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Cancer of the anal region

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ABSTRACT

Anal canal accounts for 2% of all cancer and its incidence increases with age with a predominance in woman. About 80% of all primary anal canal cancers are squamous; adenocarcinoma arising from the glands or glandular ducts shows a behaviour that is similar to that of the adenocarcinoma of the rectum.

Risk factors includes sexually transmitted infection with Human Papillomavirus, cigarette smoking, immunosuppression, and sexual practices. The standard treatment for anal canal is chemo – radiation with a combination of fluoropyrimidines and mitomycin or cisplatin. Salvage surgery may be necessary for residual disease after radiotherapy or chemoradiation, for locoregional relapse and/or for sequelae. In the metastatic setting a multidisciplinary approach is preferred and includes medical treatment, surgery, and RT, if appropriate. Discussing these possible options in the initial stage is of most importance to ensure the best quality of life (QoL) for patients.

1. Introduction

This review describes the current knowledge of biology, pathology, diagnosis, staging, prognosis, and treatment of anal cancer, focusing on the most relevant clinical trials that built the actual guidelines and presenting the ongoing research for novel treatment approach.

The level of evidence and the level of recommendation were given according to the Cochrane Method (Sackett and Straus, 2000); in case of lack of evidence, the statements have to be considered as authors' opinion or institutional practice.

2. General Information

2.1. Epidemiological data

2.1.1. Incidence

In 2014, about 6000 new cases of epithelial tumours of anal canal occurred in Europe, accounting for 2% of all cancers (RARECARE, 2019a). Incidence is higher in women than men with a rate ratio of 1.5.

In Europe during the period 2000–2007 there was a statistically increase of age-adjusted incidence from 0.8 to 1 per 100,000/year (RARECARE, 2019a). Also in the USA, as reported by SEER database, during the period of diagnosis 2003–2013 incidence increased on average 2.2% each year (SEER, 2019b).

In Europe about 54% of epithelial anal canal cancers occur in people aged higher than 65 years (RARECARE, 2019a), with a crude annual incidence rate of 3.9 per 100,000. The corresponding rates for the age groups 15–24, 25–44, 45–54, and 55–64 were 0.01, 0.3, 1.4, 2.2, respectively.

According to RARECAREnet, specific carcinomas with clinical meaning, have been identified. For the epithelial anal canal, adenocarcinoma and Paget disease of anal canal were identified. Adenocarcinoma showed an annual rate of 1.9 per million per year and the Paget disease was very uncommon. Seventy percent of the epithelial anal canal tumours are squamous cell carcinoma, the annual incidence rate being 8.1 per million.

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2.1.2. Survival

Survival for adults diagnosed in Europe with an epithelial anal canal tumour during 2000–2007 was 81% at one year and 56% at five years (RARECARE, 2019a). Five-year survival was significantly better in women than men (65% *vs.* 58%) and reduced with increasing age: 68% (15–64 years) and 56% (65+ years). Between 1999 and 2007, 5-year survival significantly improved from 52% to 57%. Prognosis was worst for adenocarcinomas (42%) and better for squamous cell carcinoma and the Paget disease of anal canal, 67% in both; the latter based on very few cases (21 cases) (RARECARE, 2019a).

2.1.3. Prevalence

Prevalence of epithelial tumour of anal canal, that is the number of people living with a present or previous diagnosis of anal canal cancer, is known for Europe thanks to the RARECAREnet project.

In 2008 about 48,000 persons were alive with a diagnosis of anal canal, the proportion was 9.4 per 100,000. The 5-year prevalence, that is the number of living people with a diagnosis of anal canal cancer made 5 or less years before the index date, was only 5.8 per 100,000. The last figure provides information of the need for clinical follow-up and treatment for recurrences. Of the total population with anal canal cancer, 21% are long-term survivors, that is people living with a diagnosis made 15 or more years before the index date (Faivre et al., 2012).

2.2. Aetiology and risk factors

For most of the past century, chronic irritation and injury were thought to be important factors in the development of anal cancer. Different studies have identified other risk factors for anal cancer, including sexually transmitted infection with Human Papillomavirus, cigarette smoking, immunosuppression, and sexual practices.

2.2.1. Human papillomavirus (HPV)

IARC considers that there is convincing evidence that infection with HPV 1618 can lead to anus cancer. In a large series of cases from Denmark and Sweden, 95% and 83% of cancers involving the anal canal in women and men, respectively, were positive for oncogenic HPV (Frisch et al., 1999; Parkin, 2006); the attributable fraction due to the HPV is taken to be 90% worldwide (Parkin, 2006).

Like in the cervical intraepithelial neoplasia, HPV has been shown to cause anal intraepithelial neoplasia, which can progress from low-grade to high-grade dysplasia, and ultimately to invasive cancer (Clark et al., 2004). Consistent condom use appears to offer a relatively good protection from HPV infections (Lam et al., 2014).

2.2.2. Smoking

Several studies have identified cigarette smoking as a risk factor for anal cancer by a factors of 2–5, independently of sexual practices (Daling et al., 1987; Holmes et al., 1988; Holly et al., 1989; Daling et al., 1992). This relation is also supported by the finding that lung cancer is twice as frequent in patients with a history of anal cancer (Rabkin et al., 1992; Frisch et al., 1994). Frisch and colleagues speculated that the findings of a strong correlation between status as a current smoker and the risk of anal cancer may be due to the lack of adjustment for confounding by sexual factors and that smoking may represent an important risk factor only among women who are not oestrogen deficient (premenopausal women) (Frisch et al., 1999; Frisch, 2002).

In a recent study (Daling et al., 2004), the effect of current smoking among men and women was evaluated by age, histology, tumour behaviour, and all risk factors for anal cancer stratified by level of exposure. The analysis produced supporting data noting a relationship between smoking and anal cancer among both women (adjusted OR: 3.8; 95%CI 2.3–6.2) and men (adjusted OR: 95%CI 3.9; 1.9–8.0). Lower ORs were reported for women aged ≥60 years and with cloacogenic tumours. Accordingly, the authors speculated that if the study of Frisch et al. had included a large number of cloacogenic tumours among postmenopausal women, that factor may have accounted for the reported absence of an association. Phillips et al. (2004) studied the smoking-related DNA adducts in samples of anal epithelium from haemorrhoidectomy specimens from current smokers (No. 20) and age-matched life-long non-smokers (No. 16). The study indicated that components of tobacco smoke inflict genotoxic damage in the anal epithelium of smokers and provide a plausible mechanism for a causal association between smoking and anal cancer.

2.2.3. Sexual practices

Several epidemiologic studies have linked sexual practices with the risk for anal cancer. In an early case-control study, Daling and colleagues found that in men a history of receptive anal intercourse (related to homosexual behaviours) was strongly associated with the occurrence of anal cancer. They also reported that men with anal cancer were more likely to never have married and to not have been exclusively heterosexual (Daling et al., 1987).

In a later study, Daling and colleague obtained similar results. The risk for anal cancer was higher in men not exclusively heterosexual (OR: 17.3; 95%CI 8.2–36.1) and in men with ≥15 lifetime sexual partners (OR: 3.9 for heterosexual men vs. OR: 6.6 for men who are not exclusively heterosexual).

Among women, the risk of anal cancer increased with the number of lifetime sexual partners and the young age at first intercourse (Daling et al., 2004).

2.2.4. Immunosuppression

Chronic immunosuppression from medications is a risk factor for several types of squamous-cell carcinomas, including those of anal canal. This risk is likely to be a result of persistent HPV infection (Ryan et al., 2000). In recipients of renal allografts, persistent Human Papillomavirus infection has been associated with a 100-fold increased risk of anal cancer (Clark et al., 2004).

Daling and colleagues evaluated the relation between anal cancer and a marker of immunosuppression: the use of corticosteroid. The risk for anal cancer associated with corticosteroid use was found to be elevated significantly among men (OR: 3.2), particularly among men who were not exclusively heterosexual (OR: 5.6), and among women (OR: 3.2). Although corticosteroid are only weakly immunosuppressive, the consistent finding of an elevated risk among both heterosexual men and non heterosexual men, as well as among women, indicates that either the drug or the conditions the drug is used for may enhance the risk of HPV related diseases (Daling et al., 2004).

2.2.5. HIV

Several studies have analysed the association between HIV infection and anal cancer however it is still unclear whether the HIV infection itself has a direct effect on the development of anal cancer (Ryan et al., 2000).

The association between anal cancer and HIV has been hard to separate from confounders. HIV-positive patients are more likely to be infected with HPV and they are more likely to have HPV-associated squamous intraepithelial lesions, particularly high-grade lesions (Uronis and Bendell, 2007).

If HIV was directly associated with anal cancer, the incidence after the introduction of the Highly Active Antiretroviral Therapy (HAART) should have decreased as reported for other HIV-related malignancies (Kaposi sarcoma and Hodgkin lymphoma). However, according to Bower and colleagues, the incidence of anal cancer in the HIV cohort observed was 35 (95%CI 15–72) per 100,000 before the introduction of the HAART and 92 (95%CI 52–149) per 100,000 in the post-HAART era ($p = 0.05$) (Bower et al., 2004). Chiao confirmed that the incidence of anal cancer increased from 0.6 in the pre-HIV era to 0.8 in the HIV era and to 1.0 in the HAART era (Chiao et al., 2005).

It has been suggested that, because of the HAART therapy, patients are living longer letting more time for transformation and development of anal cancer and dysplasia. In this case the cancer would not be associated with HIV, but with the persistent HPV infection. From the evidence available up to now it seems that further studies are necessary to establish the true nature of the relationship between HIV infection and anal cancer (Uronis and Bendell, 2007).

2.2.6. Screening

Considering the high-risk groups for anal cancer, screening for invasive anal squamous cell carcinoma and its precursors has been increasingly advocated in high-risk populations. Similar to the cervical Papanicolaou smear, anal swabs for cytology are possible screening methods for anal squamous intraepithelial lesions (ASIL) and anal cancer (Uronis and Bendell, 2007). However, some reviews (Anderson et al., 2004; Chiao et al., 2006) highlight limitations of a possible anal Pap smear screening. While it is accepted that the incidence of anal cancer is at least 20 times higher in homosexual men than the general population, the natural history of anal cancer and its precise relationship with anal intraepithelial neoplasia is not clearly understood. The screening tests have a sensitivity between 45% and 70%. There are not randomised trials on anal dysplasia screening and few trials evaluating treatment strategies for HIV/AIDS high-grade dysplasia. The currently available data does not support the implementation of a screening programme for anal intraepithelial neoplasia and anal cancer in homosexual men (Anderson et al., 2004) and further research is needed to identify improved methods for preventing, detecting, and treating anal dysplasia (Chiao et al., 2006). At the moment, there is no data in favour of screening programmes in anal cancer (Hakama et al., 2008).

3. Pathology and Biology

3.1. Biological data

Squamous cell carcinomas arise from the epithelium lining the anal canal. This tissue is derived from embryonic ectoderm, and the tumour hence has more features in common with skin carcinoma than with rectal carcinoma. High-risk types of human papilloma viruses (hrHPVs, notably HPV type 13 and 16) may integrate into the DNA of the anal squamous cells, and play a major role in the carcinogenesis of anal canal cancer. Integrated HPV-16 is found in over 80% of anal canal cancers (Machalek et al., 2012). Proteins E5, E6, and E7, codified by HPV genome, are carcinogenic molecules: when they are present in high quantities in the nucleus, they block two molecules crucial for cell cycle checkpoint control (p53 and Rb). In opposition with what is observed in other malignancies, p53 and Rb are normal, but their function is inhibited, so that the role of E6 and E7 can be compared to a genetic mutation. HPV genome integration determines also host cells chromosomal instability (the larger this instability is, the greater the expression of E7 is) as aneuploidies and chromosomal deletions. This instability is not present in HIV-positive anal carcinoma patients without HPV, where immunosuppression works as carcinogenesis promoter through alternative pathways.

3.2. Histological types

3.2.1. Histotypes

About 80% of all primary anal canal cancers are squamous, classified in subtypes as follows: giant cells keratinizing, giant cells non-keratinizing (transitional), and basaloid.

The “cloacogenic” term is used for the last two subtypes. About 15% of canal anal neoplasms belong to the adenocarcinoma subtype, the remaining 5% comprises small cell cancer, undifferentiated cancer or melanoma. Primary tumours of the anal margin are similar to skin cancers of other districts: squamous cell carcinoma, basal cell carcinoma, Bowen’s disease, Kaposi’s sarcoma, Paget’s disease, and melanoma. The latter two diseases have a different behaviour from those of the anal canal and, when a complete surgical excision (wide excision) is possible, a 5-year survival of 80% is observed/expected.

Tumours of the distal anal canal tend to be more frequently keratinized, whereas tumours growing in the proximal portion occur as cloacogenic or basaloid forms which however do not differ in behaviour. An aggressive variant of the basaloid type, called small cells, has a tendency to spread rapidly.

Adenocarcinoma arising from the glands or glandular ducts shows a behaviour that is similar to that of the adenocarcinoma of the rectum.

3.2.2. Premalignant conditions

Cytologically squamous intraepithelial lesion (SIL) of the anus is indicated by the increase in the severity of cell morphology changes such as atypical squamous cells (ASC) with undetermined significance (ASC-US), LSIL, ASC suggestive of HSIL (ASC-H), and HSIL (Solomon et al., 2002).

SIL is generally characterized by tissue sections with loss of epithelial stratification and nuclear polarity as well as nuclear polymorphisms, hypercromatism, and mitotic activity increased. It may be associated with the presence of koilocytes, which are enlarged cells characterized by a cytoplasmatic halo surrounding the nucleus and suggestive of HPV infection.

LSIL defines the replacement of 20%–30% of epithelium by abnormal cells, and HSIL defines the substitution of more than 50% of epithelium with atypical cells (Bosman et al., 2010; Palefsky and Holly, 1995).

The current terminology for HPV-associated squamous proliferations includes two stages: high-grade squamous intraepithelial lesion (HSIL) and low-grade squamous intraepithelial lesion (LSIL). Concerning anal lesions, these entities can be classified according to whether they have corresponding levels of anal intraepithelial neoplasia (AIN). AIN I corresponds to LSIL, whereas AIN II/AIN III corresponds to HSIL (Darragh et al., 2013).

Patients with AIN are usually asymptomatic, and these lesions are often found in surgical specimens as a result of minor surgeries in the anorectal region. AIN is not always evident on routine examination but may be associated with plaques, erythema and/or pigmentation. In some patients, these lesions may be associated with bleeding, irritation, and pruritus ani (Bosman et al., 2010; Jay et al., 2015).

The minimally invasive squamous cell carcinoma of the anus is called superficially invasive squamous cell carcinoma (SISCCA) and is described as a micro-invasive disease. This may be susceptible to conservative or excisional treatment and has a low risk of developing metastasis. Into the anal canal, the definition of SISCCA comprises a completely removed lesion with less than 3 mm invasion of the basement membrane and with horizontal diffusion less than 7 mm. Invasive tumours larger than SISCCA generally require more aggressive treatments.

3.2.3. ICD-O classification

Here, the list of the International Classification of Diseases for Oncology (ICD-O) classification; codes are provided in brackets (ICD-O 2000):

- Squamous cell carcinoma [8070/3]
- Transitional carcinoma [8120/3]
- Cloacogenic carcinoma [8124/3]
- Adenocarcinoma [8140/3]
- Melanoma [8720/3]
- Paget’s disease [8542/3]
- Basal cell carcinoma [8090/3]
- Adenoid cystic [8200/3]
- Mucoepidermoid carcinoma [8430/3]
- Basaloid carcinoma [8123/3]
- Small cell carcinoma [8041/3]

Table 1
Histopathological grading of anal cancer.

Grading	Characteristics
G1	Well-differentiated cancer
G2	Moderately-differentiated cancer
G3	Poorly-differentiated cancer
G4	Undifferentiated carcinoma, reserved to those tumours not showing any specific differentiation

- Anal duct carcinoma [8215/3]
- Lymphoma [9590/3]
- Leiomyosarcoma [8890/3]
- Fibrosarcoma [8810/3]
- Sweat gland carcinoma [8400/3]
- Kaposi sarcoma [9140/3]

3.3. Particular histotypes considered elsewhere

Rare histological subtypes that can arise in the anal area include small cell carcinoma, lymphoma, melanoma, leiomyosarcoma. Melanomas constitute about 1%–4% of all anal cancers, and 1%–2% of all melanomas. At a microscopic examination most are pigmented, but only few are strong melanotic melanomas. Melanoma may be confused with thrombosed haemorrhoids, an error which delays the diagnosis.

3.4. Grading

Table 1

4. Diagnosis

4.1. Signs and symptoms

Symptoms of anal cancer are not specific. Bright-red rectal bleeding, itching and discomfort are common; they are often discontinuous and may not alarm the patient; 70%–80% of anal cancers are initially diagnosed as benign conditions. Patients with Bowen's disease frequently present with long-standing perianal pruritus. Patients with Paget's disease may be asymptomatic, may have perianal pruritus or have a bleeding erythematous plaque. The frequent association of anal cancer to Paget's disease, leukoplakia, haemorrhoids, fissures, and fistulas makes the diagnosis difficult. For all these reasons the majority of patients presents with advanced disease (60%–70% of cases having tumours of 4 cm or more in maximum diameter). Symptoms such as pain during defecation, or anal discharge or change of bowel habits suggest larger lesions; incontinence and rectovaginal fistula are generally found in more advanced cases. Cancer of the anal canal generally develops as an infiltrating ulcer, with slightly raised indurated margins; in the upper part of the canal, it can rarely grow with polypoid aspect, but it maintains a relevant infiltrating component. Tumours of the lower canal may grow with expansive patterns; a lump may be felt in the anus or in the posterior part of the vagina. Involvement of the anal orifice as well as of the distal rectum is common; extension to adjacent organs – vagina, prostate, or the ischiorectal space – occurs in 15%–20% of patients; in this case the tumour may present itself as a perianal abscess or fistula. An inguinal enlarged lymph node may be the first sign of a symptom-free anal cancer. The diagnosis of inflammatory node or hernia may lead to serious delay in treatment. Sometimes hepatic metastases may lead to the diagnosis of anal cancer (Klas et al., 1999).

4.2. Diagnostic strategy

Careful digital examination of the anal region can provide essential information regarding the presence, site and extent of anal cancer. Biopsy of any suspicious area, is recommended on a type C basis. Vaginal and perianal palpation are of great help in defining the degree of infiltration of the recto-vaginal wall and the lateral tissues. If anorectal examination is painful or anular stenosis is present, re-examination under general anaesthesia is recommended on a type C basis.

Perirectal metastatic lymph nodes can be detected at digital examination, but modern imaging evaluations may be more accurate. Inguinal nodes are easily detected with palpation, but their nature is of difficult assessment in early involvement. About one third of patients has enlarged inguinal nodes, but only 50% of them have a pathological involvement (Klas et al., 1999; Gerard et al., 1998). The recent use of PET has enabled a more accurate assessment of the state of the lymph node stations with detection of pathologic uptake in the absence of clinical evidences (Cotter et al., 2006).

4.3. Pathological diagnosis

Biopsy of any suspicious area in the anal canal or margin is recommended on a type C basis. Enlarged inguinal lymph nodes need to be ascertained pathologically. In some cases biopsy is to be performed under general anaesthesia. Needle biopsy of enlarged inguinal lymph nodes is recommended on a type C basis. If fine needle biopsy is negative in a highly suspicious lymph node, a surgical biopsy is recommended on a type C basis.

5. Staging

5.1. Stage classification

5.1.1. Site definition

The anal canal, 3–4 cm long, is the terminal portion of the intestine, and extends from the ano-rectal ring to the junction with the perineal skin (Anal Verge). The ano-rectal ring, clearly identifiable with rectal examination, is defined as the muscle bundle formed by the intersection of the muscle fibres of the upper portion of the internal sphincter, of the distal portion of the longitudinal puborectalis muscle and of the deep portion of the external anal sphincter. The epithelium that covers this part of the anal canal is of columnar type. The dentate or pectinate line is the area where the anal glands open and it represents the transition zone between the columnar epithelium of the proximal channel and the stratified squamous epithelium of the distal canal. The epithelium that covers this part of the anal canal is called "of transition" and contains columnar, cuboidal, squamous, and transitional epithelium. The proximal anal canal mucosa originates from endoderma and has lymphatic and venous drainage through the hypogastric vessels. The mucosa of the distal anal canal is of ectodermal origin and has lymphatic and venous drainage through the inferior haemorrhoidal vessels. This latter area has sensory innervation from the somatic nervous system through the branches of the pudendal nerve. The anal canal is divided by the dentate line, which indicates the transition from the glandular mucosa to the squamous one. This muco-cutaneous junction is considered as the reference point to distinguish the anal canal from the anal margin (perianal skin).

The anal margin is the cutaneous area that develops concentrically within a radius of 5 cm from the anal verge and it is covered by squamous keratinized epithelium containing hair follicles.

Tumours located in the anal margin are similar to the ones of the perianal skin and have high cure rates with wide local exclusive excision, particularly when they are small (< 3 cm in maximum dimension) and well differentiated. This is also probably due to the fact that these tumours are more easily detected in a much earlier stages.

5.1.2. Classifications

Since radical surgery is no more the first option for the treatment of anal tumours, these tumours are clinically evaluated by physical examination and X-ray images.

Anal tumours are currently staged according to the size of the

Table 2
Anal margin cancer TNM staging and groupings stages (AJCC 2010) (American Joint Committee on Cancer, 2010).

Primary tumour (T)	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumour more than 5 cm in greatest dimension
T4	Tumour invades deep extradermal structures, i.e., cartilage, skeletal muscle or bone
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
Mx	Distant metastasis cannot be assessed
M0	No evidence of distant metastasis
M1	Distant metastasis present

tumour and the presence of lymph nodes and metastasis (TNM), as indicated by the American Joint Committee on Cancer (AJCC).

The tumour category (T) is determined by the size and by the invasion of adjacent structures, such as the vagina and prostate. The lymph nodal staging is based on the position of perirectal lymph nodes involved, pelvic or inguinal. The perianal skin (anal margin) cancers (melanoma included) are considered cutaneous and classified as such (Tables 2–5).

5.2. Staging and restaging procedure

5.2.1. Staging

Patients suspected of anal cancer require a careful anamnesis collection to assess known risk factors, such as homosexuality and bisexuality in men (i.e., MSM), receptive anal sex, HIV positivity, AIDS, the use of intravenous drugs, cigarette smoking as well as the risk factors associated with non-HIV-related immunosuppression, such as chronic steroid therapy as a result of organ transplantation.

The degree of rectal bleeding and sphincter incontinence must be investigated. A complete physical examination is mandatory as well as a careful inspection of the perianal skin and anal margin, followed by anorectal exploration. The sphincter function, the size and location of the tumour, as well as the involvement of contiguous adjacent structures, such as the vagina in women and prostate in men, should be documented as well as the presence of inguinal lymphadenopathy. An ano-proctoscopy is mandatory in order to identify any abnormalities such as masses, nodules, ulcers, and/or areas of dischromasia. Women should be evaluated for cervical dysplasia/cancer with Pap test and colposcopy, whereas men should receive an examination of the penis (Jay et al., 2015).

A colonoscopy can be used to determine the degree of anorectal involvement and to evaluate any other lesions of the colon; however it

Table 3
Staging grouping of anal margin cancer (UICC 2002) (Union for Internation Cancer Control, 2002).

Stage 0	Tis, N0, M0
Stage I	T1, N0, M0
Stage II	T2, N0, M0
	T3, N0, M0
Stage III	T4, N0, M0
	Any T, N1, M0
Stage IV	Any T, Any N, M1

Table 4
TNM classification of anal canal cancer (UICC 2002).

Primary tumour (T)	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumour more than 5 cm in greatest dimension
T4	Tumour of any size invades adjacent organ(s), e g. vagina, urethra, bladder*
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in perirectal lymph node(s)
N2	Metastasis in unilateral internal iliac and/or inguinal lymph node(s)
N3	Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes
Distant metastasis (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

* Note: direct invasion of the rectal wall, perianal skin, subcutaneous tissue, or the sphincter muscle(s) alone is not classified asT4.

Table 5
Staging grouping of the anal canal cancer (UICC 2002).

Stage 0	Tis, N0, M0
Stage I	T1, N0, M0
Stage II	T2, N0, M0
	T3, N0, M0
Stage IIIA	T1, N1, M0
	T2, N1, M0
	T3, N1, M0
	T4, N0, M0
Stage IIIB	T4, N1, M0
	Any T, N2, M0
	Any T, N3, M0
Stage IV	Any T, Any N, M1

is not as accurate as a high-resolution anoscopy. A complete blood analysis, renal and liver function evaluation, and HIV status should be included in the baseline tests.

Although the execution of a transrectal echoendoscopy is advisable to better define the infiltration degree of the adjacent structures, in particular when tumor extends to the lower rectum, such examination is not mandatory in any of the national or international guidelines. Computed tomography (CT) of the chest, of the abdomen, and of the pelvis should be performed to assess the presence of metastatic disease to the lungs and to the liver and the retroperitoneal region, pelvic, and inguinal lymph nodes.

Compared to CT, MRI of the pelvis provides better anatomical detail (Jones et al., 2015) of the possible invasion of the local structures, in particular the sphincter and its muscles, and for the evaluation of mesorectal lymph nodes; it should be performed without anal probe/antenna, and using vaginal contrast whenever appropriate to clearly identify the lower posterior vagina and thickness of disease spread to the ano-recto vaginal tissues.

Positron emission tomography (PET) has provided benefit in identifying the primary tumour and its spread to inguinal lymph nodes and in evaluating the response to therapy. In a retrospective study of 41 patients with anal cancer it has been shown that PET detected the tumour in 91% of patients, while CT could detect only 59% of patients. In addition, PET resulted to be able to detect the involvement of inguinal lymph nodes that were considered negative at the CT in 17%–23% of patients. HIV-positive patients have a higher rate of inguinal

lymphadenopathy positivity. Because these lymph nodes may also be responsive and show hypermetabolic activity at PET, all patients with positive or suspicious inguinal adenopathy should be needle biopsied. Inguinal node involvement is rare in early T stage of the anal canal except when disease extends to the anal margin, lower vagina and/or external iliac nodes. Most nodal spread occurs in internal iliac, mesorectal and pre-sacral areas.

5.2.1.1. Sentinel node biopsy. Patients with tumours at stage T1 and T2 with clinically negative inguinal nodes have a low incidence of inguinal recurrences. This would seem to indicate an overtreatment in most patients treated with adjuvant radiotherapy at these locations. A correct identification of patients who have microscopic inguinal disease might improve the results. Although it can be a useful tool, the available data on the use of sentinel lymph node biopsy (SLNB) do not yet support its use as routine. The current standard for its evaluation still seems to be CT associated with needle biopsy using ultrasound guidance.

A recent meta-analysis shows that FDG-PET (De Nardi et al., 2012; Mistrangelo et al., 2010, 2012; Mistrangelo et al., 2013) is a promising diagnostic tool to evaluate loco-regional lymph node involvement, despite its low sensitivity with small lymph nodes. To reduce the risk of false negative results, increased sensitivity could be achieved by combining FDG-PET with MRI. Tomography hybrid PET and upcoming hybrid MRI should improve the diagnostic performance also in these patients.

5.2.2. Restaging

Although a rapid clinical response is a favourable prognostic factor (Mistrangelo et al., 2013; Chapet et al., 2005), the slow clearance of this cancer is well known (Deniaud-Alexandre et al., 2003; Sato et al., 2005; Rousseau et al., 2005; Cummings et al., 1991).

Cummings et al. (1991) have shown that the time of regression rate is not a good measure of the effectiveness of the treatment: the median time to complete the response is 3 months and in some types of cancer may require up to 12 months. The clinical-instrumental (CT and MRI pelvis) response evaluation should therefore be performed after 12 weeks after the end of the radio-chemotherapy treatment.

A residual disease that gradually tends to shrink can still be considered in response and should not be subject to investigation biopsy because of the potential risk of local complications due to handling (risk of developing a chronic anal fistula). In such cases it may be of help a PET-CT to be performed no earlier than 2 months after the end of the radio-chemotherapy (Glynne-Jones and Lim, 2011; Bannas et al., 2011; Trautmann and Zuger, 2005; Schwarz et al., 2008).

A French study (Deniaud-Alexandre et al., 2006) shows that patients who achieved a response rate after the initial phase of RT > 80% *vs.* < 80% had a 5-year survival rate without colostomy of 65% *vs.* 25%, respectively ($p = 0.002$), and in 29% of patients who did not achieve a complete response at 11 weeks it was reached at 26 weeks.

These results suggest that it may be necessary for patients who have persistent disease, a longer clinical follow up (more than six months) to define the clinical response.

6. Prognosis

6.1. Natural history

6.1.1. Phases of disease

Local tumour gives rise to anal masses that easily infiltrate the anal sphincter and is usually symptomatic at an early stage. However, since symptoms are not specific, patients' and doctors' delay are common, and most patients (60%–70%) present with advanced tumours. Direct invasion of vagina, urethra, prostate, bladder, sacrum or bone of the pelvis sidewall may be observed in 15%–20% of patients. Regional lymphatic spread of tumour cells is common in anal canal tumour (from 10%–20% for small tumours to 60% for larger tumours) and follows the lymph vessels from the anus. Tumours in the distal anal canal primarily affect inguinal lymph nodes, while tumours in the proximal parts affect pelvic lymph nodes (pararectal or iliac). Finally the abdominal lymph nodes are involved. Twenty-five percent of lymph node positive patients have bilateral involvement. Haematogenous spread rarely (< 10% of cases) causes distant metastases mainly in the liver, lung and skin (Klas et al., 1999; Gerard et al., 1998).

6.2. Prognostic factors

Considering the different histological subtypes of the squamous form, no significant difference was reported.

It is important the T stage, whose increase is related to a poorer prognosis.

The lymph node involvement is an unfavourable prognostic factor and is related to a higher rate of local relapses as reported in the literature by two phase-III studies (Glynne-Jones et al., 2014; Linam et al., 2012), as well as the male sex. HIV infection seemed to represent an unfavourable factor; however, antiviral treatment has allowed the application of standard treatments in patients with CD4 counts greater than 200/mm^3 reporting a disease free survival similar to that of HIV negative patients.

In a retrospective study, also smoking appears to have a negative impact on survival (Schwarz et al., 2008). A poor prognosis seems to be associated to high p53 in squamous cell histotype. Tolerance to multimodal treatments appears to be a predictor of success (Roohipour et al., 2008).

7. Treatment

7.1. Precancerous lesions

Condyloma and low-grade dysplasia are treated with local therapies and surgery. In case of AIN lesions and of micro-invasive disease (superficially invasive squamous cell carcinoma SISCCA < 3 mm from the basement membrane, and < 7 mm as horizontal extension), local excision with healthy tissue margins is indicated (Richel et al., 2013) and it is not resulted less effective than the use of topical therapy, as imiquimod or 5-fluorouracil, even in HIV-positive patients.

Nevertheless the recurrence rate remains high (around 59%), and therefore careful follow-up and anoscopy monitoring quarterly is needed (Goldstone et al., 2011; Marks and Goldstone, 2012; Wilkin et al., 2013; Silvera et al., 2014).

7.2. Treatment strategy for tumours of the anal region

Tumour extension dictates different treatment approaches. Aim of treatment is definite cure possibly without any mutilating surgery. Squamous cell carcinoma of the anal margin which does not involve the anal canal should principally be considered as a skin carcinoma.

7.3. Cancer of the anal margin

7.3.1. Treatment strategy

General strategy is based on a conservative approach. Small tumours can be resected without mutilating surgery. For larger tumours treatment is mainly based on radiation therapy even if recently a combined approach containing chemotherapy and radiotherapy has been introduced.

7.3.2. In situ carcinoma of the anal margin

Standard treatment on a type C basis for in situ carcinoma is local excision with adequate margin. Laser treatment is suitable for individual clinical use on a type 3 level of evidence (Bandieramonte et al., 1993).

7.3.3. Invasive cancer of the anal margin

The standard treatment for small tumours of the anal margin (T1N0) is local excision on a type C basis (Mendenhall et al., 1996; Peiffert et al., 1997; Arnott et al., 1996). Radical surgical excision requires an adequate margin of normal tissue (1 cm). T2N0 carcinomas have a significant risk of inguinal lymph node metastasis; radiotherapy to the primary tumour and inguinal prophylactic bilateral irradiation is standard option on a type C basis (Mendenhall et al., 1996; Peiffert et al., 1997). Combined chemo-radiotherapy is suitable for individual clinical use in T2N0 carcinomas on a type 2 level of evidence (Arnott et al., 1996). In this study, patients with early tumours showed a 55% reduction in the risk of local failure when treated with combined therapy. Both T2N0 anal margin cancers and T1-T2 N0 anal canal cancers were included in the analysis (Northover et al., 2010). In patients with advanced disease (T3-T4 or N1-N3) the standard approach is radiotherapy with concomitant chemotherapy on a type C basis (Mendenhall et al., 1996; Arnott et al., 1996).

7.3.4. Recurrence of the anal cancer

Treatment choice depends on previous treatment. Local surgical re-excision is recommended in selected patients on a type R basis (anal continence is preserved as long as the excision does not involve more than half of the circumference of the anus). For gross recurrence after local excision requiring abdomino-perineal resection, the standard treatment is concurrent chemoradiation on a type R basis. In previously irradiated patients the recommended treatment is salvage surgery (abdomino-perineal resection) on a type C basis (Mendenhall et al., 1996; Peiffert et al., 1997).

Standard treatment of locally advanced carcinoma of the anal canal is concurrent chemoradiotherapy on a type 1 level of evidence (Arnott et al., 1996; Bartelink et al., 1997; Flam et al., 1996; John et al., 1996a). Abdominoperineal resection should be reserved for salvage of the few patients failing combined modality therapy. In patients with obstructive symptoms concurrent chemoradiation may be given after transient colostomy. In case of bleeding, it may rapidly stop after few days of radiotherapy. The combined approach is superior to radiation treatment alone in terms of local control (68% vs. 50%) and reduction of demolitive surgery (colostomy-free rate of 72% vs. 40%), without significant increase in late side effects (around 10%) (Bartelink et al., 1997).

Long-term results of the combined modality approach suggest that abdominoperineal resection can be avoided in patients achieving a pathological complete remission and anal sphincter function maintained in the majority of patients. Combined modality approach gives a high rate of tumour regression, including a high rate of complete remissions (80%–90%) so that extensive surgery including abdominoperineal excision can be avoided in most cases. No overall 3-year survival advantage was observed (70%-60% for both groups). Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy is still investigational (Meropol et al., 2008; Peiffert et al., 2001; Svensson et al., 1998). The presence of nodal involvement, tumor ulceration, or both is a poor prognostic factor Patients with nodal metastases, although it represents a poor prognostic factor, do not respond differently from those without nodal involvement (John et al., 1996a; Cummings et al., 1993). In selected cases with bulky nodal involvement, excision of gross lymphnodes before (Schlag, 1996) or after (Gerard et al., 2001) chemoradiation is suitable for individual clinical use on a type 3 level of evidence.

7.4. Cancer of the anal canal

7.4.1. Treatment strategy

Aim of treatment is definite cure possibly without mutilating surgery. Salvage surgery may be necessary for residual disease after radiation therapy or concurrent chemoradiation, for locoregional relapse and/or for sequelae.

7.4.2. Treatment of in situ carcinoma of the anal canal

Carcinoma in situ should be removed surgically on a type C basis. Laser treatment is suitable for individual clinical use on a type 3 level of evidence (Bandieramonte et al., 1993).

7.4.3. Treatment for cancer of the anal canal (stage I, II, III)

Standard treatment of locally advanced carcinoma of the anal canal is concurrent chemoradiotherapy with 5-fluorouracil (5-FU) and mitomycin C (MMC) on a type 1 level of evidence and recommendation level A.

Nigro has pioneered multimodal treatments with small number of patients with anal cancer treated with low-dose RT (30 Gy) in combination with 5-FU and MMC (Nigro et al., 1974). A subsequent phase II study of 45 patients treated preoperatively with the same chemoradiotherapy regimen induced complete remission in 84% of cases. No tumour recurrence occurred in patients who achieved complete response (Leichman et al., 1985). Since then, several randomized studies have addressed the role of concomitant chemotherapy, induction chemotherapy, maintenance chemotherapy, and biological therapy.

7.4.3.1. Chemoradiotherapy vs. radiotherapy. Despite the good results of the combined treatments, we wondered if chemotherapy was really necessary or whether it increased only side effects of RT. The first phase III study (ACT I) tried to answer this question. The radiotherapy with a total dose of 45 Gy was compared with RT associated with 5-FU and the MMC (Arnott et al., 1996). After a median follow-up of 42 months, the chemo-radiotherapy arm had a better local control compared to RT alone (36% *vs.* 59%; $p < 0.0001$), a higher acute toxicity (48% *vs.* 39%; $p = 0.03$), but same late toxicity (42% *vs.* 38%; $p = 0.039$) in both groups.

The survival benefit after 13 years of follow-up was not statistically significant for the chemo-radiotherapy arm, but the reduction in the risk of cancer specific death was statistically significant (Northover et al., 2010). There was a 33% decrease of deaths from cancer in the radio-chemotherapy arm ($p = 0.004$).

EORTC conducted a randomized phase III study with RT *vs.* chemoradiotherapy in 110 patients with anal canal carcinoma (Bartelink et al., 1997). The radiation dose was 45 Gy in 5 weeks, followed by a rest period of six weeks, and then one further dose of RT of 20 or 15 Gy if the patient was in partial or complete response, respectively. In this study, the chemo-radiotherapy arm had a higher complete response rate (80% *vs.* 54%). This improvement of local control has resulted in fewer rates of loco-regional recurrence and higher colostomy-free survival ($p = 0.002$) and better progression-free survival (PFS) ($p = 0.05$). Acute and late toxicity were not significantly different between the 2 groups.

ACT I and the EORTC trials confirmed the superiority of chemioradiotherapy *vs.* RT alone. Both studies have shown improvements in the loco-regional control and in PFS with the addition of chemotherapy.

7.4.3.2. Role of mitomycin (MMC). The RTOG 87-04/Eastern Cooperative Oncology Group (ECOG) 1,289 study was a phase III trial designed to answer the question whether mitomycin was necessary in the treatment scheme (Flam et al., 1996). Radiotherapy delivered together with the only 5-FU was compared to a similar dose but in combination with 5-FU/MMC. The group treated with MMC had a rate of colostomy of less than 4 years (9% *vs.* 23%; $p = 0.002$), data most evident in the stages T3 and T4 ($p = 0.019$), and an improved PFS to 4 years (73% *vs.* 51%; $p = 0.0003$). However, no statistically significant difference in OS ($p = 0.31$) was observed. Addition of MMC determined an increase in acute toxicity, particularly neutropenia and thrombocytopenia ($p < 0.001$). No difference in late toxicity in both groups ($p = 0.26$) was documented.

This study confirmed the benefit of 5-FU and MMC in addition to RT, but it also suggested that attention should be given to immunocompromised patients due to the rate of neutropenia that MMC

can cause. Currently, it is good practice to use MMC at full dose (10 mg/m^2) in patients with normal blood counts or in HIV-positive patients who are on antiretroviral therapy with CD4 counts more than 200/mm^3, and to use a reduced MMC dose (5 mg/m^2) in patients with blood abnormalities.

7.4.3.3. Role of cisplatin. Given the encouraging results of phase II studies replacing the MMC with cisplatin (Chakravarthy et al., 2011; Doci et al., 1996), a further evaluation of cisplatin was justified. In the phase III RTOG 98-11 study, it was evaluated whether cisplatin was more effective than mitomycin (Ajani et al., 2008).

Even the comparison of the standard represented by chemo-radiotherapy with 5-FU/MMC and RT with cisplatin and 5-FU induction followed by chemo-radiotherapy with cisplatin and 5-FU was evaluated. The results of this study reported a higher 5-year DFS (67.8% *vs.* 57.8%; p = 0.006) and OS 5-year (78.3% *vs.* 70.7%; p = 0.026), with an improvement of the colostomy-free survival (71.8% *vs.* 64.9%; p = 0.053) in the group treated with standard therapy (Gunderson et al., 2012).

The hypothesis of this RTOG study was that induction chemotherapy could reduce the size of the disease and make the chemo-radiotherapy most effective, with consequent improvement in the DFS. Unfortunately, the results for cisplatin and of 5-FU arm were lower, and no benefit for induction chemotherapy was observed. Several hypotheses have been proposed for negative results. The first hypothesis was that induction chemotherapy has delayed the start of definitive chemo-radiotherapy, resulting in worse outcomes, and so there was not a proper comparison of the effectiveness of chemo-radiotherapy between the two regimes. Another hypothesis was that the 5-FU and cisplatin induction may either have caused radioresistance platinum-induced or may have induced accelerated repopulation.

The phase III study UNICANCER ACCORD III has tried to improve the results of the standard chemo-radiotherapy (RT + 5-FU/MMC) with the addition of induction chemotherapy with 5-FU and cisplatin or with increasing the radiation doses (boost) to the tumour (Peiffert et al., 2012).

307 patients with anal cancer were randomized with 2 × 2 scheme to receive: 2 cycles of induction chemotherapy with 5-FU and cisplatin, chemo-radiotherapy with 45 Gy in combination with 5-FU and cisplatin, followed by a standard dose to the tumour (15 Gy) versus the same scheme with overdose at high doses (20–25 Gy) *vs.* chemo-radiotherapy with 45 Gy in combination with 5-FU and cisplatin followed by standard dose (15 Gy) *vs.* overdose at high doses (20–25 Gy). The primary endpoint was colostomy free survival. No statistically significant benefit in colostomy-free survival at 5 years with chemotherapy induction (p = 0.37) or with high doses of radiation (p = 0.067) was observed. Even the secondary endpoints examined including local control, the tumour-free survival, and cancer-specific survival showed a statistically significant benefit.

ACT II study further evaluated the role of cisplatin. In a 2 × 2 factorial design study, 940 patients were randomized to receive RT (50.4 Gy) and 5-FU or MMC or cisplatin with or without 2 cycles of maintenance chemotherapy (5-FU and cisplatin) (James et al., 2013).

No significant difference in complete response rate and toxicity or in PFS was observed.

Chemoradiation with 5-FU and MMC remains nowadays the standard of care for the anal canal carcinoma treatment on a type 1 level of evidence and recommendation level A.

Concurrent chemoradiotherapy with ciplatin and MMC can be considered as an alternative, on type 1 level of evidence and recommendation level B.

7.4.3.4. Capecitabine and oxaliplatin. New molecules have been tested in phase II studies. The ACT II phase II (Glynne-Jones et al., 2008) multicentre study evaluated a regimen of chemo-radiotherapy with capecitabine/MMC with the following scheme: RT 50.4 Gy in 28 fractions of 1.8 Gy, with MMC (12 mg/m^2) on day 1; capecitabine (825 mg/m^2 twice daily) at every RT treatment day. Thirty-one patients were enrolled. Compliance with chemotherapy was 68% without interruptions or delays, dose response for RT was 81%. Only in one patient there was diarrhoea grade 3 and three patients experienced grade 3 neutropenia. Four weeks after completion of chemo-radiotherapy, 24 patients (77%) had a complete clinical response, and 4 (16%) had a partial response. With a median follow-up of 14 months, only 3 loco-regional relapses occurred. In a phase II study the chemotherapy scheme with capecitabine/oxaliplatin (Mitchell et al., 2014) was: capecitabine 825 mg/m^2 twice daily from Monday-Friday and oxaliplatin 50 mg/m^2 weekly. The enrolled patients underwent RT modulated in relation to the stage: for T1 tumours, 45 Gy in 25 fractions; for T2 tumours, 55 Gy in 30 fractions; and, for T3 and T4 tumours, 59 Gy in 32 fractions. Grade 3 gastrointestinal and perineal skin toxicity occurred respectively in 9% and 17% of patients. With a median follow up of 19 months the 2 years local control and distant disease control were 93%, 2 years overall survival and disease free survival were 96% and 86% respectively.

Currently, the use of these molecules cannot be made with the exception clinical studies.

7.4.4. Treatment of anal canal cancer in HIV-positive patients

The presence of HIV and anti-retroviral therapy is not a contraindication for combined modality treatment, although the acute toxicity related to treatment and the recurrence rate may be higher. Chemo-radiotherapy has been successfully employed in patients with HIV AIDS; the local control, the response to therapy, and the survival of these patients are comparable to those HIV-negative. Patients with CD4 counts greater than 200/mm^3 were correlated with low toxicity and good disease control (Chiao et al., 2008; Klencke and Palefsky, 2003).

Since cisplatin seems to be less myelotoxic than MMC, this drug may be a valid alternative for this group of patients on type 1 level of evidence and recommendation level B.

7.4.5. Anal canal cancer treatment in the elderly

Although it is sometimes recommend a dose reduction, the omission of chemotherapy, or the reduction of the irradiated volumes for the elderly and frail, current data suggest that elderly patients older than 75 years should be treated similarly to younger patients.

Good physical condition of elderly patients is increasing with the expectation of longer life expected (based on actuarial tables). Therefore, this group of patients is at risk of significant undertreatments if decisions are based only on age. A good cooperation between geriatricians, nurses, clinical radiotherapists, and medical oncologists will facilitate the execution of a radical curative treatment (Lestrade et al., 2013).

7.5. Residual anal canal cancer

7.5.1. Residual disease after chemoradiation

Gross or microscopic residual disease at full thickness biopsy is present in 6%–18% after chemo-radiotherapy. Biopsies with only a few tumour cells may be repeated after 6 weeks and may lead to the result of complete remission in some patients, on a type 3 level of evidence. Standard option for these patients is abdominoperineal resection (APR, Miles operation) with permanent colostomy on a type C basis. 10 old and 5 new publications have looked at long term results after APR. The results are conflicting and include usually results of persistent and relapsing cancers: local tumour control ranges from 80% to 0%, long term survival ranges from 64% to 0%. Small number of patients analysed as well as differences in initial treatment, stages, timing of biopsy, and timing of APR may explain these differences. In an operable patient with the possibility of a R0 resection APR should be done on a type 3 level of evidence (Nilsson et al., 2002; van der Wal et al., 2001; Smith et al., 2001; Pocard et al., 1998). Pelvic or perineal wound infections

are observed in 30% of patients (Pocard et al., 1998; Allal et al., 1999; Grabenbauer et al., 1998). Non-demolitive salvage surgery is under evaluation and may be considered as investigational (Allal et al., 1999; Zoetmulder and Baris, 1995).

Brachytherapy to avoid a permanent colostomy is suitable for individual clinical use in selected cases but seems to have a higher proportion of re-relapse. Second-line chemotherapy for one cycle with cisplatin and fluorouracil in patients previously treated with mitomycin and fluorouracil, and further low dose RT radiotherapy (9 Gy) is suitable for individual clinical use on a type 3 level of evidence for persistent local disease documented by biopsies performed 4–6 weeks after the end of initial chemo-radiotherapy with up to 50.4 Gy (Flam et al., 1996). Of 22 evaluable patients, 11 (50%) are alive without disease at 4 years, but only one third (4 patients) could avoid colostomy. Patients resistant to salvage chemo-radiation have a poor prognosis, since 75% of them die for uncontrolled disease even after salvage demolitive surgery.

7.6. Locoregional recurrence of anal canal cancer

7.6.1. Locoregional relapse

In case of no response, progression of disease, or local recurrence after an initial complete response, a radical demolitive surgery is indicated. Loco-regional recurrence within the first two years of treatment occurs in 10%–32% of patients after initial chemo-radiotherapy (median recurrence time 6–8 months) (Mullen et al., 2007; Schiller et al., 2007).

Relapsed patients undergoing rescue surgery have from 40% to 60% one-year survival rate (Renehan et al., 2005). The most useful prognostic factor after rescue abdominoperineal resection (APR) was the negative resection margin (R0), with increased rates of DFS and OS ($p < 0.001$ and $p > 0.03$, respectively) (Eason et al., 2011). Median survival for patients with positive and negative margins after salvage surgery was 33 months *vs.* 14.3 months, respectively. Execution of rescue APR involves wider lateral margins up to the ischial tuberosity. If the lesion is large (for example, in proximity of the vaginal wall), a bloc resection is required due to the risk of fistulae from previous RT (Sunesen et al., 2009; Bakx et al., 2004).

Alternatively, chemotherapy with a scheme different from the previously made, concomitant to a re-irradiation (also with brachytherapy, if indicated) in selected cases may be considered in order to preserve the sphincter (if reasonably possible and has to be agreed and discussed with the patient in any case). Brachytherapy to avoid a permanent colostomy is to be considered for individual clinical use in selected cases but it seems to be linked to a high incidence of re-recurrences.

Retreatment with radiochemotherapy followed by radical surgery with radical intent, may be the recommended treatment in selected cases. The second-line chemotherapy with one cycle of cisplatin and 5-fluorouracil also followed by low dose RT (9 Gy) in patients previously treated with mitomycin and 5fluorouracile, is to be considered for individual cases.

Patients resistant to chemotherapy and radiation therapy have a poor prognosis, about 75% of them die from a not controlled disease after a demolitive rescue surgery.

7.6.2. Nodal relapse

Patients with inguinal recurrence who did not receive radiation in the inguinal area can be treated with rescue chemo-radiotherapy. Lymph node dissection should be performed if the inguinal region has already been irradiated.

7.7. Metastatic disease

7.7.1. Chemotherapy

A minority of patients (12%) will present metastatic disease and 10%–20% of those treated with curative intent will later develop metastatic disease (Arnott et al., 1996; Horner et al., 2009; Ryan and Willett, 2001). The most common site of metastasis is the liver; however, other interested sites are lungs, lymph nodes, peritoneum, bones and brain (Cummings, 2006). Patients who develop distant metastases have a poor prognosis. Surgery has been successfully used for metastases, such as solitary brain and hepatic metastases (Rughani et al., 2011; Tokar et al., 2006).

There are few studies on the treatment of distant metastases. Although the tumour is relatively chemosensitive, there are not chemotherapy schemes unanimously accepted. Most of the available literature on the treatment is based on case studies or series.

The first-line regimen in metastatic disease is the combination of cisplatin and 5-FU with overall response rates (ORR) of approximately 60% and a median survival of approximately 12 months (Faivre et al., 1999; Jaiyesimi and Pazdur, 1993; Tanum, 1993; Khater et al., 1986; Ajani et al., 1989).

Other single agents or combination regimens that are effective in other malignancies (such as head and neck, cervical cancer and gastrointestinal cancers) have been investigated.

The role of taxanes in chemotherapy combination regimens was demonstrated in short series of patients. In 2011, Golub et al. (2011) reported the results of the use of paclitaxel, ifosfamide and platinum in 3 patients (previously treated with FU and cisplatin) with recurrent metastatic anal cancer. They concluded that this regimen is highly active. Kim et al. (2013) obtained 4 complete response in 8 patients with recurrent advanced (metastatic) squamous cell anal carcinoma with a chemotherapy regimen of docetaxel, cisplatin and FU chemotherapy. Data on HPV status were available for 6 patients only; all patients in complete response were HPV-16-positive.

The effectiveness of chemotherapy regimens used for gastrointestinal cancers were also reported in two case reports.

Partial response was achieved in one patient with liver metastases and wild type KRAS after 6 cycles of FOLFIRI and cetuximab (Barmettler et al., 2012). Similar result was reported in another case report, the use of the FOLFOX regimen, followed by FOLFOX and panitumumab, then by FOLFIRI and panitumumab, reduced the primary tumor with disappearance of the metastasis in the lung (Bamba et al., 2012).

7.7.2. Novel approach

The biological characterization of anal carcinoma has been recently investigated.

Walker et al (Walker et al., 2009) in an analysis conducted on 118 HPV-positive patients with anal cancer, found that 96% of invasive carcinomas simultaneously expressed EGFR, c-Met, VEGFR1 and p16; human epidermal growth factor receptor 2 (HER2) was absent. These results are promising because they introduce tyrosine kinase inhibitors (TKIs), anti-EGFR monoclonal antibodies, AMG102 (monoclonal antibody against HGF, sole ligand of c-Met) and AEE788 (TKI of ErbB and VEGF pathways) as new agents for the treatment of metastatic disease.

Casadei Gardini et al. (2014) analyzed the KRAS, BRAF and PIK3CA status in 50 patients with squamous cell anal carcinoma treated with concomitant CRT. Though the KRAS and BRAF genes were wild-type in all cases, the PIK3CA gene was mutated in 11 (22%) cases, suggesting and that this pathway may be used for targeted therapy against anal carcinoma.

7.7.3. Immunotherapy

Recently the expression of programmed cell death-ligand 1 (PD-L1) in anal cancer was investigated.

In a retrospective cohort analysis (Ott et al., 2017), 41 patients with squamous cell carcinoma of the anal canal were tested for PD-L1 expression, then followed for recurrence and survival. The expression of PD-L1 was found in 23 patients (56%). PD-L1 positivity was associated with worse prognosis in terms of recurrence and mortality. The effect on progression-free and overall survival needs to be validated in a study

with a larger sample size.

Safety and efficacy of pembrolizumab, a humanized programmed death 1 monoclonal antibody, was assessed in KEYNOTE-028 (Govindarajan et al., 2016), a multicohort, phase Ib trial for patients with PD-L1 positive advanced solid tumors. The results for the cohort of patients with advanced anal carcinoma, showed that of the 43 patients with advanced anal carcinoma evaluable for PD-L1 expression, 32 (74%) had PD-L1-positive tumors and 25 were enrolled and treated with pembrolizumab between April and September 2014. Among the 24 patients with squamous cell carcinoma histology, four had confirmed partial response, for an overall response rate of 17% and 10 patients (42%) had confirmed stable disease, for a disease control rate of 58%. One additional patient with non-squamous histology had confirmed stable disease.

7.7.4. HPV vaccine

Squamous cell tumors of the anal canal are associated to HPV in 90% of cases (Parkin, 2006; Forman et al., 2012).

HPV vaccination showed a reduction of premalignant lesions (AIN 2/3) HPV 16/18 related in a randomized controlled trial of healthy men who had sex with men between 16 and 26 years of age (Palefsky et al., 2011).

The Advisory Committee on Immunization Practices guidelines consider the universal HPV vaccination of boys and girls at 11–12 years of age as the most effective way to prevent future HPV-associated disease.

The treatment with agent containing a segment of HPV-16 E7 protein stimulating an immune response against E7 seems clinically feasible and safe.

7.7.4.1. Technical radiotherapy. Modern techniques of intensity modulated radiation therapy (IMRT) allows to deliver an appropriate dose for the cancer treatment reducing the dose to surrounding normal tissues such as skin, intestines, bladder, femoral heads, external genitalia, and bones. The IMRT has been evaluated in various studies and it was superior to RT with 3D conformed technique, because the significant reduction in the acute toxicity to surrounding organs reduces the likelihood of treatment interruptions, diminishing the overall time of treatment, since it directly influences the response probability (Chuong et al., 2013a; Dewas et al., 2012). Several retrospective studies demonstrated the safety and feasibility of IMRT and concomitant chemotherapy (Mitchell et al., 2014; Chuong et al., 2013a; Dewas et al., 2012; Kachnic et al., 2013; Milano et al., 2005; Bazan et al., 2011; Dasgupta et al., 2013; Saarilahti et al., 2008) resulted at 2 and 3 years in terms of loco-regional control, free colostomy survival, and OS varying from 77% to 95%, from 81% to 93%, and from 87% to 100%, respectively, with acute gastrointestinal toxicity grade 3 from 0% to 28%, and skin toxicity from 0% to 38%. Better data than those reported in the RTOG 98-11 study, in which all patients were treated with conventional RT, reported higher acute GI and skin toxicity (36% and 49%, respectively) (Ajani et al., 2008; Gunderson et al., 2012). The prospective phase 2 RTOG 0529 has been completed, and has shown that IMRT reduces the acute toxicity compared to the RTOG 98-11 study (Kachnic et al., 2013); therefore, the IMRT technique is considered the standard of care in patients undergoing combined treatments (Herman and Thomas, 2013).

Target definition for radiotherapy should is performed on CT scan, according to guidelines (Myerson et al., 2009; Ng et al., 2012a; Gay et al., 2012).

GTV (gross tumour volume) includes the tumour and the positive lymph-nodes. 18- FDG PET CT images co – registered on the simulation CT scan might help in target definition. CTV (clinical target volume) includes anal canal, ischiorectal fossa, mesorectum, presacral space, internal iliac limph nodes, external iliac lymph nodes, obturatory lymph nodes and inguinal lymph nodes.

Dose prescription to different volumes according to different stage of disease is still controversial. Randomized trials proposed the dose of 45 Gy to CTV followed by a boost of 9–20 Gy to GTV. Total dose higer than 59 Gy in radiochemotherapy did not showed any benefit. (Peiffert et al., 1948; John et al., 1996b; Konski et al., 2008) (evidence Ib, B level recommendation).

Break during radiochemotherapy is detrimental on outcome, and the overall treatment time should not exceed 53 days (evidence Ib, B level recommendation) (Ben-Josef et al., 2010; Glynne-Jones et al., 2011).

The prophylactic irradiation of inguinal lymphnodes with a dose of 45 Gy increase local control and should be recommended in case of T3 – T4 tumor (Ib,A). In case of early T stage, this choice is still controversial (Ortholan and Resbeut, 2012). The irradiation of common iliac lymph nodes is still debated (Ng et al., 2012b) and suggested by some authors in case of massive involvement of superior external lymphnodes.

7.7.4.2. Brachytherapy. Brachytherapy is a technique capable of providing ablative doses directly to the tumour, allowing a saving of the surrounding normal tissues which cannot be achieved with other techniques Originally, interstitial brachytheray was first described as a curative treatment of T1 anal canal or margin, with outstanding results. (Gabriel, 1941; Dalby and Pointon, 1961). Thereafter brachytherapy was used as overdosing the tumour after external radiotherapy (Arnott et al., 1996; Lestrade et al., 2013; Papillon et al., 1989) or as salvage treatment for isolated local failures (Chuong et al., 2013b).

Numerous studies have been conducted to compare the effects of overdose with external beams radiotherapy *vs.* Brachytherapy (Khater et al., 1986; Saarilahti et al., 2008; Moureau-Zabotto et al., 2013). However, despite the improvement in local control and proctitis, the data are conflicting. Given the lack of prospective data and the advances in radiotherapy techniques that have led to improved toxicity profiles, it is difficult to support the use of brachytherapy. The benefit of brachytherapy may be limited to patients who have a poor response to initial chemo-radiotherapy thanks to the high dose that can delivered, which might be able to overcome the radioresistance of this group of patients.

8. Late effects and sequelae

8.1. Treatment of late effects and sequelae

The majority of patients treated with chemotherapy and RT after being diagnosed with anal cancer has an excellent outcome (Ajani et al., 2008). However, particular problems related to the psychological adaptation to early side effects as well as late toxicity are present and can negatively affect the quality of life. Among these effects, sexual, urological/GI dysfunction, fatigue, and reduction of the social and emotional well-being are reported (Welzel et al., 2011; Rao et al., 2014). The reporting of sexual dysfunctions is consistent with the results previously observed in women with gynaecological malignancies (Andersen et al., 1989) and in men with prostate cancer (Crook et al., 1996), in which the loss of sexual desire and/or orgasm, dyspareunia, and impotence are frequent. Das and colleagues also evaluated long-term QoL using the FACT-C functional evaluation and the Medical Outcomes Study (MOS) for sexual problems. The results of this study indicate that in patients treated with RT or chemo-radiotherapy the global QoL scores were acceptable, but poor scores for sexual functioning, while younger patients had either lower QoL and sexual scores (Das et al., 2010). Diarrheal, faecal incontinence, rectal urgency, and flatulence vary in nature and severity. However, Bentzen et al. (2013) observed in long-term survivors that the social functions and roles have been clearly reduced because these symptoms were perceived to be embarrassing, with impact on self-confidence.

8.2. Second tumours

Following successful treatment of anal carcinoma, there is an increased risk of subsequent tumours (particularly cancer of the lung, bladder, breast, vulva/vagina, cervix). Treatment of these second primaries is to be individualized according to the site and to the previous treatment the patient has already received, particularly radiation treatment.

9. Follow-up

9.1. General aims

Aims of follow-up are early detection of a loco-regional relapse after conservative treatment and after demolitive surgery. Following successful treatment of anal carcinoma, there is an increased risk of second tumours. Even though there is no evidence of the specific role of follow-up in early detection of second related primaries, a clinical surveillance is recommended on a type R basis.

9.2. Suggested protocols

After treatment completion, a manual rectal examination and anoscopy every 3–4 months for the first two years and every 6 months after two years are the standard option. In patients defined at high-risk (T3/T4, lymph node-positive) also a CT of chest, abdomen, and pelvis at 6 and 9 months and 1 year up to 3 years from the end of RT is recommended.

The use in follow-up of the pelvic MRI is still subject of controversy and its half-yearly use is reserved for patients at risk in the first two years after RT. Cases of local recurrence diagnosed at an early stage may have a favourable prognosis after abdominoperineal resection. Early detection of distant metastases is of little importance, and these patients should be treated accordingly.

Conflict of interest disclosure

The authors declare they have no conflict of interest.

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