



Professional article

Anal Carcinoma: A Series of Cases with a Literature Review

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SUMMARY

The aim of this study was to analyze the cases of five patients with squamous cell carcinoma (SCC) and to draw attention to the dilemma in the treatment of incontinence on admission of these patients and to present, through a literature review, locations of the surgical treatment.

The anal carcinoma is a rare disease which involves different histopathological (HP) types of cancer. They account for about 2.5% of all digestive cancers. The treatment of the disease is multimodal. There are dilemmas about screening of precancerous lesions and treatment of diagnosed incontinence. There is a high similarity between HPV infection and SCC. Our methods and results were compared with the data from the literature.

In the period of three years (from 2013 to 2015), five cases of the anal carcinoma were diagnosed and treated in the regional hospital. In all of our cases, the disease was histopathologically confirmed as SCC of the anal and perianal areas. It excluded the cases of anal adenocarcinoma (AAC).

Nearly half of the patients (40%) were incontinent and the rectum excision was one of the possible solutions. Distinction in histopathological structure created the confusion in the treatment of these patients. The dilemma we had was whether to do an amputation of the rectum in patients with incontinence before the standardized Chemoradiation therapy (CRT). The review of the literature sums up certain conclusions.

The diagnosis of SCC includes the perianal "ulcer" that does not heal, as well as atypical ano-perianal growths. Surgical treatment of SCC is indicated when the diameter of lesion is small (2 cm), or the disease is persistent or recurrent. In the case of anal incontinence because of the tumor changes, the abdominoperineal resection of the rectum (APR) is an alternative to performing bipolar colostomy and CRT. The review of the literature using MEDLINE/PubMed databases did not find the case with restoring anal continence after this treatment. Testing a larger number of patients with incontinence on admission would provide a more clear answer to the question of the treatment of these patients.

Key words: anal carcinoma, squamous cell carcinoma, chemoradiation therapy

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INTRODUCTION

The incidence of anal cancer is increasing. They are defined by the localization and they can be histopathologically very heterogeneous. The anal cancer makes up 1.5% (1) - 2.4% (2) of all cancers of the digestive system. The average age of the patients is 60 years. The anal carcinoma is divided into the anal canal carcinoma, perianal carcinoma (in the anal margin up to 5 cm from the entrance to the anus) and skin carcinoma (3). Histopathologically, 80% of the cancers of the anal canal are of the squamous type, 5-10% are adenocarcinoma, and the remaining 5% include neuroendocrine neoplasmas, mesenchymal tumors, lymphomas, melanocyte tumors and secondary tumors.

In the past decade, the etiology of the disease has changed, giving importance to connection between a viral infection in general and the development of SCC. There is an analogy between SCC and cervical cancer. The development of the disease is also attributed to the compromised immunological defense of the body (homosexuality, HIV, post-transplantation immunosuppression, etc).

The diagnosis is based on symptomatology (the growth of an ulcer which does not heal, itching, bleeding, etc), inspection, and biopsy. Endoanal ultrasound (EUS) is used to determinate the invasion into the anal sphincter as well as the post-therapeutic effect (4).

Computed tomography (CT) and magnetic resonance imaging (MRI) can occasionally be used for the evaluation of lymph nodes, as well as lymphnode biopsy (SLNB) or PET scan, (5) and palpation of the inguinal and abdominal lymph node. MSCT is a better solution compared with the abdominal or X-ray imaging.

Thirty years ago, the standard treatment was an abdominoperineal resection by Miles (APR) for intra-

anal cancers and a wide excision for perianal SCCs. The work of Nigro from 1974 (6) was crucial for the treatment of the intra-anal cancers by means of the CRT, and it marked the change in the treatment strategy. This strategy proposes to eradicate a tumor without sacrificing the anal sphincter. The key question is what to do when there is incontinence, complete or partial, due to tumor ingrowth into the anal sphincter.

The paper highlights and analyzes SCC. The aim of the paper is to draw attention to the dilemma in the treatment of incontinence on admission of these patients, and to present, through a literature review, locations of the surgical treatment.

CASE REPORTS

Case report No1

A male, 63-years-old, was diagnosed with the anal squamous cell carcinoma, confirmed with biopsy. He had incontinence and was prescribed the CRT (54Gy+5FU/leucovorin in standard doses) which did not result in disease regression. Ca 19-9 and CEA were high. Therefore, a wide APR was done without complications. Six months later, a local recurrence was diagnosed and, soon after that a systematic development of the diseases as well. He was the only patient who died in follow-up of four years.

Case report No 2

A male, 68-years-old with diagnosed SCC (Figure 1a) had refused any treatment until he started bleeding from the anus. Then, an anal stenosis was also diagnosed by means of the rectal examination (Figure 1b). He had no metastasis. A classic X-ray of lungs excluded lung metastasis and a CT of the abdomen showed that neither the liver nor the lymph nodes around the aortoiliac stems (of the blood ves-



Figure. 1: a Anal SCC carcinoma b Anal SCC stenosis ELAPE for advanced SCC with incontinence



Figure 2: a Ulcerous marginal SCC b Excision and the anal sphincter exposition c SCC preparation

sels) were affected. He was operated without further delay. The aforementioned dilemma about the type of the treatment was fully present here because of the stenosis at 1 cm proximally from the anal entrance. After consultations, we decided to remove the possible metastasis source using APR (Figure 1c) as soon as it was possible.

The recovery time needed after performing the anus preternaturalis, a possible period of waiting for CRT, and duration of radiotherapy can be the crucial factors responsible for the possible spreading of the disease into the inguinal lymph nodes or another node or organ. The extraction of perirectal lymph was scheduled in three months' time.

Case report No 3

The male patient we treated was 65 years old at the time of admission (Figure 2a). He had been previously treated at the Department of internal medicine for three months. The diagnosis was confirmed by excisional biopsy which was, actually, a

treatment. The state after the local excision is given in Figure 2b, and the preparation in Figure 2c. Continence was not compromised in this case. Less than six months after the first operation, a small lesion appeared, and both biopsy and a PH finding confirmed the cancer growth. A deeper and wider re-excision was done without compromising the sphincter function of the anus. Only eight weeks later, another control biopsy determined a relapse. That is why the CRT was applied, without the prophylactic radiation of the inguinal lymph nodes, which were not enlarged when checked both by palpation and CT. Today, three years after the first intervention, the patient feels good. We follow up the patient every six months.

Case report No 4

A 61-year-old man with a relatively small (T1 – T2) but dubious tumorous intra-channel lesion was prescribed the standard CRT. The thin needle biopsy determined intra-anal SCC. Laboratory results were



Figure 3: a SCC with a growth into the healthy tissue b A change excised deeply into the healthy tissue

good. The patient was treated using the conformal radiation method, with the combination of 5FU and Mitomycin. The disease regressed completely. The clinical check-up included laboratory analyses, both rectal and inguinal palpation, abdominal ultrasound, X-rays of the lungs, examinations by a urologist/gynaecologist, taking HPV smears, and occasional MRIs. The results of all analyses were in range, and we follow up the patient every six months.

Case report No 5

A female, 56-year-old, had a change in mucosa for the last six months (Figure 3a). The preoperative diagnosis of the perianal carcinoma at the T2 stage was confirmed by a deep excision all the way into the healthy tissue (Figure 3b). PH findings confirmed the existence of CSS with keratin production. The same finding shows that malignancy occurred on the terrain of an inverted condylomatous papilloma. A year after the intervention, there was no deterioration of the patient's health.

Diagnosis was established by endoscopic and excisional biopsy. Liver and lung metastasis were not diagnosed. The status of lymph nodes in the inguinal region was regular and it was confirmed by inguinal palpation and MSCT. Also, there was no metastatic disease in these five patients at the time of their admission. MRI was done only as a control method. In two patients, the treatment included APR, excision was performed in one patient, and CRT in two cases (in one patient after the second excision). Four of five patients were alive with the follow-up period of one to four years. One patient died six months after intervention due to distant metastasis.

DISCUSSION

The anal cancer is a rare disease. In the USA 4,200 new patients were registered in 2008 (7), 6,230 in 2011 (8), and about 7,000 in 2013 (9). In Canada, 515 new cases were recorded in 2007, which is the incidence of 1.3 per 100,000 people a year (10). In Serbia (the central part), 21 male and 6 female patients were registered during 2011 (11).

The ratio between gender in the USA was 1:1.8 in 2012 (it affects more women than men) (12). In our series, four men and only one woman were treated. It coincides with the data from the national disease register of Serbia (21:6). In the USA, the number of new cases has doubled over the past 30 years (13). The

number of death cases is 12.5% in relation to the newly discovered cases in 2012 (14).

The literature sources also demonstrate the cases of the rectal (15) and sigmoid (16) SCCs in the so-called transformation i.e. metaplastic zone. The etiopathogenesis of SCC of the rectum is still unclear. Four hypotheses have developed regarding the pathophysiology of the disease: 1. Some authors point to inflammation or irritation, secondary to inflammatory bowel disease; infection or radiation results in squamous metaplasia from which carcinoma develops; 2. Hicks et al. (17) have described the pluripotent stem cells capable of squamous differentiation. This theory is supported by the fact that squamous carcinoma is often found in the midst of poorly differentiated cells; 3. Michelassi et al. (18) have suggested that epithelial damage causes proliferation of uncommitted basal cells into squamous cells which then undergo malignant transformation; 4. Histological reviews of adenocarcinomas have demonstrated areas of squamous differentiation, suggesting the possibility that these carcinomas may arise out of pre-existing adenomas or adenocarcinomas (19). From 1933, seventy-three cases have been reported in the literature written in English (19). Raghavan D. et al. think that is about 100 cases or 0.2% or less (20).

Squamous cell carcinoma of this region is often associated with fistulae, hidradenitis suppurativa and inflammatory diseases of the intestines (20). The staging which is generally accepted is based on TNM classification of both Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC).

The main etiological factors are the human papilloma virus (HPV), subtypes 16 and 18, and the HIV virus. Since both the HIV and the more frequent HPV are sexually transmitted diseases, the focus of the research is the population that practises the anal sex, especially homosexuals (21). That is why a suggestion is made to do the screening only of this group (22). HPV is found in 90%–95% of the anal carcinoma patients (23,24). The same virus causes the cancer of the vulva, uterus cervix, vagina and, in men, penis. Any kind of sexual contact can lead to contamination, while condom has no protective role because the virus reservoirs are located at the base of the penis i.e. the perineum (in women) (25). All patients have to be tested for HPV. Since December 2010, the USA has approved Gardasil® and Cervarix®, the anti-HPV vaccines with defined indica-

tions hoping that the initial success will continue (11). The new 9-valent vaccine, which replaced the previous 4-valent one, has the potential to prevent 90% of the cervical cancers compared to the 70% of the protection offered by the old vaccine (26). It may also have a preventing effect on the anal carcinoma development. The other known cause of the disease is the HIV virus (4). It is logical that the anal cancer incidence is greater in the homosexual population and those who practise the anal sex. The third large group in which the disease appears is made up of the patients with some kind of an immunodeficient status, including the transplant patients (27). It has been proved that smoking of cigarettes is an independent factor responsible for gene mutations on the level of the anal region and for allowing HPV to persist (26).

That is the reason why every woman with SCC ought to be examined by a gynaecologist and every man should undergo a urological exam (of the penis and prostate), as well as to be tested for the condylomata acuminata disease. The varicose SCC (previously called gigantic condylome or Buschke-Löwenstain tumour) which looks like a big condyloma is also very interesting. Lately the so-called „Lower Anogenital Squamous Terminology“ (LAST) has been used for cervical precancers (8).

Different methods are used in order to discover the disease as early as possible (at the precancerous stage, Table 1): the anal cytology, high-resolution anoscopy (HRA), biopsy of suspiciously-looking changes, and identification of the human papilloma virus (HPV). SCC has been reported to be associated with HPV 16 in up to 93 % of tumors (28).

According to TNM classification, Bowen disease, high-grade squamous intra-epithelial lesion (HSIL) and anal intra-epithelial neoplasms II-III (AIN II-III) fall into this stage (carcinoma in situ). This classification needs to be clarified: there are low-grade squamous intra-epithelial lesions (LSIL), high-grade squamous intra-epithelial lesions (HSIL), and intra-epithelial neoplasm can be in the anal (AIN) or perianal region (PAIN) (Table 2) (9).

As for lymph node metastases, sentinel lymph node biopsy (SLNB) of inguinal nodes was proposed in 2000 by John Spratt, who suggested that prophylactic groin dissection is not required but it may be curative in many cases for enlarged nodes or in the presence of a positive SLNB (29). It was proved later that there is a correlation between the size of lymph nodes and metastasis in them, but the percentage of false negative results is so big that it leads to the conclusion that the very size of the nodes cannot be an indication for the therapeutic radiation or inguinal lymphade-

Table 1. WHO classification of premalignant lesions

Premalignant lesions
Anal intra-epithelial neoplasm (dysplasia), low grade
Anal intra-epithelial neoplasm (dysplasia), high grade
Bowen's disease
Perianal squamous intra-epithelial neoplasm
Paget's disease

Table 2. Terminology and classification of precancers

LAST ¹ proposal terminology	Bethesda terminology	AIN ² terminology	Dysplasia
LSIL/AIN1	LSIL ³	Condylomata acuminata (anal wart) AIN1	Mild dysplasia
HSIL/AIN2–AIN3	HSIL ⁴	AIN 2 AIN 3	Moderate dysplasia Severe dysplasia Carcinoma in situ

(¹LAST - Lower Anogenital Squamous Terminology; ²Anal intra-epithelial neoplasm; ³Low-grade squamous intra-epithelial lesion; ⁴HSIL - High-grade squamous intra-epithelial lesion)

nectomy. In 2013, Tehranian (30) presented a meta-analysis which included 16 studies and 323 patients. According to this analysis, the inguinal detection rate was 86.2% (73.4% – 93.4%). When both blue dye and radiotracer were used, the detection rate was 90.1% and the pooled sensitivity was 90%. This is a promising method for discovering cancer in the stage of inguinal lymph node. According to Mis-trangelo et al. (31) the detection rate was 98.4% and inguinal metastasis were registered in 20.6% of the patients (13 of 63). It is indicative for all T stages in order to select patients who are going to be submitted to the inguinal radiotherapy.

Fifty percent of the patients have no distant metastasis at the time of the diagnosis and the five-year survival is 80%; 29% of the patients have regional disease spreading into the lymph nodes and the five-year survival is 60%; 12% of the patients have distant metastases and 30.5% of them survives the period of five years (32). Depending on the stage, the patients with T1-T2 tumor have 6% and those with T3-T4 have 16% of the inguinal metastases. In total, 10% of the patients have synchronous metastases (33).

TREATMENT

The treatment of the intra-anal SCCs is primarily a combination of chemo- and radiotherapy. The radiation is performed with approximately 54 Gy in 28-30 sessions and the chemotherapy includes a combination of mitomycin and 5FU. Lately, cisplatin has been used instead of mitomycin because of high toxicity of mitomycin. The usual dose of the 5FU medicine is 1000 mg/m², from 1-4 days (1st week) to 29-32 days (5th week) with a continuous 24-hour intravenous infusion. The usual dose of mitomycin is 12 mg/m². The combination used in recent years includes 60-100 mg/m² of cisplatin, day 1 with 750-1000 mg/m² of 5FU 24 h continuous infusion, days 1-4 or 5. In case of contraindications, cisplatin could be replaced by carboplatin. Another frequently used combination consists of cisplatin (37.5 mg/m²), 5FU (500 mg/m²) and ifosfamide (2 g/m²), days 1-2 (34). It is proved that a combined treatment gives much better results than the radiation alone. As far as toxicity is concerned, various trials by UKCCCR (United Kingdom Coordinating Committee on Cancer Research), RTOG/ECOG (Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group) and EORTC (European Organization for Research and Treatment of Cancer) demonstrated significant

acute dermatologic toxicities in 48%-76% of patients, GI (gastrointestinal) toxicity in 33%-45%, and acute hematologic toxicity (HT), grade 3-4, in up to 61%.

New techniques such as intensity modulated radiotherapy (IMRT) have shown reduced acute toxicity. Brachytherapy (BT) is also an approved method (35). The combination of external beam radiotherapy (EBRT) and BT allows the clinician to deliver higher doses to the tumor and to reduce dose to the normal issue. The most frequently applied BT methods are high-dose-rate (HDR) BT (≥ 12 Gy), low-dose-rate (LDR) or pulsed dose-rate, PDR (0.5-1 Gy/h). The anal preservation rate was 61% and the five-year survival rate was 65%. In more than 90% of the surviving patients, normal anal function could be preserved (35). Today, brachytherapy is used for small tumours or as the main dose for residual or big tumors after CRT (36).

Small anal cancers, especially SCCs, are treated with a local excision extending 1 cm into the healthy tissue (maximum T1N0 stage), when the disease is either CRT-resistant or recurrent. A re-excision is done in case of recurrence. On the other hand, surgical treatment is indicated for advanced tumours in cases of the resistant disease (the disease appears within six months after the CRT) or recurrent disease (after 6 months). Salvage operation is APR or a wide APR (ELAPE) with a 5-year survival rate of 24%-47% (6). Many authors mention better results in the 5-year survival when the operation is done as a primary treatment: from 40% to 70% (even between 50%-70%) with an associated mortality of approximately 3% (37). With inguinal lymph node involvement, some series showed 5-year survivals of 10% to 20% (38). Local failure (LF) rate is about 50% (39). Because of a growing incidence of the rectal adenocarcinoma, especially the low-localized ones which can grow downward through the anal canal, they are often mixed with anal adenocancers. That is why APR is frequently done in both diseases after the CRT (40). A temporary colostomy is preferred before the definite treatment in cases of the anal canal cancerous stenosis and the anovaginal fistula development, and when acute complications appear or are threatening.

Squamous cell carcinoma usually spreads in a loco-regional manner within and outside the anal canal. Lymph node involvement in diagnosis is observed in 30% - 40% of cases, while systemic spread is uncommon with distant extra-pelvic metastasis recorded in 5% - 8% at onset, and rates of metastatic progression after primary treatment between 10% and

20% (25). The inguinal area radiation in the dose of 30-36 Gy is applied in case of positive lymph nodes in the inguinal region (13). The sentinel lymph node biopsy (SLNB) can also be applied in case of recurrence after the CRT (13). SLNB can be used within the diagnosis and before any treatment. The complete clinical response to CRT is up to 86% (37) with survival rates of more than 70% for the five-year period (9). A tumor response is checked by performing a biopsy after minimum of six weeks' time. If a diameter of the tumor is less than 2 cm and there is no tumor invasion into the anal sphincter, a local excision is recommended, too. The success rate goes up to 90%.

The prophylactic radiation of the inguinal area i.e. of the lymph nodes is questionable. Irradiating the inguinal nodal area in N0 anal canal carcinoma is not necessary. It was proved by the TROG 9902 study which had a goal to find out the rate of isolated inguinal failure in a group of 40 patients with T1 and T2 disease. The authors reported 22.5% inguinal failure with 12.5% isolated failure as a result of inadequate staging imaging. That is why they left the possibility of treating the inguinal nodes for N0 disease in the absence of adequate imaging (41, 42). Regarding stage T, the radiotherapy in all the stages except T1 is recommended, although there are contradictory opinions (42).

NCCN (National Comprehensive Cancer Network) from USA follows modern treatments of the anal cancer and presents them on its website together with regular updating, the latest version being 1.2016 (43). It contains recommendations for anal and perianal SCCs. According to NCCN, the same therapeutic references are valid for both the anal adenocarcinoma and rectal carcinoma. Beside the above-mentioned, the combinations of mitomycin/5FU or mitomycin/capecitabine are also recommended as the first line of chemotherapy, and for the metastatic disease – the chemotherapy based on cisplatin. For small tumors of the perianal area, the presented re-

commendation is the already mentioned local excision followed by a re-excision in cases of recurrence. Follow-up examinations are advised every 2 or 3 months i.e. more frequently than usual. The appearance of the disease in the inguinal lymph nodes includes the inguinal dissection (43).

The perianal cancers have a slightly better prognosis and the primary choice is a wide excision. The recommended resection margin is 1 cm (44). There are different opinions about the tumor size which is considered to be adequate for a local excision: some say it is 2 cm in diameter (T1), while others consider 7 mm in diameter with the excision into the healthy tissue of 3 mm. In case of a recurrence –18%-63% (45) or a positive margin, both a re-excision and an additional CRT are recommended (5).

A residual or recurrent disease in the pelvis is treated operatively (after restaging). A metastatic disease outside the pelvis is most frequently found in the liver, lungs and extra-pelvic lymph nodes. About 10%-20% of the patients with an anal carcinoma develop extra-pelvic MS. The appropriate treatment is CRT, and surgical intervention is recommended for certain metastatic locations, including an inguinal nodal dissection (5).

CONCLUSION

Our series of five patients shows all the varieties of anal cancers and the exigency for a multimodal approach. The SCC should always be suspected when persistent anal symptoms or persistent lesions (especially the ulcerous ones) are present. The morphological types of the anal carcinoma, either the ulcerous or the tumor (a protrusion), are classified as SCC. Neither belonging to one of the risky sexual groups nor the viral etiology of the disease was confirmed in any of our patients. Incontinence in anal carcinoma represents an indication for APR.

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Analni karcinom: prikaz mini-serije bolesnika i pregled literature

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SAŽETAK

Povod za pisanje rada je prikaz naših bolesnika. Cilj rada bio je da se skrene pažnja na analni karcinom i njegove različite histološke potkategorije i da se prikažu standardni i novi stavovi iz literature. U radu je prikazana naša serija slučajeva i mesto hirurškog tretmana, posebno kod inkontinentnih bolesnika. Analni karcinom je retko oboljenje koje čine više patohistoloških (PH) različitih tipova karcinoma, oko 2,5% svih digestivnih karcinoma. Tretman oboljenja je multimodalitetni. Još uvek ima nepoznanica u etiologiji, klasifikaciji, dijagnostici ovog oboljenja. Postoje dileme oko skrininga prekanceroznih lezija i tretmana dijagnostikovane inkontinencije. Složena anatomija i histologija analne regije je razlog nedoumica. Koincidencija sa virusnom infekcijom i razvojem prekanceroza je visoka.

U poslednje tri godine (2013 – 2015) u regionalnoj bolnici, koja zdravstveno obezbeđuje oko 300.000 stanovnika, dijagnostikovano je i lečeno pet slučajeva analnog karcinoma. Ovome je pridodat jedan slučaj od ranije, ukupno šest prikazanih u retrospektivnom radu. Primenjeno lečenje je upoređeno sa stavovima iz literature.

Bolest je u pet slučajeva patohistološki potvrđena kao analni i perianalni skvamozno-celularni kancer (SCC, squamous-cellular carcinoma), a kod jednog bolesnika analni adenokarcinom (AAC). Troje bolesnika je bilo inkontinentno na prijemu i amputacija rektuma je jedno od primenjenih rešenja. Preporuke iz literature nisu jasno određene za ove bolesnike. Opredelili smo se za amputaciju rektuma. Pregledom literature prikazujemo sve moguće opcije.

Razlika u histološkoj strukturi dovodi do konfuzije u lečenju. Polovina od ukupnog broja naših bolesnika bila je inkontinentna na prijemu, te ističemo dilemu tretmana ovih bolesnika za koje literaturne preporuke nisu decidirane. Potreban je individualan pristup. Mi smo radili amputaciju rektuma pre nego li standardizovano hemio-radioterapijsko lečenje. Osvrtom na literaturu prikazujemo sve moguće opcije.

Ključne reči: analni karcinom, skvamozno-ćelijski, hemio-radioterapija

