Carcinoma of the anal canal and anal margin

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Table of contents

According to the authors and editors, this report contains the most justified principles of diagnostic and therapeutic procedures prepared considering the scientific value of evidence and category of recommendations. These principles should always be interpreted in the context of an individual clinical situation. The recommendations do not always correspond to the current reimbursement rules in Poland. In case of doubt, the current possibilities of reimbursement of individual procedures should be established.

1. *The quality of scientific evidence*
   I — Scientific evidence obtained from well-designed and conducted randomized clinical trials or meta-analyses of randomized clinical trials
   II — Scientific evidence obtained from well-designed and conducted prospective observational studies (non-randomizedcohort studies)
   III — Scientific evidence obtained from retrospective observational studies or case-control studies
   IV — Scientific evidence obtained from clinical experiences and/or experts, opinions
2. *Category of recommendations*
   A — Indications confirmed unambiguously and absolutely useful in clinical practice
   B — Indications probable and potentially useful indications in clinical practice
   C — Indications determined individually

Epidemiology

Anal canal and anal margin cancers are rare, accounting for 1–2% of all gastrointestinal (GI) cancers. In 2017, there were 286 newly diagnosed cases in Poland [1]. This type of GI cancers is more frequent in women than in men and the age of onset is usually 60–65 years. As anal canal and anal margin cancers are different clinical entities with different treatments they will be separately discussed. In doubtful cases, when the tumor infiltrates both the skin of the anal margin and the anal canal, the diagnosis is determined by the location of the main tumor mass.

Etiopathogenesis

The risk factors of the anal canal and anal margin cancers include human papilloma virus (HPV) and human immunodeficiency virus (HIV) infection, sexual habits (passive anal intercourses), previous cervical cancer and immunosuppressive treatment after organ transplantation. HPV infection is detected in 84% of patients and therefore is considered to be the most important. Anal marginal cancer may arise from condylomas.

Anal margin carcinoma is a skin cancer that occurs within 5 cm from the anal verge. The anal canal extends 3–5 cm from the anal verge to the superior border of the puborectalis muscle, palpable *per rectum*, where it connects to the rectum. The anal margin is lined with multi-layered squamous keratinizing epithelium, and the initial segment of the anal canal is lined with multi-layered squamous non-keratinizing epithelium. The pectinate (dentate) line is the upper border of the anal canal. Above this line, the transitional epithelium begins which passes without a clear border into the typical, single-layered, cylindrical intestinal epithelium. Anal canal cancer most often arises from the transitional epithelium and therefore is usually located in the upper part of the anal canal. Sometimes, due to the lack of anatomical barriers, the tumor spreads towards the rectum, where its main mass could be palpable. If squamous cell carcinoma is detected in histological evaluation, the anal canal carcinoma should be diagnosed, rather than rectal cancer. Rectal squamous cell carcinomas are very rare and should be diagnosed only when the tumor does not connect to the superior border of the anal canal.

The lymphatic drainage pathways of anal margin skin include the inguinal, external iliac, and common iliac lymph nodes.

Lymphatic flow from anal canal goes in three principal directions:
— cephalad, initially through the perianal lymph nodes in the mesorectum, then to the lymph nodes located along the course of the upper rectal and lower mesenteric vessels;
— lateral, along the course of the middle rectal vessels to the internal iliac lymph nodes, then the common iliac and periaortic lymph nodes;
— to the inguinal, then to the external iliac and finally to the common iliac lymph nodes.

Pathology

The most common histological type of anal canal neoplasms is squamous cell carcinoma (SCC), which may arise from the so-called high grade anal intraepithelial neoplasia (HG-AIN). Previously diagnosed types of squamous cell carcinoma — carcinoma basaloides, transitionale, cloacogenes, and keratodes — are now grouped under the common name of squamous cell carcinoma because their differentiation is not clinically relevant (no difference in prognosis by cancer subtype for the same stage and identical treatment). A type of squamous cell carcinoma is verrucous carcinoma, a special form of which is malignant giant genital warts (GGWs) (the so-called Buschke-Loewenstein tumor).

Anal canal adenocarcinoma is diagnosed in 5–10% of patients. Melanoma is much less common.

The most common histological type of anal margin cancer is squamous cell carcinoma. Less common are basal cell carcinoma, extramammary Paget disease or Bowen's disease (currently perianal squamous intraepithelial neoplasia, PSIN).

Diagnosis — general principles

Rectal bleeding is the most common symptom. This is followed by pain and fecal incontinence and a visible or palpable tumor in the anus or groin area. Signs and symptoms of high tumor stage include pain in the pelvic area, symptoms of partial obstruction, rectovaginal fistula, the involvement of the ischioanal fossa and buttock skin fistulas. Metastases to the regional lymph nodes (inguinal and pelvic) occur in approximately 30% of patients, and synchronous distant metastases in approximately 10% of patients. Incorrect diagnosis of varicose veins, anal fissure or abscess, quite frequent in the first period of the disease leads to proper treatment delay.

Staging

The clinical assessment is based on a detailed *per rectum* examination and — performed under anesthesia — anoscopy with taking a specimen for histological examination. In women, *per vaginam* examination and two-handed examination (*per rectum* and *per vaginam*) are mandatory and performed in order to assess the rectovaginal septum and infiltration of the mucosa.

Description of *per rectum* examination, necessary when planning radiotherapy (RTH) to determine gross tumor volume (GTV), should include the assessment of the distance of lower and upper tumor edge from anal margin, as well as the length of the rectal involvement above the upper border of the anal canal. The anal canal wall involved, the percentage of circumference involved, and the degree of tumor mobility should be determined. Description of *per rectum* examination should also include the assessment of the mesorectal lymph nodes. They can be palpable through the unchanged rectal mucosa in the form of hard nodules, which proves their metastatic nature. The description of *per vaginam* examination should include the condition of the vaginal mucosa — when it is involved, the patient should be informed about the risk of rectovaginal fistula development after or during treatment. Careful diagnostics of the inguinal lymph nodes is essential, which is important for precise RTH planning. Histological verification is not necessary in the case of enlarged inguinal lymph nodes if clinical examination indicates their metastatic nature. In doubtful cases, a fine-needle aspiration biopsy is performed.

The diagnostic tests necessary for the diagnosis and staging of anal canal and anal margin cancer are presented in Table 1. Colonoscopy is not necessary as the lesions in the colon are not related to anal canal cancer. Table 2 presents the staging of anal canal cancer according to TNM classification [2]. It applies both to anal canal and anal margin cancer [3].

Treatment of anal canal squamous cell carcinoma (SCC)

The treatment of choice for anal canal squamous cell carcinoma is concurrent radical chemoradiotherapy (CRTH), which is indicated even in more locally advanced cases (II, A). Generally, patients with HIV do not require the modifications of the treatment regimens listed below. CRTH should also be administered in elderly patients with use of standard doses of radiotherapy and irradiated volumes as well as the regimen of cytotoxic treatment.

Principles of radiation therapy

According to the patient's general condition (PS, performance status), radiotherapy is combined with chemotherapy (CTH). Two atlases detailing the contouring principles have been published so far [4, 5]. Additionally, useful information on the practical aspects of contouring is provided in the publication on the pelvic

Table 1. Diagnostic tests essential to diagnose and stage anal canal and anal margin cancer

Diagnostic tests	The most important information
Anoscopy with taking a sample for histological examination	Assessment of tumor location and extent
	Histological verification of the tumor
	— Excision biopsy should be avoided as healing may prolong the time to initiate causal treatment
High-resolution MRI of the pelvis	Local advancement assessment
	Necessary for RTH planning, mainly for GTV contouring
	— Pelvic CT scan is not sufficient as small anal canal tumors are not visible
Abdominal and chest CT	Exclusion of metastatic changes
	Necessary before treatment in all patients
	— Chest X-ray instead of CT is allowed
PET-CT (if available)	Improves the effectiveness in detecting metastases to regional lymph nodes
	Facilitates contouring of the primary lesion
	Is not strictly necessary
Blood tests	Complete blood count
	Biochemical panel
	The clinical usefulness of squamous cell carcinoma antigen (SCCAg) has not been proven
Assessment of the presence of anti-HIV antibodies	Exclusion of active infection
Gynecological examination	Collection of material from the cervix for cytological examination
	— HPV — a common etiological factor in the development of anal canal, cervical and vaginal cancers

GTV — gross tumor volume; HIV — human immunodeficiency virus; HPV — human papilloma virus; CT — computed tomography; MRI — magnetic resonance imaging; PET-CT — positron emission tomography-computed tomography

Table 2. Anal canal cancer staging according to TNM classification (8th edition, 2017) [2]

T	Primary tumor
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade squamous intraepithelial lesion (previously termed carcinoma in situ, Bowen disease, anal intraepithelial neoplasia II–III, high-grade anal intraepithelial neoplasia)
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size invades adjacent organ(s) (e.g., vagina, urethra, bladder)
N	Regional lymph nodes
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes
N1a	Metastasis in inguinal, mesorectal, or internal iliac lymph nodes
N1b	Metastasis in external iliac lymph nodes
N1c	Metastasis in external iliac with any N1a nodes
M	Distant metastasis
M0	No distant metastasis
M1	distant metastasis
Clinical stages	
0	TisN0M0
I	T1N0M0
IIA	T2N0M0
IIB	T3N0M0
IIIA	T1-2N1M0
IIIB	T4N0M0
IIIC	T3-4N1M0
IV	Any T, Any N, M1

lymph nodes location [6]. Basic information is provided below. Intensity-modulated radiation therapy (IMRT) or its arc variant (V-MAT, volumetric modulated arc therapy) should be routinely used [7]. This allows for the reduction of acute toxicity, mainly in the perineal skin area, therefore a break in irradiation caused by skin radiation reaction is currently very rare. Studies have shown that interruptions in treatment reduce the effectiveness of local radiotherapy, so they should be avoided or shortened whenever possible [8]. Depending on the stage the most frequently used doses are 50–60 Gy in fractionated doses of 1.8 or 2 Gy. The use of irradiation doses higher than 60 Gy does not improve treatment outcomes [9]. The traditional and best-documented regimen is two-stage irradiation. Not infiltrated regional lymph nodes in the groin and the pelvis are always irradiated; the dose of 30.6–36 Gy in fractions of 1.8 Gy is given to this volume in the first stage of treatment. In the second stage of treatment, the volume irradiated with a high dose is limited to macroscopically detected lesions in the anal canal and margin as well as enlarged inguinal and pelvic lymph nodes; the fractional dose may be increased to 2 Gy. Depending on the size of these lesions, the total irradiation dose ranges from 50 Gy to 54 Gy. In patients with a residual tumor identified at the end of treatment, increasing the dose by 5.4–6 Gy may be considered, although this has not been proven (IV, B). An optional regimen is a single--stage radiotherapy using a simultaneous integrated boost (SIB) technique, assessed in a US prospective phase II study with a historical control group [7]. In patients with T3-4 or N1 stage cancers, the dose of 54 Gy in 30 fractions was administered to the primary tumor and lymph nodes over 3 cm, 50.4 Gy to enlarged lymph nodes ≤ 3 cm and 45 Gy to the elective volume; the fractional doses were 1.8 Gy, 1.7 Gy and 1.5 Gy, respectively. In patients with cancer stage T1–2N0, the dose of 50.4 Gy in 28 fractions to the primary tumor and 42 Gy to the elective volume was administered; the fractional doses were 1.8 Gy and 1.5 Gy, respectively.

Some centers use brachytherapy to the residual primary tumor instead of the second stage of irradiation with an external beam (IV, C). However, approximately 5% of these patients develop radiation necrosis of the anal canal, necessitating the creation of a stoma; this complication is practically not observed after the use of irradiation with only external beams. Furthermore, there is no evidence of an improvement in local efficacy with brachytherapy compared to treatment with only external beams.

In patients ineligible to CTH due to concomitant diseases, stand-alone RTH is used. The doses must then be increased by 5 Gy to 10 Gy compared to the above--mentioned doses. When one instead of two courses of CTH is administered due to toxicity, increasing of the total irradiation dose should be also considered.

Principles of simultaneous chemoradiotherapy

The CTH regimen consists of 2 cycles of fluorouracil in continuous infusion and mitomycin (I, A). The randomized clinical trials with cisplatin instead of mitomycin have shown similar treatment outcomes (I, A) [10, 11]. The use of neoadjuvant or adjuvant CTH does not improve treatment outcomes (I, A) [9–11]. The superiority of CRTH has been shown compared to RTH alone in

terms of better local efficacy in prolonging stoma-free survival but with no impact on overall survival (I, A) [12]. The value of mitomycin as a component of CTH was also confirmed (I, A) [13]. Retrospective studies suggest similar treatment efficacy when fluorouracil is replaced by capecitabine (III, B).

The routine CTH regimen given during irradiation consists of two cycles of fluorouracil and mitomycin given at week 1 and 5 of radiotherapy. Fluorouracil is administered at a dose of 1000 mg/m^2/24 h in a 96-hour continuous intravenous infusion. Mitomycin is administered on cycle day 1 or 2 at a dose of 10 mg/m^2 (the maximum dose is 20 mg). The cycle is repeated after 28 days. In order to reduce the toxicity, it is possible to administer mitomycin only in the first course. Retrospective studies have shown that this does not reduce treatment effectiveness (III, B) [14].

The value of consolidating CTH after completion of CRTH is not proven.

There is some controversy regarding the advisability of concurrent CRTH use in patients with cancer stage T1–2N0. However, it should be considered, because without CRTH the irradiation doses should be higher than those described above.

Surgery

A primary abdominosacral resection is a mistake; this operation is performed only as part of salvage therapy after CRTH failure and in patients with contraindications to RTH (e.g. after RTH of the pelvic region). CRTH rapidly reduces discomfort caused by the tumor, so the indications for a pre-treatment bypass stoma creation are rare; the typical indication is a vaginal fistula. The value of local resection of confirmed anal canal squamous cell carcinoma is questionable even in stage I tumors, due to frequent relapses in local or regional lymph nodes.

Surgical treatment can only be used in the case of recurrent disease, and examinations should always be performed to assess the condition of abdominal and thoracic organs in order to exclude the metastases.

Complications

CRTH is associated with a high risk of acute radiation complications. Grade 3–4 early complications occur in approximately 70% of patients and include painful radiation dermatitis, weakness, diarrhea, nausea, vomiting, pollakiuria, leukopenia, and anemia. Most patients require opioid analgesics. It is advisable to use antibacterial ointments (e.g. argosulfan) on the skin affected by radiation. The use of topical lidocaine can relieve the symptoms. The acute radiation reaction lasts for about 2–3 weeks after treatment. Due to the high risk of leukopenia, it is necessary to perform a complete blood count once a week. There is a common admixture of blood in the stools due to radiation telangiectasias in the rectum. A colonoscopy should then be performed to rule out other causes. Treatment with argon beamer to stop bleeding is not frequently necessary. The risk of femur fracture is increased. Erectile dysfunctions in men are also possible. Even small doses of radiation dispersed in the testes can cause infertility and hypogonadism. Young and middle-aged men should be informed about this complication in order to possibly deposit sperm in a sperm bank. In women, radiation-induced vaginal dryness causes painful intercourse. In those who do not have intercourse, the vaginal encroachment can occur, so artificial expansion is recommended. Young women will experience early menopause soon after CRTH. It is then advisable to consult a gynecologist regarding the advisability of using hormone replacement therapy.

Prognosis

Unfavorable prognostic factors are large primary tumor size, metastases to regional lymph nodes, male gender and skin ulceration. It should be emphasized, however, that anal margin and anal canal squamous cell carcinoma is a radiosensitive tumor. Even patients with locally advanced cancer can be cured; these patients should be treated radically. Local or regional lymph node recurrence usually occurs within the first 3 years after treatment completion. The local effectiveness of CRTH in patients with anal canal or anal margin cancer is similar and accounts for approximately 80%. After treatment, distant metastases are rare and occur in approximately 10–15% of patients.

Follow-up examinations

Post-treatment follow-up is recommended every 3 months for the first 2 years, then every 4 months for up to 3–4 years (II, B). Almost all relapses appear up to 3 years after treatment. *Per rectum* and groin examination is basic with the description of *per rectum* examination at the end of irradiation as a baseline. The presence of a residual, non-growing tumor in the follow-up examination does not justify the diagnosis of treatment failure. Biopsy of such lesions is not recommended. The tumor sample is taken only in case of progression suspected prior to salvage abdominoperineal resection. The residual tumor may shrink slowly, up to 6 months after treatment [15]. In some cases of initially very advanced cancers, it is advisable to perform a pelvic MRI examination during the first follow-up as a starting point for an objective comparison of the residual lesions in subsequent examinations performed at 1–2 month intervals until complete regression is achieved. This is especially

true in case of ulcerated anal margin cancers, which leave large scarring lesions during healing. As distant metastases are rare and usually occur together with local recurrence, the value of periodic pelvic, abdominal and chest CT examinations is doubtful. In women, a cytological examination of the material collected from the cervix is recommended once a year due Hto PV infection which is the common etiological factor of anal canal and cervical cancer.

Surgical salvage therapy

CRTH ineffectiveness most often occurs in the primary tumor, both as a result of its failure to regress completely and as a result of its recurrence after complete regression. Then, in the case of histologically confirmed local recurrence, a salvage abdominosacral resection is performed (III, A). Due to the rapid cancer progression after irradiation, these patients should be operated urgently. According to the previous high dose irradiation, this procedure is associated with a high (> 50%) risk of complications consisting in long-term impairment of perineal wound healing. For this reason, it is recommended to perform surgery in a specialized center, with perineal reconstruction, for example with a myocutaneous flap from the rectus abdominis muscle. 5-year survival rates after this treatment are approximately 50%.

Much less often, cancer recurrence can occur in the inguinal lymph nodes. In such a case, radical inguinal lymphadenectomy should be considered. In some cases, when the previously used irradiation dose does not exceed 40 Gy, pre- or postoperative CRTH is possible.

Treatment of patients with distant metastases

In patients with synchronous distant metastases, CRTH is still indicated for lesions located in the pelvis with the radical doses mentioned earlier. This is aimed at obtaining a local cure and therefore the quality of life improvement. Then, elective irradiation is applied to a limited volume.

The appearance of distant metastases is an indication for palliative CTH — the standard CTH regimen has not been clearly established, but fluorouracil (± calcium folinate) with cisplatin or carboplatin with paclitaxel is usually used (II, A). The decision to use palliative CTH should take into account the patient's age and PS, concomitant diseases and the tumor dynamics (including disease-free survival after primary treatment). The median overall survival in patients undergoing CTH is 12–20 months. There is no evidence that metastasectomy is effective.

Treatment of the oligometastatic disease is individualized. A metastasectomy should be considered. Stereotactic radiotherapy alone or in combination with irradiation of the adjacent region with an elective dose may also be used (it is possible, for example, to cure nearly 50% of patients with isolated metastases in the periaortic lymph nodes, with no distant metastases in other organs [16]). This method is also used in the case of isolated relapses in the pelvis outside the irradiation volume or in the elective volume.

Treatment of anal canal adenocarcinoma

Abdominoperineal resection is a standard of care, as in most patients, adenocarcinoma is not highly radiosensitive. Preoperative CRTH is routinely used according to the same principles as in patients with rectal cancer (III, B). The elective volume should additionally include inguinal nodes.

In patients with tumors ≤ 4 cm without lymph node metastases, encouraging results were obtained by combining local excision with CRTH or by using only a high dose of CRTH (IV, C). Then, the abdominoperineal resection is performed only in case of failure. However, this is not considered standard practice.

Chemotherapy in metastatic disease is used similarly to that in patients with colorectal cancer.

Treatment of anal margin squamous cell carcinoma

Treatment of patients with low stage anal margin cancer (≤ 4 cm without metastases to regional lymph nodes) is based on radical surgical resection of the tumor, similar to that in patients with skin cancer of a different location. The possibility to preserve free macroscopic surgical margin of at least 1 cm is a prerequisite. Patients with a narrow (< 1 cm) or positive surgical margin in microscopic evaluation require extended resection or postoperative CRTH. In patients with more advanced cancer or when local resection would impair the function of the sphincters CRTH is used, as in patients with anal canal cancer.

Conflict of interest

The authors declare no conflict of interest.

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