AN UPDATE ON ANAL CANCER DIAGNOSIS AND TREATMENT

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There have been major changes in the treatment of anal cancer in past few years with chemoradiotherapy (CRT) is now considered the first line treatment and residual or recurrent disease is best treated by salvage anorectal excision. Anal cancer is now staged clinically with emphasis on tumour size, lymph node status and the presence or absence of metastases. Pathological staging systems of resection specimens were historically validated when surgery was the primary treatment and are therefore in need of revision.

Epidemiology and risk factors

Anal malignancies are relatively uncommon, comprising 1.5% of all digestive system malignancies and 1 to 8% of all anorectal malignancies (1, 2). Traditionally, anal cancer had been a disease of older women, with onset in the 7th decade of life, and a female to male predominance of up to 5 to 1 (3, 4). However, with the increasing HIV epidemic, there has been an increase in the number of younger men affected with the disease. These patients have a 120-fold higher risk of developing anal canal cancers than those who are HIV negative (5). Human papilloma virus (HPV) infection, immunosupression, history of receptive anal intercourse, history of cervical, vulvar, or vaginal cancers, or HIV infection and smoking are associated risk factors for the development of anal cancer (6, 7, 8). HIV-positive patients have a 7-fold increased risk of persistent HPV infection, and high-risk HPV (HPV 16 and 18) has been demonstrated in up to 100% of anal cancers (9, 10). Results of peer-reviewed studies of anal cancer, including detection of HPV DNA, showed the prevalence of HPV16 and 18 in 72% of patients (11). Assessment of the cervix, vagina and vulva is suggested in female patients, and includes screening for vaginal and cervical cancer and male external genitalia, because of the common role of HPV in these tumours (12). Smoking may worsen acute toxicity during treatment and lead to a poorer outcome in terms of disease free survival, and patients are advised to stop smoking before therapy (12).

Concomitant neoplasia

Women with anal cancer are more likely to have had vulvar, vaginal, or cervical cancers (13). A study using data from the Danish Cancer Registry demonstrated that the probability of developing anal cancer after a diagnosis of cervical cancer or cervical intraepithelial neoplasia was three to five times as high as the probability of developing stomach or colon cancer (14) with a strong association between cervical cancer and anal cancer (14). Frisch et al. have found an association between anal cancer and lymphoma/leukaemia and raises a possible role of immunodeficiency in the development of anal cancer (13). Patients with immunosuppressant such as AIDS or after solid-organ transplantation are also at a higher risk of developing anal cancer (6).
Anatomy and histology

The anal canal is the terminal part of the large intestine, which extends from the ano-rectal junction to the peri-anal skin (15). The anorectal ring is a clinically palpable ring surrounding the anal canal at the upper part of the pelvic floor. The mucosa below it represents longitudinal folds called the anal columns (transitional zone; ATZ) which end at the dentate line above which is the anal transitional zone (ATZ).

The histologic anal canal begins at the level of the histological anorectal junction (beginning of ATZ) and ends at the junction with the anal margin skin (16). The ATZ is defined as the area between the colorectal type mucosa above and the pure squamous epithelium below, irrespective of the type of epithelium present in the zone itself (17).

The anatomic anal canal is the segment between the dentate line to the anal verge (15, 16). However, the surgical definition of the anal canal, which is the area from the palpable anorectal ring to the peri-anal skin, is the one most widely accepted for practical reasons and is the preferred definition of the American Joint Committee on Cancer (AJCC) (18).

The importance of tumour location cannot be overemphasized and tumours involving the anorectal junction should be classified as rectal cancers if the epicentre is more than 2 cm proximal to the dentate line and as anal cancers if the epicentre is 2 cm or less from the dentate line (18).

Tumours of the peri-anal skin are classified as perianal cancers and are biologically similar to other skin tumours and are staged according to the classification for cancers of the skin (18).

The above distinction is important as anal canal cancers are more aggressive (2) than cancers of the peri-anal skin and also the incidence of anal canal lesions is up to 5 times more common than that of anal margin lesions.

Pathology

Pre-malignant lesions

Anal squamous dysplasia (anal intraepithelial neoplasia; AIN) may be found in tissues removed for a variety of disorders with a prevalence of 2 to 3 per 1000 individuals, but may be as high as 4.4% in at-risk populations that contain a greater proportion of homosexual men (19). Carcinoma in situ may be graded into mild (grade 1), moderate (grade 2) and severe (grade 3) dysplasia. Grade 1 is defined as nuclear abnormalities confined to the lower third of the epithelium, grade 2 to the lower two-thirds of the epithelium and grade 3 as abnormalities involve the full epithelial thickness (20). Progression of AIN is largely related to the immune status of the patient. Up to two thirds of immunosuppressed patients progress from low- to high-grade ACIN within 2 years (21). The rate of progression of in-situ carcinoma to an invasive neoplasia is uncertain, but it is estimated to be up to 5% of patients will ultimately develop invasive disease (22).

Histological classification and grading

Epidermoid carcinoma is the most common type of cancer in the anal canal, seen in up to 80 to 85% of all tumours (1). Squamous cell carcinoma (SCC) of the anal canal has been divided into basaloid, large non-keratinising and large-keratinising variant. However, the diagnostic reproducibility of these subtypes has been low and there are no significant prognostic differences between these types (23). Therefore, the current WHO classification (tab. 1) recommends that the term ‘squamous cell

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<tr>
<th>Table 1. WHO histological classification of tumours of the anal canal (20)</th>
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<tr>
<td>1. Epithelial tumours</td>
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<tr>
<td>a) intraepithelial neoplasia (dysplasia)</td>
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<td>b) squamous or transitional epithelium</td>
</tr>
<tr>
<td>c) glandular</td>
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<td>d) Paget disease</td>
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<tr>
<td>2. Carcinoma</td>
</tr>
<tr>
<td>a) squamous cell carcinoma</td>
</tr>
<tr>
<td>b) adenocarcinoma</td>
</tr>
<tr>
<td>c) mucinous adenocarcinoma</td>
</tr>
<tr>
<td>d) small cell carcinoma</td>
</tr>
<tr>
<td>e) undifferentiated carcinoma</td>
</tr>
<tr>
<td>f) others</td>
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<tr>
<td>3. Carcinoid tumour 8240/3</td>
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<tr>
<td>4. Malignant melanoma 8720/3</td>
</tr>
<tr>
<td>5. Non-epithelial tumours</td>
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<td>6. Secondary tumours</td>
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carcinoma’ be used to cover all histological types of SCC of the anal canal (20). Using additional descriptive comment regarding specific histologic features, such as basaloid features as prominent basaloid features and small tumour cell size are usually linked with ‘high-risk’ human papilloma virus infection is recommended (20). SCC with a predominantly basaloid differentiation pattern was formerly known as cloacogenic carcinoma, but this term is now obsolete (24). Verrucous carcinoma (giant condyloma or Buschke-Lowenstein tumour) which resembles a condyloma macroscopically but is larger and does not usually respond to conservative therapy is also worthy of note separately. This is regarded by some as biologically intermediates between condyloma and SCCs, with a better prognosis than SCC.

Histological grades for anal canal squamous carcinoma are as follows (18): grade X, grade cannot be assessed; grade 1, well-differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated. It should be stressed, however, that neither the histology type, nor the degree of differentiation have major prognostic significance (25), and therefore, have not been included in the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) staging system (18, 26).

It is worth noting that some groups have demonstrated that carcinomas arising below the dentate line tend to be better differentiated and keratinizing compared with those that arise above the dentate line (27). However, determining the precise site of these tumours can be difficult especially with the use of preoperative chemotherapy which also affect the pathologist’s ability to determine the correct site of origin of the neoplasm (6).

Staging and prognosis

As the primary treatment of anal cancer do not involve a surgical excision, most tumours are staged clinically, with a special emphasis on the primary tumor size assessed by clinical examination with the aid of histological confirmation (18).

Staging of anal cancer should be performed in accordance with the AJCC/UICC staging system for anal cancer which includes assessment of the tumour size, lymph node status and distant metastasis. The “T” category is assessed by clinical examination, imaging and/or surgical exploration as the “N” and the “M” categories. The latest TNM classification of cancer of anal canal 2009 includes the following categories (18, 26) (tab. 2).

Physical examination includes digital rectal examination and vaginal examination and should determine the site and the size of the primary tumour and nodal status. Local staging should include MRI of the pelvis and distant metastases should be assessed with CT.

Tumour size is a major determinant of the clinical outcome with a size between 4-5 cm has been shown to distinguish good and poor prognostic groups (12, 28) with a significant difference in survival for tumours greater or lesser than 4 cm. Similar results have been found in patients receiving salvage anorectal excision after failed CRT, where a tumour size > 5 cm has been shown to affect adversely the survival of these patients (29).

A recent prospective study showed tumor diameter as an independent prognosticator of poorer 5-year disease free and overall survival and confirms nodal involvement and male sex as poor prognostic factors (30). One study had shown a specific pattern of recurrence according to the size of the tumour (31), i.e. in T1 patients, no recurrences were observed; in T2 tumours, the recurrence pattern was local; in T3 tumours, it was loco regional and to the groin area; and in T4 tumours, it was loco regional and distant. The study from Memorial Sloan-Kettering showed that when salvage anorectal excision was performed after CRT, the depth of invasion had a major impact on outcome (32).

Regional lymph nodes (N) include the perirectal (anorectal, perirectal and lateral sacral), the internal iliac, and the inguinal (superficial and deep) (18). All other nodal groups represent sites of distant metastasis (M).

Nodal metastasis was found to be associated with a worse outcome as reported by European Organization for Research and Treatment of Cancer (EORTC) trial (33).

If nodal disease is present at the time of salvage surgery for patients with failed CRT, there appears to be both an increase in recurrence and a decrease in survival (34).

With respect to tumor stage, the reported 5-year survival rates are 82% for stage I, 71% for stage II, and 53% for stage III disease. Worse survival has also been observed among
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Table 2. AJCC staging system for anal cancer (18, 26)

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<th>Primary Tumour (T)</th>
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<td>TX</td>
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<td>T4</td>
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* Direct invasion of the rectal wall, perianal skin, subcutaneous tissue, or the sphincter muscle is not classified as T4

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<th>Regional Lymph Nodes (N)</th>
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<tr>
<td>NX</td>
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<td>N2</td>
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<td>N3</td>
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** Regional perirectal/pelvic lymph node dissection requires examination of at least 12 lymph nodes. However, histological examination of inguinal lymph nodes will require 6 lymph nodes. If the lymph nodes are negative but the required number is not met classify as pN0

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<th>Distant Metastasis (M)</th>
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<td>M0</td>
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<table>
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<th>Stage groupings:</th>
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<td>Stage 0</td>
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<td>Stage I</td>
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<td>Stage IV</td>
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patients with node-positive tumors versus node-negative tumors (35, 36).

Hill et al. (25) showed that when the lateral excision margin was >1 mm, further pelvic recurrence occurred in 25% as opposed to 60-75% when the lateral excision margins were less than 1 mm. These data, however, need to be validated but for the time being we suggest that the microscopic distance between the excision margin and the tumour is measured and recorded. Fixation of tumour to the pelvic sidewall at operation and invasion into the perirectal fat in the resection specimen adversely affected outcome of salvage surgery after CRT (32). Positive surgical margins seem to be the best predictor of worse outcome (37).

One study found that no patient survived beyond 2 years when the lateral margin was involved after APR, a result that was similar to those not undergoing surgery (34). Other risk factors for failure of surgical salvage include the presence of persistent rather than recurrent disease (34) inguinal adenopathy at presentation, and an administration of less than 55 Gy of radiation (38). Risk factors for local failure include inability to tolerate complete treatment and gaps in treatment due to toxicity (37, 39). Tumor size at time of presentation has also been associated with locoregional failure (34, 40).

Treatment

The traditional treatment in the early 1970s for anal cancer was abdominoperineal resection (APR) with a 5-year survival of 38-71% (41-44). In patients with small lesions, local excision was performed in an attempt to spare the anal sphincter; however, the results were poor in patients with anal canal lesions and only seemed to benefit those with anal margin lesions less than 2 cm in size (45). In 1974, Nigro et al. (46) introduced combined chemotherapy and radiotherapy (CRT) in an attempt to downstage the disease before surgery. They
were, subsequently, able to achieve 2-11 year survival rates of 80% reserving APR as a salvage procedure for residual or recurrent disease (47). Reported initial complete response following CRT was 75-95% (48-51).

Tumour regression with CRT led to its use as a primary treatment (52, 53) with subsequent disease-free survival of 65-75% at 5 years (34). Currently, most anal canal carcinomas are managed without surgery, using CRT (54).

There are few randomized control trials which demonstrate a significantly lower local failure rate with chemoradiation compared with radiation alone with a significantly higher disease-free and colostomy-free survival with the addition of mitomycin C (33, 55). Combined chemotherapeutic regimens have been advocated in the treatment of metastatic disease; however, these treatments have not been standardized (56) with Cisplatin-based treatments commonly utilized in these patients.

Surveillance regimens after CRT are not standardized, and controversies exist regarding evaluation for recurrent disease (56). It is well known that anal cancers continue to regress well after treatment but the exact timing of maximal tumor regression is unclear (56). Up to 12 weeks are needed for complete clinical response in the majority of patients, and it is the initial response that has been shown to be an independent factor for overall survival (57). Routine biopsy is controversial in monitoring response to treatment with CRT, with some clinicians advocating multiple random biopsies every 3 months, whereas others only target clinically suspicious lesions (56, 57).

Following CRT 10-15% will have persistent disease and around 10-30% of patients can be expected to have recurrence at a later date. The usual treatment for persistent and recurrent disease is APR (48, 49).

Assessment of clinical response takes place at 6-8 weeks after completion of treatment with 60-85% of patients expecting to achieve complete clinical (54). Good partial regression can be managed by close follow-up to confirm that complete regression is achieved, which may take 3-6 months. A decision regarding salvage surgery can be deferred safely in these circumstances. Residual or ‘recurrent’ tumour must be confirmed histologically before considering proceeding to radical surgery (12).

Complete response on PET/CT at 8 weeks following CRT may predict long-term outcome. Patients in complete remission at 8 weeks should be evaluated every 3-6 months for a period of 2 years, and 6-12 monthly until 5 years, with the appropriate clinical examination.

Surgical excision remains an important treatment modality for residual or recurrent anal cancer there is a need for a validated staging system for post-CRT APR specimens to provide clear prognostic information and to decide on possible further treatment after salvage surgery.

Haboubi et al. showed that, in the salvage surgery, the prognosis is worse in the following categories: non responders than recurrence, initial tumour size of 5 cm or over, depth of invasion into and beyond the lavator ani, 55 years or over age groups and lymph node involvement (58). They also showed that cancer of the anal canal margin tends to have a higher cure rate with wide local excision but if the tumour was well differentiated, small and superficially located. Location therefore is very important and need to be documented by the clinician. The factors, which were shown not to affect the outcome in the salvage operation, are the degree of tumour differentiation and lymphovascular or perineural invasion.

Recent guidelines from the European Society of Medical Oncology suggest that local excision can be considered for small well-differentiated carcinomas of the anal margin (T1 N0) i.e. <2 cm in diameter, without evidence of nodal spread (12).

Recurrence vs persistence disease

Differentiating residual disease (positive biopsies < 6 months after the completion of CRT) from tumour recurrence (complete response initially, with positive biopsies >6 months after cessation of treatment) is important as the latter has a better prognosis than the former at salvage surgery (59). Approximately half of treatment failures will be persistent and half recurrent (60).

Pathological examination of the surgical specimens following salvage surgery (APR)

Haboubi et al. and Washington et al. (24, 58) recommended minimum dataset for re-
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porting of excision specimens from salvage surgery (tab. 3). These should include information regarding the site of the tumour and the tumour size (length, width and depth) recorded in mm as well as the histological type together with the histological grade. The tumour should be specified whether recurrent or persistent.

Assessment of the state of the margins is important and should include the proximal,

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<td>Hospital</td>
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<td>Date of Receipt</td>
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<td>Pathologist</td>
<td>Clinician</td>
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**Gross description**
- Site of original tumour
- Site of current tumour
- Recurrent tumour
- Persistent tumour
- Specimen length in mm
- Tumour length in mm
- Tumour width in mm
- Tumour depth in mm

**Microscopic findings**
- Tumour type
  - Squamous cell carcinoma
  - Verrucous variant
  - Mucinous microcysts variant
  - Non-squamous carcinoma
  - Adenocarcinoma
  - Mucinous adenocarcinoma
  - Small cell carcinoma
  - Undifferentiated carcinoma

**Local invasion**
- T1 tumour limited to the internal anal sphincter
- T2 tumour involving the external anal sphincter
- T3 tumour extending outside the anal sphincters/muscularis propria of the rectum
- T4 guz nacieka sąsiednie tkanki / T4 tumour involving adjacent tissue

**Tumour margins from excision (mm)**
- Long
- Circumferential

**Metastatic disease**
- No. lymph nodes recovered
- No. positive nodes (pN1 1–3 nodes, pN2 > 3 nodes)
- Tumour nodules not associated with lymphocytic infiltrate/ extra nodal deposits (END’s)
- Site of histologically proven distant metastases

**Pre-surgical treatment modality**
- Chemotherapy
  - Dose
  - Schedule
- Radiotherapy
  - Dawk / Dose
  - Schemat / Schedule
- Leczenie skojarzone / Combined modality treatment
  - Dose
  - SSchedule

**Concomitant squamous neoplasia**
- Cervical
- Vaginal
- Vulval
- Perineal
- Penile

**Concomitant non-squamous neoplasia**

Table 3. Template for post-radiochemotherapy pathological reporting of anal cancer resectates (58)
distal as well as the radial/circumferential margins which should be inked when the specimen is received for examination. The distance should be specified in mm.

Treatment Effect (histological tumour response to the previous chemotherapy or radiation therapy) should be reported and graded, although this has mainly been used for rectal cancers and its applicability to anal cancers has not been well studied. However, the three-category system described by Ryan et al. in 2005 is recommended to be used as it provides a good interobserver reproducibility and prognostic information (61). Many studies in rectal cancer specimens have demonstrated that histological quantification of tumour regression is a useful method of determining tumour response to CRT and showed its prognostic significance with regard to local recurrence and disease free survival (62). Although this needs further research, we suggest adopting the following scheme of grading tumour regression in salvage APR:

Grade 0*: no viable cancer cells (complete response),
Grade 1: single cells or small groups of cancer cells (moderate response),
Grade 2: residual cancer outgrown by fibrosis (minimal response),
Grade 3: extensive residual cancer (poor response).

* A complete pathological response is combined with grade 1 in Ryan’s classification.

Additional information represents documenting the presence of Condyloma acuminate, dysplasia, associated rectal carcinoma, solid organ transplantation, HIV/AIDS and Human papilloma virus infection. Details of the neo-adjuvant therapy should also be included.

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