can be documented. It is in this way that new entities are described and significant new information emerges regarding uncommon neoplasms.

Immunohistochemistry has contributed significantly in recent years as an aid to diagnosis in the field of gynaecological neoplasia and several reviews are available on this subject [2–6]. There are many scenarios in which immunohistochemistry may be extremely useful, including in the diagnosis of rare and uncommon ovarian neoplasms. For example, new markers of ovarian sex cord-stromal tumours have been described, including inhibin, calretinin and CD56 [7–9]. These markers may be of value in confirmation of a sex cord-stromal neoplasm and in excluding other neoplasms. It has been already pointed out that it may be difficult to distinguish a sex cord-stromal tumour from an endometrioid adenocarcinoma and the aforementioned sex cord markers may be useful in conjunction with epithelial markers, such as epithelial membrane antigen (EMA) and cytokeratin 7, which are positive in endometrioid neoplasms and negative in sex cord-stromal tumours. Immunohistochemistry has also been of value in helping to confirm that in pseudomyxoma peritonei, the appendix is usually the site of the primary tumour and the coexistent ovarian mucinous neoplasm is due to spread from the appendix; differential cytokeratin staining has shown that the mucinous epithelium in the appendiceal, peritoneal and ovarian neoplasms is CK20 positive and CK7 negative, in keeping with a large intestinal phenotype [10]. These markers, in conjunction with others, such as CA125, CA19.9, CEA, CDX2, TTF1 and hormone receptors, may also be of value in diagnosing metastatic adenocarcinomas within the ovary and in determining the primary site in an adenocarcinoma of unknown origin. They may also be used in cytology specimens, for example, peritoneal and pleural fluids. Neuroendocrine markers (chromogranin, synaptophysin, PGP9.5, CD56) are of value in confirmation of a neuroendocrine neoplasm and melanocytic markers (S100, melan A, HMB45) in the diagnosis of malignant melanoma. Other markers useful in a diagnostic setting in gynaecological pathology include WT1, which is positive in most ovarian, tubal and peritoneal serous carcinomas [11, 12]. Interestingly, this marker is usually, although not always, negative in uterine serous carcinomas and this may be helpful in ascertaining the site of origin of a disseminated serous carcinoma [13]. p16 is a useful surrogate marker in the cervix of the presence of high-risk human papillomavirus (HPV) [14]. HPV-related cervical neoplasms, including squamous carcinomas, adenocarcinomas and neuroendocrine carcinomas, are usually diffusely positive. However, some non-HPV-related tumours, such as serous carcinomas of the ovary and uterus and uterine leiomyosarcomas, may be p16 positive [15–17].

A few general points are made regarding the use of immunohistochemical markers in a diagnostic setting. The first is that immunohistochemistry is used as an adjunct to pathological examination and that the results should always be interpreted in the light of the gross pathological and morphological features; consideration of the clinical scenario and imaging findings may also be of value. A panel of markers should always be chosen and this should be focused depending on the differential diagnosis under consideration. In general, markers should be chosen which are expected to be positive and negative in the various neoplasms considered in the differential diagnosis. It is stressed that no marker is specific for any given tumour, and as experience with many markers increases, they are often found to be less specific than was originally thought. One example of this is the recent demonstration that thyroid transcription factor 1 (TTF1), which was considered to be a relatively specific marker of pulmonary and thyroid neoplasms, has now been shown to be positive in some gynaecological adenocarcinomas [18, 19]. Thus, there is always the possibility of unexpected positive and negative staining reactions and the pathologist needs to be aware of this.

In general, immunohistochemistry is most valuable and used most often in a diagnostic setting and, as yet, in the field of gynaecological pathology there are few markers which are of value in a prognostic or predictive sense. However, it is anticipated that this will change in the future and that large studies will identify markers of prognostic or predictive value in a particular tumour type. It is also anticipated that targeted therapies will be developed against specific proteins, the presence of which will be demonstrated on tissue sections of neoplasms using immunohistochemistry. Immunohistochemistry is already used in certain scenarios in a therapeutic sense. For example, the

demonstration of hormone receptor (oestrogen receptor and progesterone receptor) positivity in a recurrent or metastatic gynaecological neoplasm may be used to predict a response to hormonal agents, such as gonadotropin releasing hormone agonists.

Currently, molecular pathology has a relatively minor role in the broad field of diagnostic gynaecological pathology. Identification of HPV types by polymerase chain reaction (PCR) can now be done with relative ease. This can be used to confirm an HPV-related neoplasm. For example, in a metastatic adenocarcinoma, the identification of HPV is helpful in pointing to the cervix as the site of origin. HPV studies may also be useful in the sometimes problematic distinction between an endometrial and an endocervical adenocarcinoma. HPV studies have also assisted in establishing that two distinct types of vulval squamous carcinoma exist, a non-HPV-related squamous carcinoma, usually of keratinising type, and an HPV-related type, usually with basaloid morphology [20]. Molecular studies have also demonstrated characteristic genetic abnormalities in different tumour types and this has been paramount in establishing the histogenesis of various neoplasms. As an example, high-grade serous carcinomas in the uterus and ovary have been demonstrated to consistently harbour p53 mutations, while endometrioid adenocarcinomas arising in the same organs not uncommonly exhibit microsatellite instability and mutations in beta catenin, k-RAS, PIK3CA and PTEN genes [21]. Molecular studies have also been instrumental in demonstrating that there are two distinct types of ovarian serous carcinoma, termed low-grade and high-grade serous carcinoma [22, 23]; these are two different neoplastic types rather than high-grade and low-grade variants of the same neoplasm. The much more common high-grade ovarian serous carcinomas are characterised by p53 mutations and BRCA1 and BRCA2 abnormalities, while low-grade serous carcinomas are characterised by k-RAS and BRAF mutations. The demonstration of identical p53 mutations in the epithelial and mesenchymal components of carcinosarcomas has helped to confirm that these are monoclonal neoplasms and, in effect, carcinomas with sarcomatous metaplasia rather than collision tumours [24, 25]. Some gynaecological tumours have relatively specific chromosomal translocations. For example, many endometrial stromal sarcomas (low-grade endometrial stromal sarcomas) harbour a characteristic chromosomal translocation t (7; 17) (p15; q21), which results in the JAZF1-JJAZ1 gene fusion product [26]. This may be useful in the diagnosis of problematic cases and in the exclusion of other neoplasms.

The establishment of carefully regulated and funded tissue banks is vitally important both in common tumour types and in unusual gynaecological neoplasms. Such tissue banks will enable the procurement of significant numbers of uncommon neoplasms by combining samples from different banks. This will facilitate future research into biomarkers and molecular markers of use in a diagnostic setting as well as in a predictive or prognostic sense.

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The Contribution of Diagnostic Imaging in Rare Gynaecological Malignancies

4

Rachel Connor

4.1 Introduction

The goal of imaging at initial patient presentation is to pre-operatively predict gynaecological malignancy, potentially identify a tumour type and to provide appropriate staging information which will influence management and likely inform patient prognosis. Following treatment, imaging allows assessment of response and differentiation of potential relapse from treatment related complications. The identification of localised relapse, before it is clinically apparent, has the potential to offer selected patients a chance of curative salvage therapy.

Unfortunately, many gynaecological tumours are too rare to provide an evidence base for reliable, specific predictive imaging information. Some tumours will be characterised by particularly aggressive or unusual behaviour and for these tumours, modifying either initial investigation or a follow-up imaging strategy can be helpful.

Radiology has embraced major advances in technology with developments within the modalities of ultrasound, CT, MRI, CT/PET and nuclear medicine and there are exciting future prospects for targeted molecular imaging. This anatomic and functional imaging is changing survival data not only by more accurate initial staging, but by assessing response to therapy early on in a treatment cycle, allowing individual, tailored changes in management. All these modalities have their place in the optimal management of these patients with rare tumours.

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Many of the rare tumours will only be seen once in a career by many general radiologists and the importance of referral to a dedicated Gynaecological Oncology multi-disciplinary team, before surgery, cannot be underestimated to provide the best treatment plan, tailored to improve the chance of patient survival.

4.2 Imaging Techniques for Evaluating the Primary Gynaecological Malignancy

4.2.1 Ultrasound

Ultrasound is inexpensive, readily available and is often the initial imaging modality used to assess patients with symptoms and signs suspected to be of gynaecological origin. More than other modalities, ultrasound is limited by patient obesity and excessive bowel gas. It is also limited by operator experience and initial hard copy images have a more limited value in external review. Nevertheless, transvaginal imaging is the modality of choice to evaluate patients with post-menopausal bleeding [1], providing an accurate measurement of assessing endometrial thickness, overall uterine morphology and the presence or absence of adnexal masses and ascites. Although ultrasound will detect adnexal masses and effectively triage patients with unscheduled bleeding into those who will then require endometrial biopsy and hysteroscopy, it is not accurate in staging endometrial or uterine neoplasms. Ultrasound morphology is useful to characterise benign vs. malignant adnexal masses, particularly when this is combined with Doppler assessment and this forms the basis of a risk of a malignancy index (RMI) when combined with CA 125 levels and the patient's menopausal status [2, 3].

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Adoption of an RMI will triage patients into groups which require either intervention or follow-up. When trying to determine whether an adnexal mass is benign or malignant, MRI is more accurate than either ultrasound or CT, by providing exquisite soft tissue detail and additional tissue characterization not possible with other modalities [5]. Both CT and MR will stage the abdomen more comprehensively than ultrasound, but MR is more accurate than CT for nodal staging in the abdomen and pelvis [6].

4.2.2 CT

CT is an imaging modality that is now widely available in developed countries and newer multi-slice machines are rapid, with scan times of a just a few minutes to cover the entire chest, abdomen and pelvis, which removes some of the problems associated with movement artifact, particularly in unwell or poorly cooperative patients. CT is preferable to MR in assessing the lungs and thorax and this is particularly important in tumours with a propensity for haematogenous metastases or in advanced or relapsed disease. In gynaecological malignancy, it is important that scan coverage for the whole chest, abdomen and pelvis includes the supraclavicular fossa, (where there may be unexpected involvement of supraclavicular nodes), without contiguous mediastinal involvement, extending to inguinal node regions. However, until there is confirmation of a malignant pelvic mass, there is no evidence base to support scanning the entire thorax, although imaging of lung bases is essential to detect possible pleural effusions or enlargement of paracardiac nodes [7]. Multi-slice CT allows volume acquisition of data and isotropic multi-planar reconstructions for example in coronal or sagittal planes. CT scans should be performed with intravenous and either positive or negative intraluminal bowel contrast. Despite advances, CT still does not have the soft tissue discrimination of MRI and it has the major drawback of ionising radiation.

Cumulative diagnostic radiation dose is now recognised as an increasingly important issue. Females and young patients in particular are at increased risk for stochastic, or long-term effects of ionising radiation. Although exact risks are difficult to establish, the likelihood of inducing a solid cancer or leukaemia from a single CT scan of the abdomen or chest (dose 10 mSv) in a female, is estimated at approximately 1:1,000 depending on patient age [8].

Most CT scans of chest abdomen and pelvis will result in a dose in the 15–20 mSv range. For young patients requiring long term follow-up, e.g. those patients with ovarian granulosa cell tumours or leiomyosarcoma (LMS), the cumulative radiation burden of repeated CT imaging should be considered and ultrasound or MRI imaging substituted [9].

4.2.3 CT/PET

CT/PET is now increasingly utilised in the staging and follow-up of some categories of gynaecological malignancy. CT/PET is more accurate than either CT or PET alone in the detection of metastatic disease. This technique involves fusion of images from a PET scanner, after the patient is injected with a suitable isotope (most commonly 18 – fluorodeoxyglucose – 18 FDG PET) with images from an in-line CT scanner, which provides the anatomic resolution lacking in pure PET images. FDG-PET essentially relies on the higher metabolic activity of most neoplasms having increased affinity for the injected glucose isomer. It is therefore not specific to tumour cells and uptake is also seen in other metabolically active normal tissue, such as heart and bowel as well as inflammatory tissues. False negative uptake is also seen in neoplastic tissue with low metabolic activity or very small tumour foci. This results in the sensitivity of PET diminishing rapidly in lymph nodes less than 5 mm in size. The use of SUV (standard uptake values) provides quantitative measurement of PET activity which can help to differentiate benign from malignant processes. The exam preparation requires patients to fast and diabetic patients need to control blood sugars within normal ranges. PET scans can be limited in grossly obese patients in whom MR and CT can still provide morphological nodal assessment (Fig. 4.1).

The role of CT/PET has increased in many centres to encompass the role of assessing response to chemoradiotherapy after completion of treatment and determining which patients will be most likely to relapse and which will benefit from salvage therapy, before significant disease progression has occurred. These selected patients then appear to have improved prospects for long term survival [18].

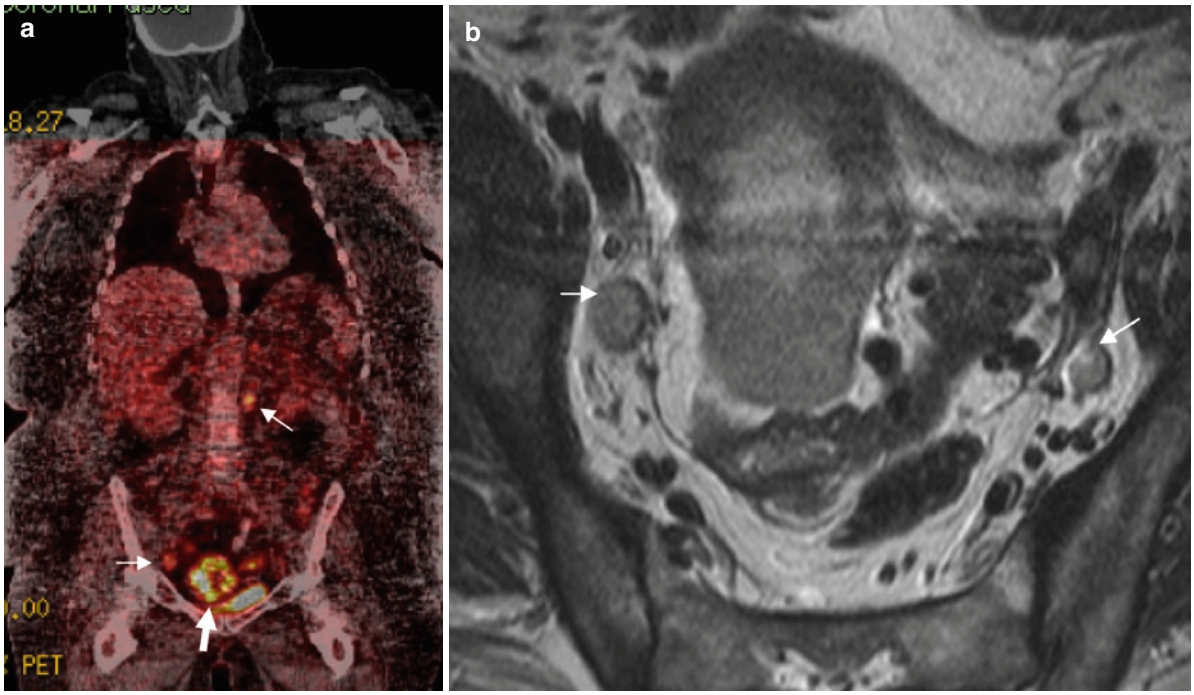


Fig. 4.1 (**a**) CT/PET coronal fused image. Note poor image quality due to gross obesity. (**b**) Corresponding MRI T2W axial. Grossly obese patient. High para-aortic node and right obturator node confirmed in patient with Stage 2B cervical carcinoma (*broad arrow*) with bowel uptake and obesity obscuring left pelvic adenopathy. MR scan detects bilateral obturator nodes only, with small focus of necrosis on left (*arrows*)

CT/PET results in higher levels of diagnostic Ionising radiation (approximately 25 mSv) and the same considerations of accumulated dose apply for the routine use of this modality in long term follow-up as for CT.

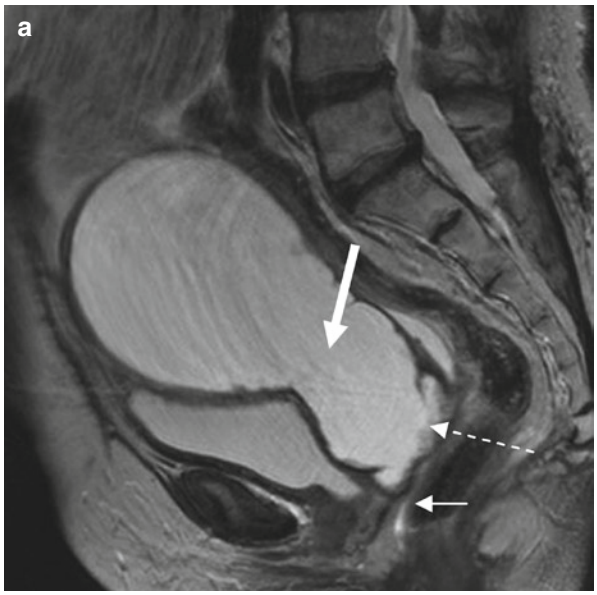
Future developments in PET imaging include fusing FDG-PET images with MR. Preliminary reports suggest this will improve accuracies for detection of involved lymph nodes by combining the better soft tissue discrimination and spatial resolution of MRI, with the functional/metabolic discrimination of PET imaging. Reported sensitivity and specificity of CT/PET and fused MR/PET, 44.1, 93.9 and 54.2 and 92.7% respectively [21, 36].

New horizons in functional PET tumour imaging include mapping uptake of radiopharmaceuticals isotopes of copper (Cu^{60} and Cu^{64} – copper(II)-diacetyl-bis(N4-methylthiosemicarbazone)(copper-ATSM). This assesses of the degree of tumour hypoxia which has been found to correlate with prognosis in cervical and other cancers, as hypoxic tumours respond less favourably to chemoradiotherapy [22].

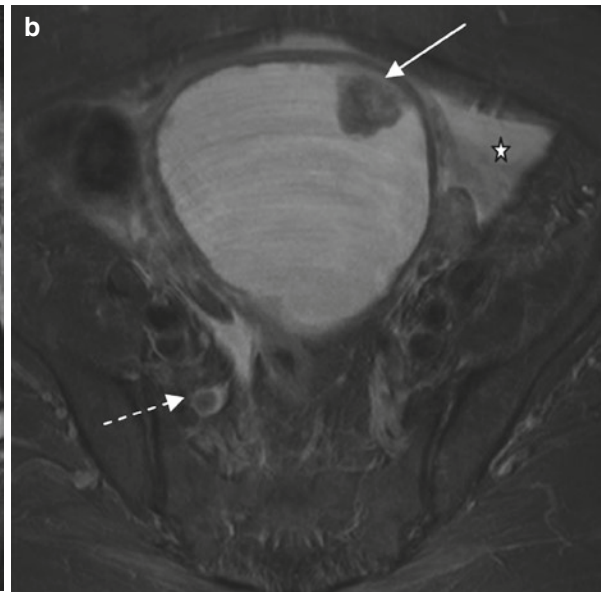
4.2.4 MRI

MRI is particularly useful for evaluating gynaecological masses and when compared to ultrasound and CT, it is the most accurate modality for characterising adnexal masses with accuracy of 60–95% in discriminating benign from malignant masses [4]. In elderly, unfit and obese patients, with vaginal or cervical stenosis, the attendant risks of anaesthesia can make endometrial sampling impossible and MRI in particular, is useful for assessing a pelvic mass in the presence of post-menopausal bleeding (Fig. 4.2).

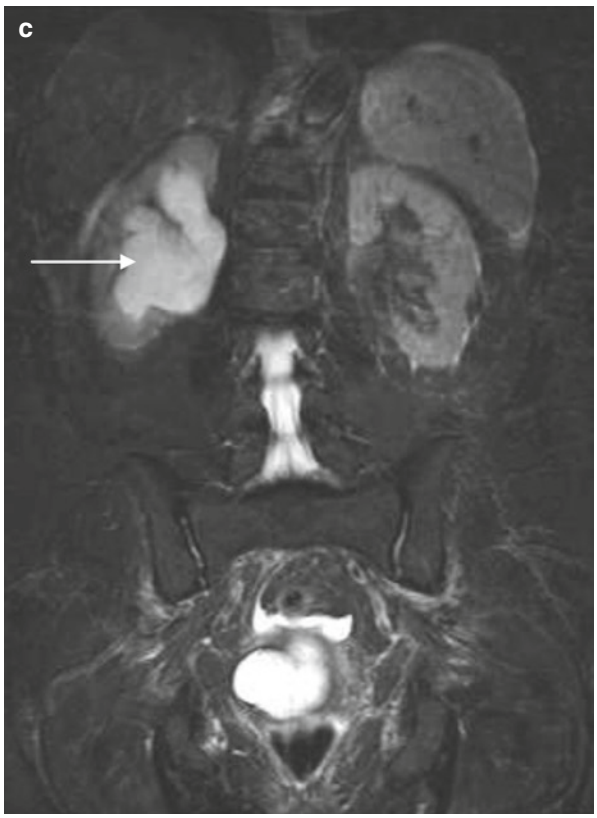
MR can also characterise soft tissue, accurately identifying fluid, fat and blood products Blood less than 3–4 weeks old (methaemoglobin) will characteristically show increased signal on T1 weighted sequences and decreased signal on T2 sequences (Fig. 4.3). Chronic blood products (haemosiderin) will be of low signal on all MR sequences. This helps to characterise endometriomas and haemorrhagic cysts, vs. other solid or cystic adnexal masses as well as identifying haemorrhagic uterine tumours. Macroscopic fat within tumours



MRI Sagittal T2W



MRI Axial T2W Fat Sat



MRI T2W Coronal Fat Sat

Fig. 4.2 Serous Endometrial cancer Elderly patient with scant vaginal bleeding, vaginal stenosis and a pelvic mass. Treated 20 years previously with radiotherapy for cervical cancer. (**a**) Distended endometrial cavity and endocervical canal (*arrow*); endocervical tumour seeding (*broken arrow*); vaginal stenosis (*thin arrow*); (**b**) polypoid endometrial serous neoplasm (*arrow*); ascites (*star*); obstructed right ureter due to serosal and parametrial involvement (*broken arrow*). (**c**) Unexpected right hydronephrosis (*arrow*)

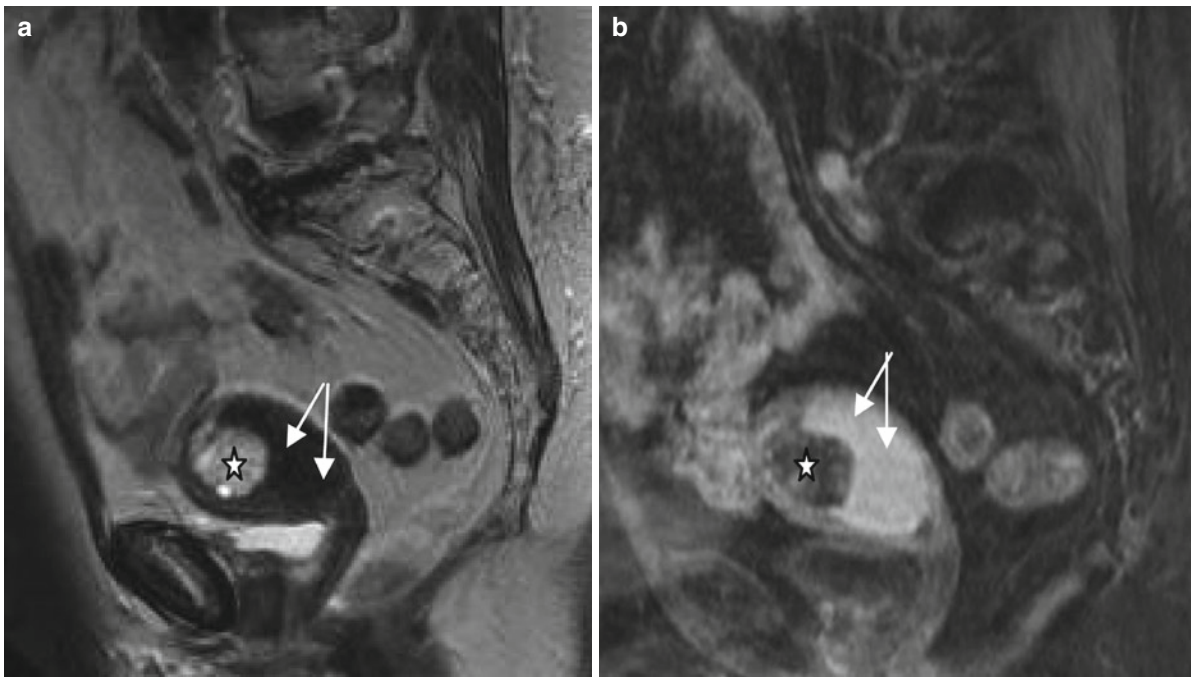


Fig. 4.3 (**a**) MRI sagittal T2W. (**b**) MRI sagittal T1W fat saturated. Post-menopausal patient with vaginal bleeding and cervical stenosis. Endometrial cavity is distended with blood (*arrows*) bright on T2 weighted sequences and dark on T1 weighted sequences. A typical hyperplastic benign high signal fundal polyp is present (*star*). Note change of subcutaneous fat from bright on T2 weighted image, to dark on fat saturated image increasing conspicuity of high signal blood products (and proteinaceous fluid in bowel)

e.g. Teratomas, will follow the signal of subcutaneous fat, appearing dark on fat saturated sequences and bright on T1, and most T2 weighted images. Unfortunately, MRI has significant limitations in identifying calcification, seen clearly on CT exams, which contributes important imaging characteristics to both epithelial and non-epithelial ovarian malignancy.

With MRI, it is therefore important to routinely include a range of sequences to characterise an unknown, complex adnexal mass and these should include, T1 and T2 weighted as well as pre and post-contrast fat saturated T1W sequences.

In gynaecologic imaging generally, an anti-peristaltic bowel agent, such as hyoscine butylbromide, is also routinely recommended, to reduce artefact from bowel movement and allow better discrimination of tissue margins.

MR examinations are contraindicated in patients with some metallic implants e.g. pacemakers and may not be suitable for claustrophobic or acutely unwell patients. Most current MR scanners have a magnetic field strength of 1.5 Tesla (T), necessitating long scan times with sequences usually taking 4–5 min each, and an examination of pelvis and abdomen requiring between half to 1 hour. This may be reduced with increasing availability of 3 T scanners. MRI does not use ionising radiation and is therefore more suitable for repeated imaging and scans in pregnant patients. Routine use of MR is not recommended in the first trimester of pregnancy, but is a preferable alternative to CT. The use of gadolinium contrast in MR provides additional information in characterising adnexal and uterine masses and in staging, particularly of endometrial neoplasms, but as gadolinium crosses the placenta, its use is not recommended in pregnancy.

Recent developments in dynamic contrast imaging sequences, allow quantitative measurements of tissue enhancement with contrast over time. This can help to distinguish for example, the rapid uptake of contrast by tumour tissue from radiation induced fibrosis in a potential recurrent cervical cancer.

Diffusion weighted MR imaging is an established technique in neurological imaging, but more recently utilised in body imaging. This non-invasive technique utilises the difference in movement of free water molecules in normal and abnormal tissues, to distinguish benign from malignant tissue characteristics and has been successfully used for imaging cervical and endometrial tumours and assessing response to therapy [13]. Whole body diffusion imaging also shows a promise as a method of surveying for metastatic disease.

4.3 Lymph Node Imaging in Gynaecological Malignancy

The correct, pre-operative identification of metastatic nodal disease, particularly when this extends beyond conventional pelvic radiotherapy fields, still remains a great diagnostic challenge. The identification of affected lymph nodes changes the prognosis and FIGO staging for most categories of gynaecological malignancy.

Ultrasound has limited value in identifying metastatic adenopathy, largely due to the deep retroperitoneal location of lymph nodes. The exception is in the assessment of enlarged, superficial inguinal nodes, most often secondary to vulval or vaginal cancers, but occasionally involved in aggressive ovarian or uterine malignancy through retrograde spread along round ligament lymphatics. High resolution and Doppler ultrasound can accurately identify these abnormal nodes by morphology and vascularity and provide image guided fine needle node aspiration if necessary [14].

Both MRI and CT will identify macroscopic involvement of pelvic and para-aortic lymph nodes, primarily by virtue of size criteria, with round (instead of oval) and large nodes more likely to reflect metastatic disease. The shortest diameter measurement of a lymph node is more reproducible and is regarded as standard for a single axis measurement. Pelvic and para-aortic nodes greater than 10 mm short axis diameter, have a high likelihood of neoplastic involvement, but this size cut-off results in a low sensitivity for metastatic disease. An upper limit of 8 mm in the pelvis is preferable and will increase sensitivity without significant loss of specificity [16]. MRI can also identify macroscopic extra-capsular nodal spread which appears as a slightly speculate outline (Fig. 4.4) [17] and when combined with nodal tissue characterisation, is more sensitive in detecting nodal neoplasia than CT.

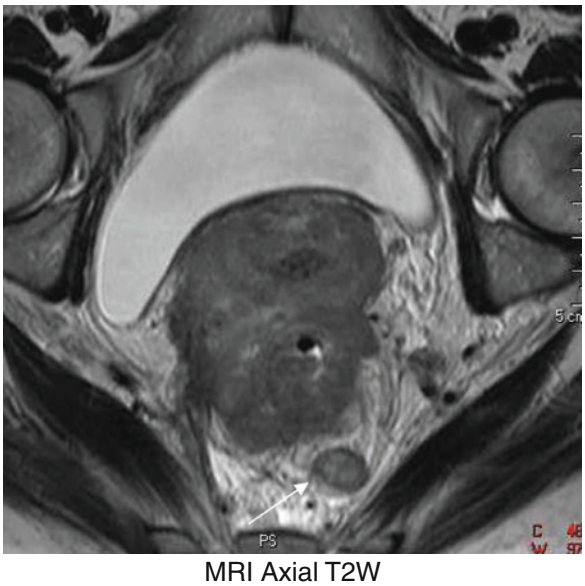


Fig. 4.4 Stage 4 cervical carcinoma extending posteriorly to involve the rectum. Enlarged pre-sacral nodes (11 mm short axis) show slightly irregular spiculated margin (*arrow*)

Nodal necrosis, seen as fluid attenuation within the node on both CT (density less than 20 HU) and high signal on T2 weighted MRI, (Fig. 4.1) has a reported positive predictive value of 100% for neoplastic involvement [32]. Unfortunately, both CT and MRI still have limited overall sensitivities and specificities for detection of neoplastic lymph node involvement; in the pelvis sensitivity 40–60%, specificity 80–90% and para-aortic region sensitivity 43% and specificity 91%. This is a consequence of metastases occurring in nodes smaller than 8 or 10 mm and large, reactive nodes enlarging greater than 10 mm.

With the advent of conformal and intensity modulated radiotherapy fields, MR or CT identification of nodal chains provides a necessary treatment-related road map for accurate planning of radiotherapy fields and the reporting of involved lymph nodes outside normal radiotherapy fields (Fig. 4.4) is therefore essential [16, 34].

More recently, non-invasive MR diffusion weighted imaging has been used to identify involved lymph nodes but early results do not appear to be as accurate as CT/PET.

Newer imaging techniques using specific nanoparticle iron oxide lymphographic contrast agents (ultra