Anal Carcinoma

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Contents

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A.-L. Grosu, C. Nieder (eds.), *Target Volume Definition in Radiation Oncology*,
DOI 10.1007/978-3-662-45934-8_11, © Springer-Verlag Berlin Heidelberg 2015

11.1 Introduction

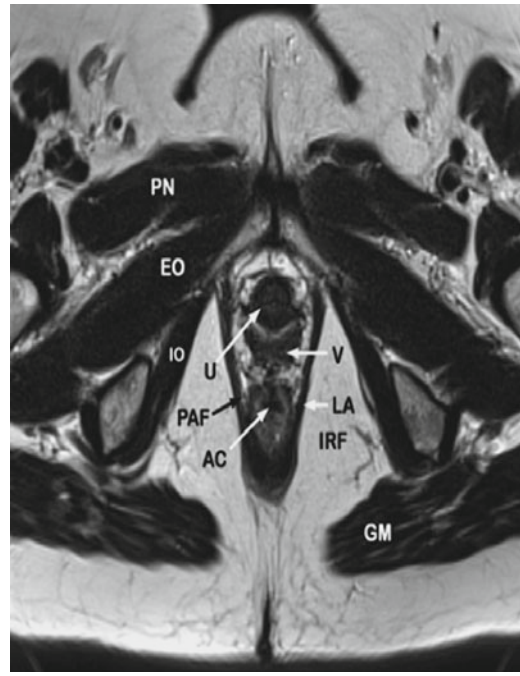
Squamous cell carcinoma of the anus (SCCA) is a rare cancer but its incidence is increasing throughout the world (Bilimoria et al. 2009; Hartwig et al. 2012; Bentzen et al. 2012; Jin et al. 2011). SCCA spreads in a locoregional manner within and outside the anal canal and to surrounding draining lymph nodes depending on the site of origin. Distant metastases appear relatively late. The primary aim of treatment therefore is to achieve locoregional control and preserve anal function, with the best possible quality of life. Due to these tumours' high sensitivity to chemoradiation, this modality has become the standard of care.

In this chapter we aim to provide a clear practical guide to target delineation (both elective and gross tumour) for external beam radiotherapy (EBRT) in anal cancer. We wanted to determine the optimal imaging modalities for anal cancer and how best to define involved lymph nodes. We review the probability of lymph node metastases within the pelvis and groins and patterns of local recurrence after CRT – although no prospective randomised trials have been able to provide this data in any detail. We describe target volumes, constraints to organs at risk (OARs) and recommendations for external beam radiation therapy (EBRT). We have not addressed the issue of brachytherapy. Also recommendations regarding optimal doses to gross and elective target volumes are beyond the scope of this chapter.

Anatomical textbooks, published studies and reviews with data from lymphangiograms, computerised tomography (CT) and more recently magnetic resonance imaging (MRI) and positron emission tomography (PET) are used to define the anatomical distribution of normal pelvic and inguinal lymph nodes, the boundaries of the anal canal and relevant organs at risk. Historical surgical series document the site of involved lymph nodes. We have examined many old chemoradiation series (Nigro et al. 1983; Leichman et al. 1985; Hughes et al. 1989; Luna-Pérez et al. 1995) and also the results of recent retrospective studies detailing sites and patterns of anal cancer recurrence (Das et al. 2007; Wright et al. 2010; Sebag-Montefiore et al. 2012).

There are several excellent guidelines showing anatomical borders to define the clinical target volumes for anal cancer. The recently published Australasian planning guidelines interpret CT definitions and provide a high-resolution atlas for contouring gross disease and organs at risk (Ng et al. 2012). The descriptions of the elective target volumes or compartments are useful and reproducible. This data therefore complements the existing Radiation Therapy Oncology Group (RTOG) elective nodal anorectal atlas (Myerson et al. 2009). However, we consider that the RTOG recommendations have not integrated specific clinical data and patterns of recurrence but derive from a subjective approach (superposition of targets drawn by a few individual experts), and issues such as genital sparing are insufficiently precise. There are also RTOG pelvic normal tissue contouring guidelines (Gay et al. 2012) available as a CT image atlas on the RTOG website.

However, although comprehensive, we also have issues with accepting without qualification the recommendations of the above (Ng et al. 2012). Many of the Australasian recommendations for CTVs appear unnecessarily extensive in the light of our experience in the UK with the



U	Urethra
PAF	Perianal fat
AC	Anal canal
V	Vagina
LA	Levator ani
IRF	Ischiorectal fossa
PN	Pectineus
EO	External obturator
IO	Internal obturator
GM	Gluteus maximus

Fig 11.1 Axial MRI image demonstrating the proximal anal canal in a female

ACT II trial, and it is a 'one-size-fits-all' strategy since they advise all nodal volumes described should be covered for all stages (with the possible exception of frail patients with T1N0 tumours). We have hypothesised that SCCA at the anal margin, involving predominantly the anal canal and finally extending above the dentate line into the rectum, has three anatomically different vascular and lymphatic drainage patterns, which require different approaches and different field sizes.

Conventional pelvic fields have usually referenced anatomical bony structures to deliver pelvic radiation therapy, which achieves suboptimal coverage of the nodal areas. Contouring vessels on CT images is now used as surrogate for lymph node localisation (which is usually not visualised) to achieve more precise and individualised target delineation. We advise the use of CT and co-registration with MRI and/or PET/CT to define appropriate and different algorithms for T1/T2 cancers (<4 cm) and larger (>4 cm (T3, T4)) tumours; see Fig. 11.1. We have incorporated bone, soft tissue and vessel landmarks into an MRI-/CT-based atlas provided by Vicky Goh (consultant radiologist) as part of this group.

11.2 Pathology

More than 80 % of anal SCCs contain one or more subtypes of human papilloma virus (HPV – and usually HPV16 or HPV18). HPV-associated tumours retain wild-type *P53*, and hence patients with HPV-associated tumours appear to have a good response to concurrent chemoradiotherapy, although most of the evidence has been derived from small retrospective studies (Yhim et al. 2011).

SCCA originates from the transitional and squamous mucosa of the anal canal. Terms such as basaloid, transitional or spheroidal and cloacogenic have largely been replaced by the general term squamous cell carcinoma (SCC), because all have a similar natural history and patterns of spread. The biology and prognosis of keratinising and non-keratinising tumours of the anal canal also appear to be similar. Verrucous carcinomas are another variant and are sometimes described as giant condylomas or Buschke-Lowenstein tumours, which

are often enormous exophytic tumours but may have a better prognosis than SCC.

11.2.1 Tumour Grade

Tumours of the anal canal are often defined as poorly differentiated SCC, whereas tumours at the anal margin are well differentiated, but histological grading has been subject to interobserver variability. There is also considerable heterogeneity particularly in larger tumours. Hence, although high-grade tumours are generally accepted to have a worse prognosis, this has not been confirmed in multivariate analysis (Shepherd et al. 1990; Hill et al. 2003).

11.3 Historical Background

Three phase III trials demonstrated that radiotherapy (RT) with concurrent 5FU and mitomycin (MMC) (UKCCCR 1996; Bartelink et al. 1997; Flam et al. 1996) achieves better outcomes in terms of local control and recurrence- or disease-free survival (RFS/DFS) compared to RT alone or RT combined with 5FU alone. In contrast, phase III trials by the Radiotherapy Therapy Oncology Group RTOG 98–11 (Ajani et al. 2008; Gunderson et al. 2012) and the Action Clinique Coordonnees en Cancerologie Digestive ACCORD-03 phase III trial (Peiffert et al. 2012) failed to show benefit for the addition of cisplatin-based neoadjuvant chemotherapy (NACT) prior to CRT in terms of colostomy-free survival (CFS). In the RTOG 9811 trial, the DFS and colostomy rate actually appears inferior with cisplatin (Gunderson et al. 2012). The ACCORD-03 trial also failed to show a benefit in CFS from an increase in the radiotherapy boost dose (Peiffert et al. 2012). Preliminary results of the United Kingdom National Anal Cancer Trial (ACT II) confirm the standard of 5FU/MMC CRT. Results show excellent complete response rates (90 %), with 3-year recurrence-free survival rates overall of 73 % (81 % in T1/T2 tumours, but 64 % for more advanced T3/T4 tumours) (James et al. 2013). The dose and treatment schedule used in the ACT II trial is now the current standard of care in the UK.

11.4 Conventional Radiotherapy Treatment Planning of Anal Cancer

Historically, anal cancer has been treated in all randomised phase III trials with doses of 1.8 Gy per day, using a shrinking-field technique over the course of treatment (UKCCR 1996; Bartelink et al. 1997; Flam et al. 1996; Ajani et al. 2008; Peiffert et al. 2012; James et al. 2013). There have been various previous trial planning techniques. Conventional 2-D large APPA pelvic radiation fields in anal cancer (with generous length and widths of field sizes such that a geometrical miss was extremely unlikely) used the pelvic bones as reference extrapolating the position of the pelvic nodes – based on historical data from studies imaging lymph nodes with lymphangiograms (Davey et al. 1996; Chao and Lin 2002) and early CT scans and from surgical series which defined the sites of pelvic lymph node pathological involvement at laparotomy (Hightower and Judd 1967; Stearns and Quan 1970; Beahrs 1979).

These techniques caused significant acute toxicity of the perineal skin and genitalia; genitourinary, gastrointestinal and haematological toxicity; and poor late function (Ajani et al. 2008; Myerson et al. 2009), often associated with radiotherapy breaks which increase the overall treatment time (OTT), and may compromise efficacy (Allal et al. 1997; Weber et al. 2001; Graf et al. 2003; Huang et al. 2007; Ajani et al. 2008). In April 2012, the National Comprehensive Cancer Network (NCCN) panel agreed that multifield techniques are now preferred over APPA techniques for radiation delivery in anal cancer (Benson et al. 2012). Hence, many institutions are now moving to use multifield techniques, with a range of techniques and different recommended doses.

11.5 Modern Techniques (Intensity-Modulated Radiation Therapy and Volumetric Modulated Arc Therapy)

Delivery of radiotherapy in anal cancer is complex because of the heterogeneity in size, the irregular shape of the target volume and the proximity to

dose-sensitive critical structures (small bowel, femoral heads, perineum and external genitalia). Intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) allow sophisticated dose-painting treatment planning. Comparisons between 3D-CRT, IMRT and VMAT in SCCA demonstrate the same dose coverage in the target but 3D-CRT exposes the surrounding tissue and consequently the OAR to much higher doses (Chen et al. 2005; Stieler et al. 2009).

However, the narrow constraints and high precision of treatment raise concerns about potential geographical misses or compromise of target coverage due to systematic or random radiotherapy errors. Clear definitions of target volumes are therefore essential to ensure accurate and reproducible contouring, treatment planning, delivery and quality assurance. This in turn will require strong engagement with the wider multidisciplinary team including physicists and radiographers to optimise treatment outcome for individual patients.

The International Commission on Radiation Units and Measurements (ICRU) report 83 provides additional recommendations on the selection and delineation of the targets volumes and the organs at risk (ICRU 83 2010).

11.6 Image-Guided Radiotherapy (IGRT)

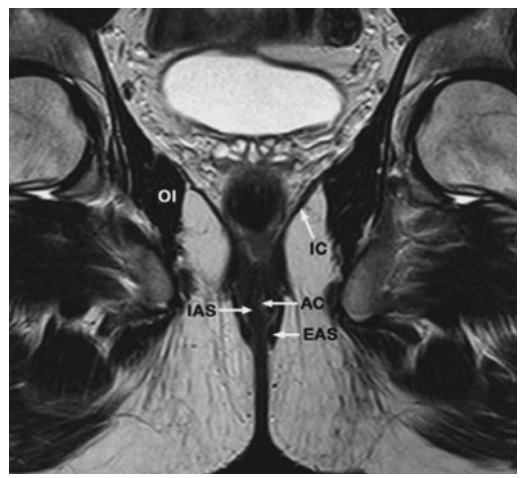
During a treatment course, individual day-to-day tumour position can be variable. On-line daily imaging can correct both systematic and random errors. Off-line imaging should be interpreted by the radiation oncologist for at least the first 3 fractions and then at weekly intervals to deal with systematic errors. The radiation oncologist can therefore use the on-board imaging system (OBI) or the cone beam CT (CBCT). Verification should use bone landmarks, because soft tissues inferiorly are often blurred.

11.6.1 Anatomy

Knowledge of the location and terminology of lymph node groups in the pelvis is essential for accurate staging in a standardised manner.

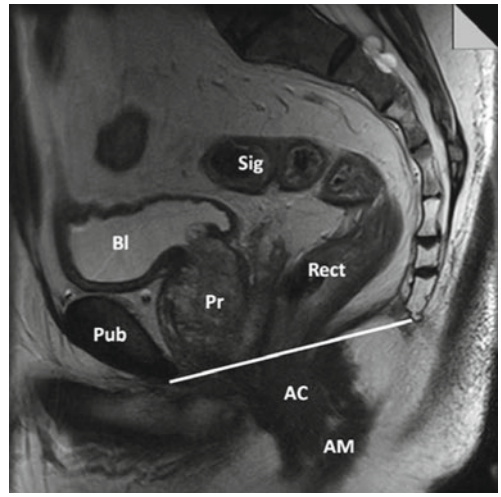
11.6.2 The Anal Canal

The anal canal is the most distal part of the large bowel beginning at the anorectal junction. It is approximately 4 cm in length, ending at the anal orifice where the true skin is found at the anal margin. Because the dentate line (which defines the level of the upper limit of the internal sphincter) is the most easily identified landmark in the mucosa of the anal canal, many have suggested that the anal canal is divided into infra-dentate and supra-dentate regions (Wendell-Smith 2000). The components of the anal canal of relevance to surgical disease and treatment are demonstrated on axial (Fig. 11.1), sagittal (Fig. 11.2) and coronal (Fig. 11.3) magnetic resonance imaging (MRI) of the anal canal.



IAS	Internal anal sphincter
EAS	External anal sphincter
AC	Anal canal
IC	Iliococcygeus
OI	Obturator internus

Fig. 11.2 Coronal MRI image demonstrating the anal canal in a female



Sig	Sigmoid colon
Rect	Rectum
AC	Anal canal
AM	Anal margin
Pr	Prostate
Bl	Bladder
Pub	Pubis

Fig. 11.3 Sagittal MRI image demonstrating the anal canal in a male

11.6.3 Anal Sphincter

The internal anal sphincter (IAS) is formed by a thickened segment of the circular muscle coat in the distal rectum. From the MRI obtained in the sagittal orientation (Fig. 11.2), the superior aspect of the anal canal can be determined and can usually be defined superiorly by a line joining the tip of the coccyx and the most inferior aspect of the pubis – reflecting the anorectal junction. The ischiorectal fossa, ischial tuberosities and sacrotuberous ligaments lie laterally (best appreciated on MRI obtained in the coronal orientation (Fig. 11.3), the contents of the urogenital triangle anteriorly (Fig. 11.1) and the anal orifice inferiorly (Figs. 11.2 and 11.3)).

11.6.4 Anal Margin

The anal margin is a region of pigmented skin with skin folds surrounding the anus. Although the lateral border of the anal margin has not been defined, anal margin cancer is usually considered as within a radius of approximately 5 cm from the anal orifice.

11.6.5 The Inguinal Nodes

The inguinal nodes are in the inguinal region (*superficial* inguinal nodes are often larger than nodes from other lymphatic areas) anterior to Scarpa's femoral triangle and are bounded superiorly by the inguinal ligament, laterally by the medial border of sartorius and medially by the upper border of adductor longus.

From the *superficial* inguinal nodes, there is an extension to the *deep* inguinal nodes which are within the fatty tissue of the femoral canal and medial side of the femoral vein. If the superficial nodes are clinically negative, it may be reasonable to avoid treating the deep region.

11.6.6 Femoral Nodes

We have rarely if ever seen involvement of the femoral nodes in anal cancer and do not recommend routine contouring of the femoral nodes.

11.6.7 Presacral Nodes

Presacral nodes are sited around lateral and medial sacral arteries. These lie along the lateral borders of the sacrum and anterior to the sacral pelvic surface usually just medial to the foramen.

11.6.8 Pararectal Nodes

Pararectal nodes lie within the mesorectum usually posteriorly on both left and right sides –

probably extending for no more than 4 cm cephalad to the anorectal tumour.

11.6.9 Common Iliac Lymph Nodes

Common iliac lymph nodes are grouped around the common iliac vessel (lateral, intermediate and medial groups).

11.6.10 Internal Iliac Nodes

Internal iliac nodes are sited lateral to the mesorectum and presacral space and are associated with the internal iliac vessels, arising superiorly from the bifurcation of the common iliac artery (at the level of S1) and ending at the level of obturator internus.

11.6.11 External Iliac Nodes

External iliac nodes are usually grouped around the external iliac vessels forming three distinct chains (the lateral, middle and medial groups of external iliac).

Examples of the definitions of the appropriate nodal groups can be found on the ATC website, http://atc.wustl.edu.

11.7 Normal Lymph Node Drainage

Lymphatic drainage depends on the position within the canal. The canal above the dentate line drains to internal pudendal nodes and to the internal iliac system. The canal below the dentate line drains to the medial group of superficial inguinal nodes with further extension to the deep inguinal nodes and some communication superiorly to external iliac nodes and inferiorly with femoral nodes. The upper half of the canal drains mainly by the superior rectal vein to the inferior mesenteric vein and thence potentially to the para-aortic nodes (Hill et al. 2003).

Involvement of regional lymph nodes represents the most common mode of spread from cancer of the anal canal and margin (Kuehn et al. 1968). The perirectal, inguinal, femoral and iliac lymph nodes are the most frequent sites for nodal metastases (Beahrs 1979; Stearns and Quan 1970; Greenall et al. 1985; Gérard et al. 2001). Patients developing inguinal nodal disease invariably do so in the ipsilateral groin (Gérard et al. 2001), unless the tumour is in the midline allowing bilateral nodal recurrence. Nodal involvement is rare if the primary tumour was $\leq$2 cm in maximum diameter but increased to 35 % when the tumour invaded into adjacent pelvic tissues (Boman et al. 1984). Nodal metastases are also more likely in poorly differentiated cancers (Boman et al. 1984).

11.8 Imaging in Anal Cancer

Available imaging modalities are computerised tomography (CT), magnetic resonance imaging (MRI), endo-anal ultrasound (EUS) and positron emission tomography (PET). Together they allow assessment of the local extent including involvement of other structures and spread to inguinal, pelvic and abdominal nodes and distant sites. Each modality has advantages and limitations, the most crucial being the difficulty in differentiating metastatic from uninvolved reactive nodes of equivalent size.

CT scans are conventionally used to image the pelvis and whole body, but some have recorded that CT failed to reveal an anal primary tumour in 10 of 40 patients, i.e. there were 25 % false negatives (Mistrangelo et al. 2012). MRI scans provide the most detailed anatomy of the primary tumour, the sphincter mechanism and the lymphatic network. MRI is now recommended for locoregional staging of anal cancer in European and NCCN guidelines and is routinely performed in the UK (NCCN 2015 - Benson et al. 2012; Glynne-Jones et al. 2010). A comparison of EUS and MRI (Otto et al. 2009) suggested that EUS may be superior to MRI in detecting small superficial tumours.

Anal cancer is FDG avid even in small tumours (1–2 cm), and PET has a high detection rate of the primary tumour of 90–100 % (Cotter et al.

2006; Nguyen et al. 2008; Winton et al. 2009). Hence positron emission tomography (PET)/CT is gaining ground as an initial staging modality since initial descriptions in 2005 and has been part of NCCN treatment guidelines since 2007.

11.8.1 Criteria for Identifying Involvement of Lymph Nodes

Suspicious perirectal and internal iliac nodes on imaging are rarely biopsied so there is significant risk of false positives. There is no international consensus regarding the normal limit for size in the diagnosis of pelvic and inguinal nodal metastases from pelvic tumours. Size criteria also are different for different histologies and different primary sites (Koh et al. 2006). Authors discussing inguinal node recurrences do not clearly define their CT and MRI criteria to determine uninvolved inguinal lymph nodes (Matthews et al. 2011; Ortholan et al. 2012), nor is this feature clear from any of the randomised trials.

Many use 10 mm as a conventional cut-off. Other criteria such as shape, signal intensity pattern, central necrosis and the degree of contrast enhancement in pelvic nodes are often useful but have not been validated.

11.9 Co-registration for Planning

CT is usually ideal for planning in the pelvis, because it provides anatomical detail with the electron density data essential for dosimetry. It is vital to use contrast with the correct windows and take advantage of multiple orthogonal views (axial, sagittal and coronal) to delineate target volumes (Steenbakkers et al. 2005). It is also advisable to involve your radiologist in person in the planning session. However, contouring the target volume with CT alone is difficult and may provide a major source of errors. A major advantage is that contouring vessels on the CT image can now be used as a surrogate for lymph node localisation and can offer a more precise and individualised elective nodal target delineation compared to that achieved previously.

Advances in the quality of MRI and PET/CT now allow us to determine areas of gross tumour volume more accurately and to delineate tumour and organ boundaries more confidently. The conventional planning CT scan can be co-registered with either diagnostic quality MRI imaging or PET.

11.9.1 MRI

There is little movement within the pelvis, and MRI allows the bone structures of the pelvis to be readily co-registered. Diffusion-weighted sequences are particularly useful to delineate the tumour extent, because it is a squamous cell carcinoma. But it is still vital to have the appropriate and high-resolution small field of view. MRI provides excellent anatomical definition of these structures and the components of the sphincter mechanism (see Figs. 11.1 and 11.2) and defines involvement of normal-sized lymph nodes seen on CT. If MRI is to be co-registered, it is important to use a hard couch top to avoid posterior distortion.

11.9.2 PET

An Italian group has found PET/CT useful in target volume delineation (Krengli et al. 2010). PET/CT can define both primary and nodal sites of metabolically active tumour (Bannas et al. 2011), although to our mind PET shows a larger extent than MRI. It is important to note that the positive predictive value of PET for lymph nodes is high, but the negative predictive value is less secure.

11.10 Consensus Atlas

The area of most potential variability and error is between individual radiation oncologists outlining of target and normal tissue volumes. There is a clear role for an agreed consensus/atlas (Nijkamp et al. 2012) with continuous education, training

and cross-collaboration of the radiation oncologist with other specialties especially radiologists to reduce the degree of variability in tumour delineation and enhance the quality assurance within radiotherapy trials. The proposed atlas provides a delineation protocol for anal cancer.

The delineation of pelvic nodes radiologically is described in some relevant pelvic nodal atlases (Portaluri et al. 2005; Taylor et al. 2007; Lengele and Scalliet 2009; Japan Clinical Oncology Group 2010), but these are not sufficiently relevant to anal cancer. It is also curious that there are several different algorithms, which have been proposed for contouring the same pelvic nodes in prostate cancer, anorectal cancer and cervical cancer – and no consensus. The RTOG made suggestions specifically for the definitive treatment of anal cancer based on a consensus of nine experts in radiation oncology (Myerson et al. 2009) partly because of inaccurate contouring in some cases enrolled on RTOG 0529 but confined guidance to elective nodal volumes.

There is a tendency with each new atlas to design larger and larger volumes with more extensive fields and more complex methods, but there is no evidence yet that these developments improve outcome. Hence, there is no widely accepted consensus on proper selection and delineation of lymph node areas for definitive chemoradiation. In general algorithms defining CTV close to bone landmarks carry less variation than those which rely on soft tissue landmarks – particularly landmarks which vary such as the bladder. We have therefore tried to both simplify the structure to produce more compact CTVs and at the same time design individualised targets appropriate to the site of origin and clinical stage. Even then, these targets will vary according to the tumour size and stage, the sex and the individual shape of the patient.

11.11 Clinical Assessment of Primary Tumour

Clinical assessment of the tumour is essential. Information is required on the size and position of the tumour within the anus and whether it is infiltrating or exophytic. It is important to measure the distance the tumour extrudes beyond the anal margin and how far it extends cephalad (i.e. whether it extends above or below the dentate line and levators). Additionally females require a vaginal examination particularly in anterior tumours to assess if the vagina itself is directly involved or if the tumour is palpable by involving the rectovaginal septum. However should pain prevent per rectal (PR) examination, an EUA (examination under anaesthetic) should be considered. It is recommended that the treating radiation oncologist is present during the procedure to ensure that precise measurements are noted, facilitating target volume delineation and treatment planning. We consider a clinical proforma an absolute essential for accurate target delineation (clinical proforma – see Appendix 11.2).

11.12 Clinical Assessment of Inguinal Nodes

Clinical assessment of inguinal nodes is also required. Involved nodes tend to be found medially, just lateral to the pelvic tubercle, and are firm, almost analogous to a hard marble. Fixed nodes may be palpated more laterally beyond these areas in patients presenting with more extensive T3/T4 tumours.

11.13 Details of Imaging Proforma for Each Patient (Appendix 11.3)

An imaging proforma based on MRI should be completed by the MDT radiologist.

11.14 Planning

The use of a planning CT scan with target volumes delineated (primary and nodal) on each slice- and pixel-based inhomogeneity correction is considered standard practice. There are arguments for planning both in the supine and prone positions. We recommend patients should be

simulated and planned in the supine position because it is more stable and reproducible without any custom immobilisation device. Although we accept that local practices may vary, some prefer that patients with very exophytic tumours extending well outside the anal canal are planned prone and bolus used. Hence, appropriate immobilisation and a treatment position with which the centre is familiar should ideally be used.

11.15 Patient Data Acquisition

The CT scan limits are the superior aspect of L3 superiorly to the mid-femur or 6 cm below a radio-opaque marker/ball bearing indicating the anal verge or the inferior extent of tumour, whichever is more inferior and can be wired. The recommended slice thickness is 3 mm. Immobilisation devices such as Vac-Lok are recommended. All patients must be scanned with a comfortably full bladder (>250 ml). For optimal set-up techniques, it is important to consider patient interventions which promote ideal imaging and the patient keeping still, i.e. advice on diet, bowel preparation, pain relief and even methods of relaxation.

11.15.1 Contrast

Intravenous contrast is mandatory unless contraindicated by virtue of allergy or renal impairment. Small bowel contrast is recommended if the small bowel is intended to be contoured as an OAR. Gastrografin 20 ml in water 45–60 min prior to the planning scan or dilute contrast agents in routine diagnostic use are useful. An intravaginal marker should be used in females.

11.15.2 Bolus

Application of bolus is more difficult if the patient is placed supine. If there are concerns, to ensure adequate dose at the anal margin, as an alternative to bolus, the patient's buttocks can be taped together at the time of simulation and for treatment, although this position may not be easily reproducible. Bolus is not recommended to the skin overlying the groins unless tumour extends to skin surface, because the oblique incidence of the IMRT beams usually increase the superficial dose. Anyway we aim to spare the most superficial 5 mm of skin unless there are fungating nodes in the groin. However, it may be important to provide adequate photon fluence in air near the skin in these areas to account for set-up variations.

11.16 Definition of Target Volumes

Definition of target volumes and OARs has been standardised in ICRU reports 50 (ICRU 50 1993) and ICRU 62 (ICRU 62 1999).

Details of imaging proforma for each patient (Appendix 11.3)

Additional information will be available from CT, MRI and PET/CT.

11.16.1 The Primary Gross Tumour Volume

The primary gross tumour volume (GTVp), and the nodal GTV (GTVn), i.e. all involved nodal regions (on imaging or biopsy proven), should be defined and outlined on each CT slice, using all radiological imaging available, and ideally co-registered with the planning scan. The overall GTV is defined but described separately by all macroscopic tumour together with the entire circumference of the anal canal wall (GTVp) and the involved nodes' GTVn. GTVp will extend from either the ball-bearing marker or the demarcated inferior aspect of the tumour extending below the anal margin – whichever is more inferior. Where the primary tumour cannot be identified on the CT images – often Tx (excisional biopsy with positive margins but no macroscopic disease), the anal sphincter complex, will be contoured (in addition to any observed perianal tumour extension) and will be designated as the CTVa.

Whether using a single-phase DP-IMRT or two phases (IMRT and conformal), it is

recommended that all phases of treatment are planned at the same time, as the primary site and even involved lymph nodes may regress rapidly on commencement of CRT.

11.16.2 The Primary Tumour Clinical Target Volume (CTV)

The clinical target volume (CTV) represents extension around tumour and subclinical disease which cannot be seen or imaged. The CTV needs to encompass gross primary tumour CTVp, involved lymph nodes and lymph node stations potentially at risk of microscopic disease (CTVn), the mesorectum (CTVm) and the entire anal canal (CTVa). Defined landmarks should be easy to recognise.

A CTVp should be created by expanding the GTVp anisotropically by 10 mm radially to cover microscopic spread and by 15 mm superiorly and 15 mm inferiorly. This volume is created according to a computer-generated algorithm and therefore does not follow anatomical landmarks. However, anatomical boundaries should be respected, so CTVp in air, bone or any tissues, normally considered natural barriers to tumour infiltration and hence not at risk for microscopic spread, should be manually edited to avoid overlap into these nontarget areas.

11.16.3 The Primary Tumour Planning Target Volume (PTV)

A further expansion to allow for set-up and day-to-day internal organ movement should be created. 10-mm expansion is recommended on CTVps to generate these PTVs. Very little data exists for the use of IGRT and adaptive treatment plans for anal cancer. It may be necessary to insert fiducial markers into or close to the primary tumour and the anal margin to track the movement of these to provide confidence regarding tumour position. Alternatively cone beam CT scanning may be used with off-line correction. Due to the relatively poor visualisation with cone beam imaging, visualisation of the primary tumour may be difficult, and a surrogate of potential tumour movement might be required, for example, the degree of rectal gas distortion. Daily imaging and a knowledge of the department's systematic and random errors may allow the clinician to reduce the CTV to PTV margin to 5–7 mm particularly for patients treated in the supine position. Hence, each department should audit its margin of errors to ensure the PTV margins allocated are reasonable.

11.16.4 Elective Volumes

11.16.4.1 Anal Canal CTV (CTVa)

We believe that the whole anal cancer should be considered at risk of microscopic disease and, if not covered in the initial GTV expansion, should be delineated separately and then expanded to form part of the CTV, i.e. CTVa alongside the primary tumour CTVp to create the primary tumour PTVp + a. This is rarely the case as expansion of 15 mm caudal and cephalad means the anal canal will invariably be included in the CTVp, unless the tumour involves the rectum above the dentate line. The superior extent of the anal canal can be determined on MRI scans and is usually defined superiorly by a line joining the tip of the coccyx and the most inferior aspect of the pubis. However, we do not agree with the Australasian atlas (Ng et al. 2012) that the entire ischiorectal fossa should be contoured as CTVa.

11.16.4.2 Mesorectum (CTVm)

The perirectal mesorectal region should be contoured to include perirectal nodes, but the lower part of the mesorectum is poorly visualised on CT and is even less clear more superiorly, particularly anteriorly, because other structures are not available to define its boundaries. Hence there may be a need to be more generous anteriorly. The archives suggest that in anal cancer Papillon did not formally treat the lymph nodes – although he used arc therapy. He is said to have commented that recurrences were always within the reach of his finger (i.e. 6–9 cm) and probably reflect recurrent mesorectal lymph nodes. We do

not therefore recommend treatment of the upper portion or the entire mesorectum unless tumour extends to the peritoneal reflection and enlarged presacral nodes are imaged. The lower portion of the mesorectum to a maximum distance of 5 cm cephalad to the tumour should be sufficient for CTVm unless tumour extends from the anal canal above the dentate line. We suggest that CTVm = mesorectum with no further expansion + 10 mm for PTV will then suffice.

11.17 Elective Nodal Volumes (CTVn)

Much of the basis of pelvic atlases and anatomical details have been defined in patients with cervical cancers, where it was apparent that conventional techniques for cervix irradiation based on bone references often failed to encompass the planning target volume (Zunino et al. 1999).

Inclusion of the common iliac nodes, and full coverage of the entire internal iliac nodal system, by defining an upper CTV border at, or near, the sacral promontory (Das et al. 2007; Wright et al. 2010) remains an area of discussion. In the RTOG and European CTV recommendations, the elective nodal regions include common iliac nodes up to the 5th lumbar vertebra to a dose of 45 Gy. Yet, common iliac nodal involvement appears rare (1 %), and few recurrences are observed in this site. Standard inclusion within the radiotherapy field may therefore not be justified. In the Norwegian National Population Cohort (Bentzen et al. 2012), the standard superior border was at the level of the lower border of the SI joints. Only if the primary cancer extended into rectal mucosa or the nodes were considered involved did the field extend to the sacral promontory. Thus despite the fact that approximately 50 % of patients had a field extending to the lower end of the SI joint, no recurrences were observed above this treatment field (Bentzen et al. 2012).

In ACT II the superior aspect of the initial APPA field was defined as 2 cm *above* the inferior aspect of the sacroiliac joints, i.e. usually at the S1/S2 interface, and with the beam divergence, the estimated dose to the common iliac nodes was small (Aggarwal et al. 2012). Very few isolated recurrences are observed above this field in the ACT II dataset (Sebag-Montefiore et al. 2012).

We therefore recommend that only the more advanced (T3/T4) cancers with presacral nodes may need higher superior border extending the nodal/elective CTV to the origin of external and internal iliac nodes.

Normal-sized but potentially involved nodes cannot be reliably seen on CT or routine pelvic MRI scans. Three-dimensional lymph node mapping with the aid of lymphangiograms has been used to generate a nodal CTV guideline for gynaecologic malignancies (Chao and Lin 2002). Meticulous pioneering work by Taylor et al. (2005 and 2007) proposed the targeting of pelvic lymph nodes determined upon their predicted relationship to the pelvic vasculature which can be easily identified on CT scan especially following the administration of intravenous contrast.

The use of a margin of 7 mm was shown to cover 91, 98, 94 and 98.6 % of the common iliac, medial external iliac, anterior external iliac, and internal iliac lymph nodes, respectively. Although this study was performed in gynaecological cancer, it has gained acceptance as the basis for lymph node outlining in many pelvic cancers including high-risk prostate, bladder and penile cancer. The outlining of the vessels and subsequent expansion according to Taylor was used by the Australasian Gastrointestinal Tumour Group (AGITG) to form the basis of their atlas for IMRT planning of anal cancer (Ng et al. 2012). We have therefore recommended a 7-mm margin for elective nodal CTV around vessels.

11.17.1 External Iliac Nodes

The external iliac vessels extend anteriorly along the pelvic sidewall as they descend through the pelvis. In terms of definition, the external iliac nodes refer to those above the inguinal ligament distinguishing them from the inguinal nodes which lie below. The lateral external nodes are less well covered using the 7-mm margin. Hence

a wider 10-mm margin following the iliopsoas margin should be considered. Consideration should be given to contouring the superficial iliac circumflex vein in clinically node-positive patients.

11.17.2 Internal Iliac Nodes

The internal iliac vessels sometimes have subdivisions which should be outlined and then expanded by 7 mm. Care should be taken to extend the target volume to the pelvic sidewall.

11.17.3 Obturator Node

The obturator node is not well covered using a simple expansion from the pelvic blood vessels. To cover this nodal group, a strip of 15–18 mm along the pelvic sidewall connecting the external iliac nodes to the internal iliac nodes is recommended.

11.17.4 Inguinal Lymph Nodes

Agreed boundaries of the inguinal region and the position of uninvolved inguinal lymph nodes are difficult to determine on CT imaging alone. We agree with the RTOG suggestion that the inguinal region should be contoured as a compartment (Myerson et al. 2009), rather than just using vessels. The inguinal node positions were not defined within the Taylor proforma (Taylor et al. 2007). The original ACT II protocol called for a 3-cm margin to field inferior to the anal verge treating the inguinal and femoral nodes inferiorly to this distance. This would seem to extend unnecessarily far inferiorly.

The inguinal nodes lie below the inguinal ligament (not easily visible on CT scans). We consider the inguinal compartment as extending from the superior aspect of the femoral head to 1–2 cm below the junction of the saphenous vein and femoral vein. The superficial inguinal lymph nodes form a T-shape: one row (the horizontal group) is running parallel to and below the inguinal ligament, while the other superficial row (the vertical group) is arranged vertically along the femoral/great saphenous vein. We have rarely if ever seen clinical involvement of the femoral nodes in anal cancer, unless the inguinal nodes are already grossly involved, and do not therefore recommend routine contouring of the femoral nodes.

Sartorius may be a difficult landmark. Anteriorly, the skin is not part of the volume, and the first 5 mm can be spared except in case of skin invasion from involved nodes. We prefer to use a faint line anteriorly defining the fascia and the spermatic cord more medially. Posteriorly is the deep femoral vein. The edge of the iliopsoas muscle defines the lateral border, and the edge of the adductor longus muscle, the medial border. Again there is considerable variability on the medial aspect.

The RTOG 0529 RT guidelines recommend that if there are no positive nodes (on biopsy or imaging) in the inguinal/femoral nodal region, the caudad extent of elective CTV groin coverage should be at the level of the takeoff of the profunda femoris vessels (approximately the inferior aspect of the obturator foramina). The caudad extent of the inguinal region (CTVC) should be 2 cm caudad to the saphenous/femoral junction (which usually lies 4 cm below and 4 cm lateral to the pubic tubercle) and cranially should extend to the upper edge of the superior pubic rami.

11.18 Planning Target Volume (PTV)

The RTOG 0529 acknowledges that set-up variations can occur and recommend a PTV margin of about 10 mm to be appropriate. Specifying margins around a CTV for PTV is by no means an exact science.

We distinguish between primary CTVp (anisotropic expansion as above) and involved nodal CTVn, where we recommend an isotropic 10-mm expansion to be added to generate the PTV. In contrast, the elective nodal CTVs are only expanded by 5 mm.

11.19 Summary of Volume Definitions

The AGITG guidelines and atlas for IMRT in anal cancer are also available for a pictorial atlas of some of these volumes (Ng et al. 2012).

- *GTVp* = includes the gross primary and anal tumour volume
- *GTVn* = includes all involved nodal regions
- GTV combined (*GTV comb*) = GTVp + GTVn
- *CTVp* = GTVp + 10-mm expansion radially and 15 mm sup/inf
- *CTVa* = the entire anal canal
- *CTVp* + *a* = includes the GTVp and the entire anal canal from the anorectal junction to the anal verge including the internal and external anal sphincters
- *CTVn* = includes GTVn with a 10-mm expansion
- *CTVn elective* = uninvolved nodal regions
  CTVcombined(*CTVcomb*) = CTVp(+a) + CTVn
  PTV = *CTV comb* + 10 mm circumferentially
  PTV elective = *CTVn elective* + 7-mm margin

11.20 The Pelvic Organs at Risk (OARs)

The pelvic organs at risk (OARs) include the anal canal, small bowel, bladder, skin, external genitalia/perineal skin (penis and scrotum in men and vulva in women), iliac crests (from the bony top to the superior part of acetabulum inferiorly), femoral heads (from the bony top to the lesser trochanter inferiorly) and lumbosacral plexus. It is recommended that all these radiation-sensitive structures are outlined as part of the planning process by the radiation oncologist. Guidelines on dose constraints may be found per the RTOG 0529 closed study protocol (http://www.rtog.org). The tolerance of these structures will be contextual in that exceeding some OAR doses is never acceptable, while others are relative. Imaging an organ does not necessarily mean that IMRT plans can be designed to spare it, because the organ's location with respect to the target may not allow this. Nevertheless, objectives (desired achievements) and constraints (necessary achievements) will need to be set for clinical targets and critical structures with priorities or weighting for these structures.

11.20.1 The Anal Canal

The anal canal is a radiation-sensitive structure. Its function is compromised by high doses of radiotherapy leading to late complications (Buettner et al. 2012; Peeters et al. 2006; Heemsbergen et al. 2006; Vordermark et al. 1999) and occasionally necessitating a stoma. In some ways it should be considered as an OAR. However, this is also the site of primary disease, and it is therefore not possible to restrict the dose prescribed to the anal canal as this may compromise disease control.

11.20.2 Lumbosacral Plexus

Some have contoured the lumbosacral plexus (Badin et al. 2008) from the L4–5 interspace to the level of the sciatic nerve in the greater sciatic foramen caudal to piriformis.

11.20.3 Femoral Head and Neck

The entire femoral head and neck should be contoured using bone windows down to the lesser trochanter and considered as an organ at risk. The incidence of insufficiency fractures in the hips and femoral heads and late pathological fracture has been shown to be increased after pelvic radiotherapy especially in women (Baxter et al. 2005; Tomaszewski et al. 2012). The present authors have experience of hip fractures in this elderly female treated population.

11.20.4 Bone Marrow

Mell and colleagues (Mell et al. 2008) showed that the volume of bone marrow receiving 10–20 Gy was associated with increased toxicity. Functional bone marrow is difficult to visualise

but can be assisted with the use of dynamic MRI sequences which are fused to the planning CT. A recent UK study of IMRT suggested that haematological toxicity could be minimised by using the low superior field border (standard in UK), and therefore sparing the bone marrow (Petkar et al. 2012). Our recommendations do not give concern for overall pelvic bone marrow doses, but there may be implications of IMRT on bone marrow volume irradiated – and particularly the impact of using VMAT as there will be a low-dose bath.

11.20.5 Urinary Bladder

The external outline of the bladder wall should be contoured. Patients should have a comfortably full bladder pretreatment (≥250 ml). This may help move small bowel out of the pelvis and reduce toxicity, as the bladder is relatively radioresistant compared to the small bowel.

11.20.6 Small Bowel

There is a significant correlation between small bowel volumes receiving at least 15 Gy and acute grade 3 gastrointestinal toxicity (Robertson et al. 2010).

Tolerance of small bowel reflects the volume of small bowel receiving 15 Gy (threshold of 100–200 cm^3) – and 30 and 50 Gy (thresholds of 35–300 cm^3) (Martin et al. 2010). Devisetty found a significant correlation between dosimetric parameters and acute GI toxicity for a V30 >450 cm^3 (33 % GI toxicity) (Devisetty et al. 2009).

Since small bowel is a mobile organ which extends into the upper abdomen, it is not practical to outline the whole organ. Some contour small bowel from the rectosigmoid junction to at least 20 mm above the superior extent of any PTV as individual bowel loops. We consider that the small bowel should be contoured tightly around the bowel wall as individual bowel loops to 3 cm above the PTV. The RTOG recommended three separate dose volume constraints for small bowel (Kachnic et al. 2013). In contrast, we have 4 constraints outside the PTV (<200 cm^3 to more than 30 Gy, <150 cm^3 to more than 35 Gy, <30 cm^3 to more than 45 Gy and none to more than 50 Gy).

11.20.7 External Genitalia and Perineum

In males the testes are highly sensitive to the effects of radiation, and it is unlikely that an IMRT plan would be sufficiently conformal to spare the testis to prevent loss of spermatogenesis. We contour from the base of the penis inferiorly. Little data exists regarding scrotal skin tolerance as a specific organ of risk; however, the development of skin toxicity around the external genitalia is one of the most distressing side effects of anal cancer RT. In females, there is an even greater lack of data regarding tolerance of clitoris, labia majora and labia minora. The vulva and soft tissues should be contoured up to the level of the mons pubis.

11.20.8 Radiotherapy Dose Prescription

Elective – 42 Gy in 28 fractions (1.5 Gy per fraction) in 5.5 weeks

Macroscopic disease – 50.4–52 Gy in 28 fractions (1.8–1.86 Gy per fraction) in 5.5 weeks

11.21 Discussion

The RTOG guidelines are a one-size-fits-all consensus of experts for elective volumes (Myerson et al. 2009). However, anal cancer is not really a single disease entity but has different modes of spread depending on whether the tumour is large or small; demonstrates involved nodes or not; is lateral, anterior or posterior; or lies in the upper canal/extends above the dentate line or low canal or beyond the margin. Hence, the CTV needs customising according to clinical and MRI staging and tumour site. Much of the present guidance is

merely judgement, based on experience and not an exact science. Each recommendation will be trading off perceived advantages and disadvantages, but the delineation needs to be in the main reproducible. However, it is not designed to be a rigid framework, because diagnosing a clinically involved node in a particular site may persuade the radiation oncologist to extend the CTV beyond our recommended constructs.

Conclusions

In this chapter we have presented guidelines for imaging and contouring gross disease and elective nodal and anatomical volumes for target delineation in anal cancer for EBRT based on stage and location, which represents our 'index' suggested algorithm. We recommend both a clinical proforma (Appendix 11.1) and an imaging proforma (Appendix 11.2) and a planning proforma as an absolute essential for accurate target delineation, for quality assurance and to facilitate audit. We hope these proposals will decrease uncertainties and observer variation, while also facilitating training. In future, we also need to agree exacting dose constraints by European consensus.

We are not aware of any ongoing phase III trials for anal cancer in any country. We hope therefore that this chapter and the recommendations will be helpful in combination with the RTOG and Australasian atlases – each has strengths and limitations. Ongoing education and real-time quality assurance will be essential for future phase III studies incorporating IMRT or VMAT. But it should be stressed that there is no 'gold standard' for target delineation in anal cancer. All recommendations will inevitably change, develop and be modified till we have international consensus.

Appendices

Appendix 11.1

APPENDIX 1
Proforma for documenting initial clinical extent of anal cancer: please draw on diagrams from exam under anaesthetic (EUA) or clinical and/or MRI measurements

Patient Number ☐☐☐☐☐☐☐☐ Initials ☐☐☐
EUA yes ☐ no ☐

Clinical staging

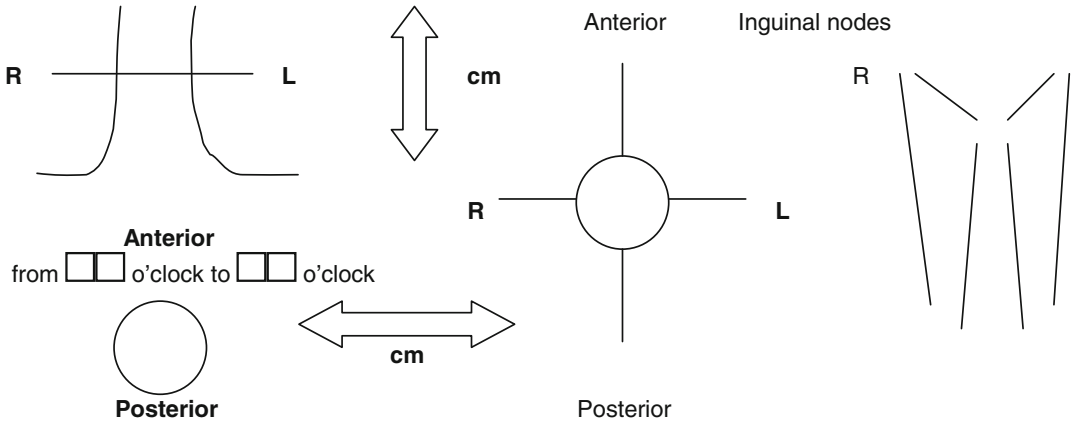
Site Canal ☐ Margin ☐ Rectum ☐ Not known ☐

T* stage T1 ☐ T2 ☐ T3 ☐ T4 ☐ TX ☐

N* stage N0 ☐ N1 ☐ N2 *(canal only)* ☐ N3 *(canal only)* ☐ NX ☐

caudal extent above dentate line ☐ or **below dentate line** ☐

Canal tumours **Caudal Extent** **Margin tumours** **Nodes**



Pathology **Tumour type** Squamous ☐ Basaloid ☐

Differentiation Poor ☐ Moderate ☐ Well ☐

Margins N/A biopsy ☐ Not clear ☐ Excision Clear ☐

***Staging of Anal Cancers – TNM**

	Anal Canal	**Anal Margin**
T1	2 cm or less in greatest dimension	2 cm or less in greatest dimension
T2	> 2 cm but ≤5 cm in greatest dimension	>2 cm but ≤ 5 cm in greatest dimension
T3	>5 cm in greatest dimension	>5 cm in greatest dimension
T4	Tumour of any size invading adjacent organ/s e.g. vagina, urethra, bladder (sphincter muscle involvement alone is not T4)	Tumour invades deep extradermal structures i.e. muscle, bone etc.
N0	No regional lymph node metastasis	No regional lymph node involvement
N1	Peri-rectal lymph node involvement	Ipsilateral inguinal lymph node involvement
N2	Unilateral internal iliac &/or inguinal lymph node/s	-
N3	Peri-rectal & inguinal lymph nodes &/or bilateral internal iliac &/or inguinal lymph node involvement	-

Appendix 11.2

TNM staging for anal canal cancer

Primary tumour (*T*)	
Tx	Primary tumour cannot be assessed
Tis	Carcinoma in situ [Bowen's disease, high-grade intraepithelial lesion (HSIL), anal intraepithelial neoplasia (AIN) II–III]
T1	Tumour less than 2 cm in greatest dimension
T2	Tumour between 2 and 5 cm in greatest dimension
T3	Tumour more than 5 cm in greatest dimension
T4	Tumour invading adjacent organs [vagina, urethra, bladder, sacrum]
Regional lymph nodes (*N*)	
NX	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in perirectal nodes
N2	Metastasis in unilateral internal iliac and/or inguinal nodes
N3	Metastasis in perirectal and/or bilateral internal iliac or inguinal nodes
Distant metastasis (*M*)	
M0	No distant metastasis
M1	Distant metastasis

Appendix 11.3: MRI Protocol for ANAL CANCER – Acquisition and Reporting

High-resolution MRI is an accurate tool for locoregional staging and response assessment. MRI provides an accurate depiction of tumour site and tumour size, defines the relationship of the tumour to adjacent structures and enables locoregional lymph nodes to be assessed.

The aim in anal cancer is to:

- Identify patients with T3- or T4- and/or node-positive disease who have a poorer prognosis
- Define the locoregional extent of disease to assist radiotherapy planning
- Define the locoregional extent and degree of disease regression post therapy in order to tailor further treatment

Patient Preparation

In terms of patient preparation, we do not advocate the routine use of bowel cleansing (purgative or enema) or luminal distension. The use of an antiperistaltic (Buscopan or glucagon IM) may be helpful.

Table 11.1 MRI acquisition

Pelvis	Sequences and orientation
5 mm/no gap	T1 axial
To enable evaluation of locoregional lymphadenopathy and pelvic metastatic disease	T2 axial
	T2 sagittal
	DWI axial: $b=0$, 100, 1,000, 1,200 s/mm^2
Primary tumour	
3 mm/no gap	STIR and T2 axial and coronal
To enable evaluation of tumour extent and involvement of local structures	T2 axial and coronal
	STIR axial and coronal
	DWI axial: $b=0$,100, 500, 800 s/mm^2

The posttreatment MRI sequences should match the orientation and angles of the pretreatment MRI

Table 11.2 Node size criteria. The following maximal size criteria are used to define the upper limit of normal nodes

Sites	Size (mm)
Perirectal	5
Inguinal	15
External iliac	10
Internal iliac	7
Common iliac	9

Sequences

Imaging may be performed on 1.5- or 3-T systems. Following localisation sequences, pelvic and tumour sequences are acquired. Pelvic sequences provide an overview of the entire pelvis and locoregional nodes reflecting the lymphatic drainage of the tumour. The axial sequences are from the level of L5/S1 to below the symphysis pubis. Tumour sequences are taken axial and coronal to the anal tumour and canal.

Table 11.1 summarises the sequences applied. These include T1-weighted, T2-weighted and diffusion-weighted sequences.

MRI Reporting

MRI reporting should reflect the site and locoregional extent of the tumour and the presence and site of nodal disease and provide the maximal tumour dimension (RECIST 1.1.) and an overall stage (TNM).

At baseline, reports should include:

- .Involvement of the anterior urogenital triangle
- Lymph node disease including the location and size of nodes
- TNM stage
- RECIST

Posttreatment reports should include:

- Site of tumour (low, mid- or upper anal canal)
- Size (maximal transaxial dimension) of the primary tumour
- Maximal length of the primary tumour
- Height of tumour from the anal verge
- Morphologic appearance of tumour including any necrotic component
- Extent of extramural spread, which should be reflected by descriptors of locoregional extent:
  - Involvement of the rectum
  - Involvement of the levator ani
  - Involvement of the ischiorectal fossa
  - Involvement of the anterior urogenital triangle
  - Lymph node disease including the location and size of nodes
  - TNM: tumour downstaging, lymph node downstaging
  - RECIST response
  - Presence of post-CRT changes: fibrosis, desmoplasia, inflammatory change, submucosal oedema and necros*is*

RECIST Response

This is as per RECIST 1.1 and the maximal tumour length is used.

Appendix 11.4

Lymph node volumes should follow vessels as defined by contrast CT using asymmetric manual expansions to nodes along tissue planes as defined in the table below from Taylor et al. *Clinical Oncology*. 2007;19:542–550

Lymph node group	Recommended margins
Common iliac	7-mm margin around vessels; extend posterior and lateral borders to psoas and vertebral body
External iliac	7-mm margin around vessels; extend anterior border by additional 10 mm anterolaterally along iliopsoas muscle to include lateral external iliac nodes
Obturator	Join external and internal iliac regions with 18-mm-wide strip along pelvic sidewall
Internal iliac	7-mm margin around vessels; extend lateral borders to pelvic sidewall
Presacral	10-mm strip over anterior sacrum
Inguinal	Not described

Appendix 11.5: Algorithm for Planning According to Site and Stage

1. Anal canal – T1/T2			
Site: *anal canal*	Recommended GTV/CTV/PTV	Imaging	Additional
Stage T1,T2 N0[a] IMRT or VMAT or 3D conformal IMRT or VMAT	(i) GTV primary + 10 mm ant/post/laterally + 15 mm sup and inf = CTVp CTVp + 10 mm = PTVp (ii) CTVm mesorectal nodes to 5 cm CTVn = vessels + 7 mm External iliac, internal iliac obturator nodes from the level of S2 inferiorly (ACT II – 2 cm above the most inferior aspect of SI joints) Inguinal nodes as compartment (CTVm + CTVn) + 5 mm = PTVn	TRUS and/or MRI and CT scanning	Patient supine Fiducial markers only if involved field only for small T1 Anal canal (see Table 11.1) Nodes (see Table 11.2)
B			
Stage T1,T2, N1[b] (metastasis in lower perirectal nodes) IMRT or VMAT or 3D conformal	(i) GTV primary + 10 mm ant/post/laterally + 15 mm sup and inf = CTVp CTVp + 10 mm = PTVp (ii) CTVm mesorectal nodes to superior rectal artery + presacral nodes CTVn = vessels + 7 mm Pelvic nodes below bifurcation of common iliac vessels, i.e. external iliac, internal iliac, obturator nodes Inguinal nodes as compartment (CTVm + CTVn) + 5 mm = PTVn	TRUS and/or MRI and CT scanning PET/CT recommended	Patient supine Anal canal (see Table 11.1) Nodes (see Table 11.2)
C			
Stage T1,T2, N2–N3[c] (N2-metastasis in unilateral internal iliac and/or inguinal nodes or N3) IMRT or VMAT or 3D conformal	(i) GTV primary + 10 mm ant/post/laterally + 15 mm sup and inf = CTVp CTVp + 10 mm = PTVp (ii) GTV nodes + 10 mm = CTVn (iii) CTVm mesorectal nodes + presacral nodes CTVn = vessels + 7 mm Pelvic nodes below bifurcation of common iliac vessels, i.e. external iliac, internal iliac, obturator nodes Inguinal nodes as compartment extending inferiorly if involved superficial inguinal nodes (CTVm + CTVn) + 5 mm = PTVn	TRUS and/or MRI and CT scanning PET/CT highly recommended	Patient supine Anal canal (see Table 11.1) Nodes (see Table 11.2)

2. Anal canal – T3/T4			
Anal canal/anal margin/rectum			
C			
Stage T3,T4, N0–N3 (N2-metastasis in unilateral internal iliac and/or inguinal nodes or N3) IMRT or VMAT or 3D conformal	(i) GTV primary + 10 mm ant/post/laterally + 15 mm sup and inf = CTVp CTVp + 10 mm = PTVp (ii) GTV nodes + 10 mm = CTVn (iii) CTVm mesorectal nodes + presacral nodes CTVn = vessels + 7 mm Pelvic nodes below bifurcation of common iliac vessels, i.e. external iliac, internal iliac, obturator nodes Inguinal nodes as compartment extending more inferiorly if involved superficial inguinal nodes (CTVm + CTVn) + 5 mm = PTVn	TRUS and/or MRI and CT scanning PET/CT highly recommended	Patient supine Anal canal (see Table 11.1) Nodes (see Tables 11.2 and 11.3)

[a]T1/T2N0 and T1/T2N1 (inguinal nodes) anal margin treat as above A, except ensuring adequate coverage inferiorly
[b]Anal canal/rectum, i.e. anal canal extending >1 cm above dentate line, treat whole mesorectum/presacral area as for rectal cancer, but also the whole anal canal to the anal margin as CTV, i.e. treat as C above
[c]For T3/T4 cancers at any site – use algorithm C above even if cNO

Appendix 11.6: Anal IMRT Planning Sheet

Diagnosis: Squamous Cell Carcinoma Anus

Stage:.....

Date:.....

Patient Sticker

Organ	OAR / Target	Dose constraint	Dose received	Signature
PTV	95 % of PTV	Min 95 %		/
	99 % of PTV	Min 90 %		/
	50 % of PTV	Between 99 % – 101 %		/
	5 % of PTV	Max 105 %		/
	2 % of PTV	Max 107 %		/
				/
Small Bowel	>30 Gy	<200 cc		/
	>35 Gy	<150 cc		/
	>45 Gy	<20 cc		/
	>50 Gy	0 cc		/
				/
Femoral Heads	>30 Gy	<50 %		/
	>40 Gy	<35 %		/
	>44 Gy	<5 %		/
Pelvic bone marrow/iliac crests				/
				/
Genitalia				/
				/
Bladder				/
				/

Table 11.3 Various guidelines for pelvic node CTV drawing

	Common iliac	External iliac	Internal iliac	Obturator
Portaluri et al. (2005)	Cranial: aortic bifurcation	Cranial: common iliac bifurcation (L5–S1)	Cranial: common iliac bifurcation (L5–S1)	Cranial: cranial sections of the obturator muscle
	Caudal: common iliac bifurcation	Caudal: femoral ring (disappearance of lateral muscles of the abdominal wall, artery becomes lateral)	Caudal: cranial sections of the coccygeal muscle	Caudal: superior margin inferior branch of the pubic bone
	Anterior: mesocolon	Anterior: fat of small bowel, deferent duct or round ligament	Anterior: bladder, uterus	Anterior: external iliac vein
	Lateral: psoas muscles	Lateral	Lateral	Lateral
	Posterior: sacrum	Cranial: psoas, int iliac vein, iliac bone, sacroiliac joint	Cranial: psoas muscle, int iliac vein, iliac bone, sacroiliac joint	Cranial: acetabulum
		Caudal: piriformis muscle, internal obturator muscle	Caudal: piriformis muscle, int obturator muscle	Caudal: internal obturator muscle
		Posterior	Posterior	Posterior: internal obturator muscle
		Cranial: ext iliac vessels	Cranial: sacral wing	Medial: bladder
		Caudal: pubic bone (superior branch)	Caudal: piriformis muscle	
		Medial: mesocolon, uterus, bladder	Medial: mesocolon, uterus, bladder	
Taylor et al. (2005, 2007)	7 mm around common iliac vessels, extending posterior and lateral borders to psoas and vertebral body	7 mm around ext iliac vessels, extending anterior border by additional 10 mm anterolaterally along the iliopsoas muscle to include lateral external iliac nodes	7-mm margin around int iliac vessels, extending lateral borders to pelvic sidewall	18-mm-wide strip along pelvic sidewall joining external and internal iliac regions
Shih et al. (2005)	2.0-cm expansion around the distal 2.5 cm of common iliac vessels superior to bifurcation	2.0-cm expansion around ext iliac vessels for 9 cm from common iliac bifurcation	2.0-cm expansion around int iliac vessels for 8.5 cm extending from common iliac bifurcation	Not specified
RTOG 0418	7 mm around common iliac vessels, with superior border at 7 mm below L4–L5 interspace	7 mm around ext iliac vessels, terminating at the level of the femoral head	7 mm around int iliac vessels	Not specified
Australasian atlas (Ng et al. 2012)	Not specifically recommended	7 mm around ext iliac vessels, from bifurcation of common iliac terminating at the level within the pelvis	7 mm around int iliac vessels, from bifurcation of common iliac terminating at obturator canal	From the acetabulum to obturator canal (3–5 mm)

References

Aggarwal A, Gayadeen S, Robinson D et al (2012) Clinical target volumes in anal cancer; calculating what dose was likely to have been delivered in the UK ACT II protocol. Radiother Oncol 103:341–346

Ajani JA, Winter KA, Gunderson LL et al (2008) Fluorouracil, mitomycin and radiotherapy vs fluorouracil, cisplatin and radiotherapy for carcinoma of the anal canal: a randomised controlled trial. JAMA 199:1914–1921

Allal JS, Mermillod B, Roth AD et al (1997) The impact of treatment factors on local control in T2-T3 anal carcinomas treated by radiotherapy with or without chemotherapy. Cancer 79(12):2329–2335

Badin S, Iqbal A, Sikder M, Chang VT (2008) Persistent pain in anal cancer survivors. J Cancer Surviv 2(2):79–83

Bannas P, Weber C, Adam G, Frenzel T, Derlin T, Mester J, Klutmann S (2011) Contrast-enhanced [(18)F] fluorodeoxyglucose-positron emission tomography/computed tomography for staging and radiotherapy planning in patients with anal cancer. Int J Radiat Oncol Biol Phys 81(2):445–451

Bartelink H, Roelofsen F, Eschwege F et al (1997) Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol 15:2040–2049

Baxter NN, Habermann EB, Tepper JE, Durham SB, Virnig BA (2005) Risk of pelvic fractures in older women following pelvic irradiation. JAMA 294(20):2587–2593

Beahrs OH (1979) Management of cancer of the anus. Am J Roentgenol 133:790–795

Benson AB 3rd, Arnoletti JP, Bekaii-Saab T et al (2012) Anal Carcinoma, Version 2.2012: featured updates to the NCCN guidelines. J Natl Compr Canc Netw 10(4):449–454

Bentzen AG, Guren MG, Wanderås EH, Frykholm G, Tveit KM, Wilsgaard T, Dahl O, Balteskard L (2012) Chemoradiotherapy of anal carcinoma: survival and recurrence in an unselected national cohort. Int J Radiat Oncol Biol Phys 83(2):e173–e180, Epub 2012 Mar 19

Bilimoria KY, Bentrem DJ, Rock CE, Stewart AK, Ko CY, Halverson A (2009) Outcomes and prognostic factors for squamous-cell carcinoma of the anal canal: analysis of patients from the National Cancer Data Base. Dis Colon Rectum 52(4):624–631

Boman BM, Moertel CG, O'Connell MJ et al (1984) Carcinoma of the anal canal. A clinical and pathologic study of 188 cases. Cancer 54:114–125

Buettner F, Gulliford SL, Webb S, Sydes MR, Dearnaley DP, Partridge M (2012) The dose–response of the anal sphincter region–an analysis of data from the MRC RT01 trial. Radiother Oncol 103(3):347–352

Chao KS, Lin M (2002) Lymphangiogram-assisted lymph node target delineation for patients with gynecologic malignancies. Int J Radiat Oncol Biol Phys 54(4):1147–1152

Chen YJ, Liu A, Tsai PT, Vora NL, Pezner RD, Schultheiss TE, Wong JY (2005) Organ sparing by conformal avoidance intensity-modulated radiation therapy for anal cancer: dosimetric evaluation of coverage of pelvis and inguinal/femoral nodes. Int J Radiat Oncol Biol Phys 63(1):274–281

Cotter SE, Grigsby PW, Siegel BA, Dehdashti F, Malyapa RS, Fleshman JW et al (2006) FDG-PET/CT in the evaluation of anal carcinoma. Int J Radiat Oncol Biol Phys 65(3):720–725

Das P, Bhatia S, Eng C et al (2007) Predictors and patterns of recurrence after definitive chemoradiation for anal cancer. Int J Radiat Oncol Biol Phys 68(3):794–800

Davey P, Saibil EA, Wong R (1996) Bipedal lymphography in the management of carcinoma of the anal canal. Br J Radiol 69(823):632–635

Devisetty K, Mell LK, Salama JK et al (2009) A multi-institutional acute gastrointestinal toxicity analysis of anal cancer patients treated with concurrent intensity-modulated radiation therapy (IMRT) and chemotherapy. Radiother Oncol 93(2):298–301

Flam M, John M, Pajak TF et al (1996) Role of mitomycin in combination with fluorouracil and radiotherapy and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized Intergroup Study. J Clin Oncol 14:2527–2539

Gay HA, Barthold HJ, O'Meara E, Bosch WR, El Naqa I, Al-Lozi R, Rosenthal SA, Lawton C, Lee WR, Sandler H, Zietman A, Myerson R, Dawson LA, Willett C, Kachnic LA, Jhingran A, Portelance L, Ryu J, Small W Jr, Gaffney D, Viswanathan AN, Michalski JM (2012) Pelvic normal tissue contouring guidelines for radiation therapy: a Radiation Therapy Oncology Group consensus panel atlas. Int J Radiat Oncol Biol Phys 83(3):e353–e362, Epub 2012 Apr 6

Gérard JP, Chapet O, Samiel S, Morignat E, Isaac S, Paulin C et al (2001) Management of inguinal lymph node metastases in patients with carcinoma of the anal canal: experience in a series of 270 patients treated in Lyon and review of the literature. Cancer 92:77–84

Glynne-Jones R, Northover JM, Cervantes A (2010) Anal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 21(Suppl 5):v8

Graf R, Wust P, Hilderbrant B et al (2003) Impact of overall treatment time on local control of anal cancer treated with radiochemotherapy. Oncology 65:14–22

Greenall MJ, Quan SH, Urmacher C, DeCosse JJ (1985) Treatment of epidermoid carcinoma of the anal canal. Surg Gynecol Obstet 161(6):509–17.7–92

Gunderson LL, Winter KA, Ajani JA et al (2012) Long-term update of US GI intergroup RTOG 98–11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol 30:4344–4351

Hartwig S, Syrjänen S, Dominiak-Felden G, Brotons M, Castellsagué X (2012) Estimation of the epidemiological burden of human papillomavirus-related cancers and non-malignant diseases in men in Europe: a review. BMC Cancer 12:30, Review

Heemsbergen WD, Peeters ST, Koper PC, Hoogeman MS, Lebesque JV (2006) Acute and late gastrointestinal toxicity after radiotherapy in prostate cancer patients: consequential late damage. Int J Radiat Oncol Biol Phys 66(1):3–10

Hightower BM, Judd ES (1967) Squamous cell carcinoma of the anal canal and anus: current status of therapy. Mayo Clin Proc 42:271

Hill J, Meadows H, Haboubi N, Talbot IC, Northover JM (2003) Pathological staging of epidermoid anal cancer for the new era. Colorectal Dis 5(3):206–213

Huang K, Haas-Kogan D, Weinberg V, Krieg R (2007) Higher radiation dose with a shorter treatment duration improves outcome for locally advanced carcinoma of anal canal. World J Gastroenterol 13(6):895–900

Hughes LL, Rich TA, Delclos L, Ajani JA, Martin RG (1989) Radiotherapy for anal cancer experience from 1979–1987. Int J Radiat Oncol Biol Phys 17(6): 1153–1160

ICRU (2010) Prescribing, recording and reporting photon-beam intensity-modulated radiation therapy (IMRT). ICRU report 83. ICRU, Bethesda.

ICRU (1993) Prescribing, recording and reporting photon beam therapy, ICRU Report 50. ICRU, Bethesda, Oxford University Press, Oxford.

ICRU (1999) Prescribing, recording and reporting photon beam therapy, ICRU Report 62 (Supplement to ICRU Report 50). ICRU, Bethesda, Oxford University Press, Oxford.

James RD, Glynne-Jones R, Meadows HM et al (2013) Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2×2 factorial trial. Lancet Oncol 14:516–524

Japan Clinical Oncology Group, Toita T, Ohno T, Kaneyasu Y et al (2010) A consensus-based guideline defining the clinical target volume for pelvic lymph nodes in external beam radiotherapy for uterine cervical cancer. Jpn J Clin Oncol 40(5):456–463

Jin F, Stein AN, Conway EL et al (2011) Trends in anal cancer in Australia, 1982–2005. Vaccine 29(12):2322–2327

Kachnic LA, Winter K, Myerson RJ et al (2013) RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 86:27–33

Koh DM, Hughes M, Husband JE (2006) Cross-sectional imaging of nodal metastases in the abdomen and pelvis. Abdom Imaging 31:632–643

Krengli M, Milia ME, Turri L, Mones E, Bassi MC, Cannillo B et al (2010) FDG-PET/CT imaging for staging and target volume delineation in conformal radiotherapy of anal carcinoma. Radiat Oncol 5:10

Kuehn PG, Eisenberg H, Reed JF (1968) Epidermoid carcinoma of the perianal skin and anal canal. Cancer 22:932–938

Leichman L, Nigro N, Vaitkevicius VK et al (1985) Cancer of the anal canal. Model for preoperative adjuvant combined modality therapy. Am J Med 78(2):211–215

Lengele B, Scalliet P (2009) Anatomical bases for the radiological delineation of lymph node areas. Part III: pelvis and lower limbs. Radiother Oncol 92(1): 22–33

Luna-Pérez P, Fernández A, Labastida S, Lira-Puerto V, Vázquez-Curiel JA, Herrera L (1995) Patterns of recurrence in squamous cell carcinoma of the anal canal. Arch Med Res 26(3):213–219, Review

Martin E, Pointreau Y, Roche-Forestier S, Barillot I (2010) Normal tissue tolerance to external beam radiation therapy: small bowel. Cancer Radiother 14(4–5):350–353

Matthews JH, Burmeister BH, Borg M, Capp AL, Joseph D, Thompson KM, Thompson PI, Harvey JA, Spry NA (2011) T1–2 anal carcinoma requires elective inguinal radiation treatment–the results of Trans Tasman Radiation Oncology Group study TROG 99.02. Radiother Oncol 98(1):93–98

Mell LK, Schomas DA, Salama JK et al (2008) Association between bone marrow dosimetric parameters and acute haematologic toxicity in anal cancer patients treated with concurrent chemotherapy and intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 71:1431–1437

Mistrangelo M, Pelosi E, Bellò M et al (2012) Role of positron emission tomography-computed tomography in the management of anal cancer. Int J Radiat Oncol Biol Phys 84(1):66–72

Myerson RJ, Garofalo MC, El Naqa I, Abrams RA, Apte A, Bosch WR, Das P, Gunderson LL, Hong TS, Kim JJ, Willett CG, Kachnic LA (2009) Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring atlas. Int J Radiat Oncol Biol Phys 74(3):824–830

National Comprehensive Cancer Network (NCCN) (2015) Clinical guidelines in oncology. Anal carcinoma, version 2. National Comprehensive Cancer Network. http:// www.nccn.org/professional/physicians_gls/pdf/analpdf. Accessed 2 February 2015

Ng M, Leong T, Chander S et al (2012) Australasian Gastrointestinal Trials Group (AGITG) contouring atlas and planning guidelines for intensity-modulated radiotherapy in anal cancer. Int J Radiat Oncol Biol Phys 83:1455–1462

Nguyen BT, Joon DL, Khoon V, Quong G, Chao M, Wada M et al (2008) Assessing the impact of FDG-PET in the management of anal cancer. Radiother Oncol 87:376–382

Nigro MD, Seydel HG, Considine B et al (1983) Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal. Cancer 51(10):1826–1829

Nijkamp J, de Haas-Kock DF, Beukema JC et al (2012) Target volume delineation variation in radiotherapy for early stage rectal cancer in the Netherlands. Radiother Oncol 102(1):14–21, Epub 2011 Sep 6

Ortholan C, Resbeut M, Hannoun-Levi JM, Teissier E, Gerard JP, Ronchin P, Zaccariotto A, Minsat M, Benezery K, François E, Salem N, Ellis S, Azria D, Champetier C, Gross E, Cowen D (2012) Anal canal cancer: management of inguinal nodes and benefit of prophylactic inguinal irradiation (CORS-03 Study). Int J Radiat Oncol Biol Phys 82(5):1988–1995

Otto SD, Buhr HJ, Frericks B et al (2009) Staging anal cancer: prospective comparison of transanal endoscopic ultrasound and magnetic resonance imaging. J Gastroinst Surg 13:1292–1298

Peeters ST, Hoogeman MS, Heemsbergen WD et al (2006) Rectal bleeding, fecal incontinence, and high stool frequency after conformal radiotherapy for prostate cancer: normal tissue complication probability modeling. Int J Radiat Oncol Biol Phys 66(1):11–19

Peiffert D, Tournier-Rangeard L, Gérard JP et al (2012) Induction chemotherapy and dose intensification of the radiation boost in locally advanced anal canal carcinoma: final analysis of the randomized UNICANCER ACCORD 03 trial. J Clin Oncol 30:1941–1948

Petkar I, Lee Y, Brooks C et al (2012) Intensity Modulated Radiation Therapy (IMRT) with concurrent chemotherapy for Anal Cancer – Retrospective study evaluating toxicity profile and response rates In: National Cancer Research Institute (NCRI) (ed) Cancer conference 2012, NCRI, Liverpool, 4–7 Nov 2012. Abstract RCR22 Available from: http://www.ncri.org.uk/ncriconference/2012abstracts/naviation/search.html

Portaluri M, Mambace S, Perez C et al (2005) A three-dimensional definition of nodal spaces on the basis of CT images showing enlarged nodes for pelvic radiotherapy. Int J Radiat Oncol Biol Phys 63(4):1101–1107

Robertson JM, Söhn M, Yan D (2010) Predicting grade 3 acute diarrhea during radiation therapy for rectal cancer using a cutoff-dose logistic regression normal tissue complication probability model. Int J Radiat Oncol Biol Phys 77(1):66–72

Sebag-Montefiore D, James R, Meadows H, et al (2012) The pattern and timing of disease recurrence in squamous cancer of the anus: mature results from the NCRI ACT II trial. J Clin Oncol 30(Suppl; abstr 4029)

Shepherd NA, Scoffield JH, Love SB et al (1990) Prognostic factors in anal squamous carcinoma: a multi variant analysis of clinical, pathological and flow cytometric perimeters in 235 cases. Histopathology 16:545–555

Shih HA, Harisinghani M, Zietman AL et al (2005) Mapping of nodal disease in locally advanced prostate cancer: rethinking the clinical target volume for pelvic nodal irradiation based on vascular rather than bony anatomy. Int J Radiat Oncol Biol Phys 63: 1262–1269

Stearns MW Jr, Quan SH (1970) Epidermoid carcinoma of the anorectum. Surg Gynecol Obstet 131:953–957

Steenbakkers RJ, Duppen JC, Fitton I, Deurloo KE, Zijp L, Uitterhoeve AL, Rodrigus PT, Kramer GW, Bussink J, De Jaeger K, Belderbos JS, Hart AA, Nowak PJ, van Herk M, Rasch CR (2005) Observer variation in target volume delineation of lung cancer related to radiation oncologist-computer interaction: a 'Big Brother' evaluation. Radiother Oncol 77(2): 182–190

Stieler F, Wolff D, Lohr F et al (2009) A fast radiotherapy paradigm for anal cancer with volumetric modulated arc therapy (VMAT). Radiat Oncol 4:48

Taylor ARA, Rockall A, Reznek RH et al (2005) Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 63:1604–1612

Taylor A, Rockall AG, Powell ME (2007) An atlas of the pelvic lymph node regions to aid radiotherapy target volume definition. Clin Oncol (R Coll Radiol) 19(7):542–550

Tomaszewski JM, Link E, Leong T et al (2012) Twenty-five-year experience with radical chemoradiation for anal cancer. Int J Radiat Oncol Biol Phys 83(2):552

UKCCCR Anal Cancer Working Party (1996) Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil and mitomycin. Lancet 348:1049–1054

Vordermark D, Sailer M, Flentje M, Thiede A, Kölbl O (1999) Curative-intent radiation therapy in anal carcinoma: quality of life and sphincter function. Radiother Oncol 52(3):239–243

Weber DC, Kurtz J, Allal AS (2001) Impact duration of local control in anal canal carcinoma treated by split course radiotherapy and concomitant chemotherapy. Int J Radiat Oncol Biol Phys 50:675–680

Wendell-Smith CP (2000) Anorectal nomenclature. Fundamental terminology. Dis Colon Rectum 43:1349–1358

Winton E, Heriot AG, Ng M, Hicks RJ, Hogg A, Milner A et al (2009) The impact of 18-fluorodeoxyglucose positron emission tomography on the staging, management and outcome of anal cancer. Br J Cancer 100(5):693–700

Wright JL, Patil S, Temple L et al (2010) Squamous cell carcinoma of the anal canal: patterns and predictors of failure and implications for intensity modulated radiation treatment planning. Int J Radiat Oncol Biol Phys 78(4):1064–1072

Yhim HY, Lee NR, Song EK et al (2011) The prognostic significance of tumor human papillomavirus status for patients with anal squamous cell carcinoma treated with combined chemoradiotherapy. Int J Cancer 129(7):1752–1760

Zunino S, Rosato O, Lucino S, Jauregui E, Rossi L, Venencia D (1999) Anatomic study of the pelvis in carcinoma of the uterine cervix as related to the box technique. Int J Radiat Oncol Biol Phys 44(1): 53–59