

Advanced Anal Squamous Cell Carcinoma – Radiotherapy or Surgery?

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Rezumat

Carcinom scuamos anal avansat - radioterapie sau chirurgie?

Premize: Cancerul rectal și anal este a treia cauză de deces în Polonia. Adenocarcinomul este cea mai frecventă tumoră din acest grup. Carcinomul scuamos este relativ rar. Acest tip de carcinom afectează mai degrabă anusul decât rectul. Deși leziunea este percepută a nu fi foarte malignă și a fi responsabilă la radioterapie, unele cazuri pot necesita tratament chirurgical.

Material și Metodă: În perioada 1999-2008 (perioadă observațională de 10 ani) au fost 18 pacienți tratați pentru carcinom scuamos anal în Departamentul de Chirurgie Toracică Generală și Oncologică a Universității de Medicină din Lodz, la Departamentul de Chirurgie al Spitalului Ministerului de Interne și Administrație din Lodz și la Departamentul de Teleradioterapie al Spitalului Mikolaj Kopernik Voivodship din Lodz. Fiecare pacient a urmat radiochimioterapie cu Mitomycină și 5-Fluorouracil cu Leucovorin. Dozele de radioterapie aplicate au fost între 45-54 Gy în optsprezece fracții 2.0 Gy. Rezecția abdominoperineală a rectului a fost efectuată la 3 pacienți (16,5%) care nu au prezentat regresia completă a carcinomului. În toate cele 3 cazuri diagnosticul histopatologic a precedat intervenției chirurgicale.

Rezultate: Pentru toate cele 18 cazuri de pacienți cu carcinom scuamos anal, perioada de urmărire medie a fost de 5,5 ani, în

grupul pacienților operați rata medie de supraviețuire a fost de 48 luni (mediana a 14-74 luni) în timp ce pentru grupul de pacienți tratat conservator rata de supraviețuire medie a depășit 55 luni (mediana a 17-82 luni, $p=0,23$). Rata medie de supraviețuire fără boală la 5 ani a fost similară cu a grupului general în timp ce complicațiile postoperatorii au apărut la 66% din intervențiile chirurgicale și la 27% din procedurile de teleradioterapie.

Concluzii: asocierea radioterapiei cu chimioterapia poate fi metoda de elecție în tratamentul carcinomului scuamos anal. Chirurgia este necesară în cazurile avansate, la care nu se observă regresia completă după radiochimioterapie. Rezecția abdomino-perineală a rectului este o intervenție chirurgicală care poate fi acompaniată de numeroase complicații. Totuși, aceasta rămâne o metodă terapeutică necesară în cazurile descrise.

Cuvinte cheie: carcinom anal, APR (rezecție abdomino-perineală a rectului), radioterapie, carcinom scuamos anal avansat

Abstract

Background: Anal and rectal cancers occupy the third position of death causes in Poland. Adenocarcinoma is the most frequent among the tumours in this group. Squamous cell carcinoma can be relatively less common. This kind of carcinoma may rather affect the anus than the rectum. Although the lesion is perceived as not very malignant and as such responsive to radiant energy therapy, some cases may require surgical treatment.

Methods: Within 1999-2008 (the observation period of 10 years) there were 18 patients treated for anal squamous cell

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carcinoma at the Department of Thoracic Surgery, General and Oncological Surgery of the Medical University of Lodz, at the Surgical Department of the Ministry of Interior and Administration Hospital in Lodz and at the Teleradiotherapy Department of Mikolaj Kopernik Voivodship Specialist Hospital in Lodz. Each patient underwent radiochemotherapy with Mitomycin and 5-Fluorouracil and Lucovorin. The applied radiation doses ranged between 45-54 Gy in eighteen 2.0 Gy fractions. The abdomino-perineal resection of the rectum (APR) was performed in 3 patients (16.5%) who did not show full regression of the carcinoma. In all three cases the histopathological diagnosis preceded the surgical procedure.

Results: For the total number of 18 patients with anal squamous cell carcinoma the mean observation period was 5.5 years, in the group of the operated patients the mean survival rate was 48 months (the median of 14-74 months) while for the group of the patients treated conservatively the mean survival rate amounted to 55 months (the median of 17-82 months, $p=0.23$). The mean 5-year disease-free survival rate was rather similar to the same rate of the general group, whereas the post-operative complications occurred in 66% of surgical procedures and 27% of teleradiotherapeutic procedures.

Conclusions: Combined radiotherapy and chemotherapy can be the method of choice in treating anal squamous cell carcinoma. Surgery should be used in advanced cases, when complete regression on radiochemotherapy cannot be observed. The abdomino-perineal resection of the rectum is the kind of a procedure that may be accompanied with a vast number of complications. Nevertheless, it still remains a necessary therapeutic method in the described cases.

Key words: anal carcinoma, APR, radiotherapy, advanced anal squamous cell carcinoma

Introduction

Anal and rectal cancers are the third most common cause of cancer death in Poland. Adenocarcinoma occurs in approximately 98% of cases. Squamous cell carcinoma is relatively rare and occurs in about 1.2%-2.3% of all the large intestine cancers (1). This kind of cancer is definitely more common in the anus than in the rectum. From the pathogenetic point of view the carcinoma of this region can be divided into:

- Squamous cell carcinoma of the anal margin;
- Squamous cell carcinoma of the anal canal.

The border-line of the two carcinoma types is marked by the 10-12 mm thin transitional layer of the anus, where the cylindrical epithelium changes over to the squamous epithelium. Squamous cell carcinoma can be diagnosed in both these regions. However, other neopathologies within that area should also be considered in the everyday practice. Other neoplastic lesions of this region include (2):

- squamous cell papilloma;

- papilliferous syringocystadenoma;
- keratoakanthoma;
- polyps;
- cloacogenic polyps (due to inflammatory changes);
- oleogranuloma (granuloma resulting from the use of lipid substances that can obliterate varicose veins);
- Buschke-Lowenstein tumour

Due to positive effects of combined radiotherapy and chemotherapy, this kind of treatment has become a therapeutic standard in patients with anal cancer. However, some cases need a surgical intervention. Merely few dozen of the anal and rectal squamous cell carcinoma treatment cases have been described in the world literature since 1949. Although the treatment of this disease seems to be known and understood, there are still approximately 40% patients of Mount Vernon Cancer Centre, UK, who are subject to surgery, for example (3).

Some data support the notion that squamous cell carcinoma can originate from the endothelium of the anus and/or the rectum that has been infected by the human papillomavirus (HPV), or less common other viruses such as HIV (4,5,6). Mainly because no certain cause of this cancer is known, some attempts with teleradiotherapy, chemotherapy and both methods together with surgery have been made. Presently, the assumed procedure algorithm on this cancer is presented by NCCN – the National Comprehensive Cancer Network (www.nccn.org).

Methods

In the period 1999-2008 (over 10-year observation period) eighteen patients with anal squamous cell carcinoma were treated at the Department of Thoracic Surgery, General and Oncological Surgery of the Medical University of Lodz, at the Surgical Department of the Ministry of Interior and Administration Hospital and at the Department of Cancer Chemotherapy of the Medical University of Lodz. Each patient underwent a standard qualification for the adjuvant therapy. The Mitomycin, 5-Fluorouracil and Lucovorin – based radiochemotherapy was used in each case. The radiation doses of 45-54 Gy were applied in eighteen 2.0 Gy fractions.

When no rests of the tumour could be noticed, the patient was referred to surgery. In- and out-patient history cases as well as operation protocols were read retrospectively. The follow-up was performed in 14 patients (78%).

Results

The mean observation period for the 18 patients with anal squamous cell carcinoma was 66 months (16-120 months). The recovery rate amounted to 78%. The mean total radiation dose amounted to 54.2 Gy (the range of 26-68 Gy). In three cases (16.5%) resistant to two radiotherapy cycles the abdomino-perineal resection of the rectum (APR) had to be performed. In all three cases the histopathological diagnosis preceded the operation. In the group of the operated patients

the 5-year overall survival rate and the disease-free survival rate amounted to 66%, whereas in the group of nonsurgical patients (the patients had undergone chemo- and/or radiotherapy) the rates were 74% and 61% respectively. Statistically significant differences could be observed in the group of the 5-year overall survival, while in the disease-free survival group such differences were not noticed. In the group of the operated patients the mean survival time was 4 years (14-72 months), and 4.2 years (17-82 months) in the group of the patients who underwent conservative therapy ($p=0.23$). Complications due to the abdomino-perineal resection of the rectum amounted to 66%, while complications after radiotherapy came to 27% ($p<0.05$), the latter being a major difference from a statistical point of view.

Discussion

Depending on the individual indications, radiotherapy was assumed to be useful before the anal resection because of its advantages such as:

- reduction of the tumour mass – often inoperable tumours can be resected;
- in some cases, after radiotherapy a change of the decision on the extent of the surgical procedure is possible (the decision on the anterior resection of the rectum rather than the abdomino-perineal resection of the rectum);
- it results in the sterilisation around the region of a prospective surgical procedure, which further decreases the risk of neoplastic cell spread and the risk of leaving neoplastic cells in the lymph glands nearby.

In the past the pre-operative radiotherapy (PR) was attributed a number of disadvantages which could influence its regular use. For example, the patients with metastases to the liver (the metastasis was diagnosed before surgery) or the cases in very early stages did not seem to require any irradiation T1-T2, N0, M0 (5).

Moreover, PR was believed to cause difficulties in surgical procedures within the irradiated region or possible increase in the number of complications after an operation. It might also lead to a potential delay in the resection of a growing tumour, which only slightly responded to ionizing energy (because of misused radiobiological parameters). It resulted in qualifying just the patients with large and/or immovable tumours that could hardly be operated on, after prior excluding remote metastases (8).

As far back as last year, in many randomized clinical tests the number of local failures could be statistically decreased and the disease-free survivals could be lengthened. Unfortunately, the total doses were too low (below 45 Gy) and the time period between radiotherapy and surgery was too short in the majority of the tests (3,6,9).

Nowadays the pre-operative radiotherapy (PR) is highly considered by surgeons, radiographers and pathomorphologists. PR is a routine procedure in many centres all over the world. It can be used directly before an operation in a form of a short pre-operative radiotherapy course or planned pre-operative

radiotherapy with a precise histopathological description before and after surgery, as well as with a break between PR and surgical treatment. Also, a number of reports on 3D and 4D radiotherapy were issued at the beginning of this century (10,11).

Thus, independently on the kind of a planned surgical operation, the pre-operative radiotherapy is used in every patient who does not reveal any remote metastases, even in early tumours T1N0M0. This procedure is based on the assumption that micrometastases in local lymph nodes may appear as early as in the first stage of the disease (12).

Currently, preferable optimal doses amount to 45-50 Gy in 25-28 fractions. Irradiations are usually conducted over 5-6 weeks and the surgical procedure is performed - in 2-4 weeks following the last irradiation fraction. The period of 4-6 weeks after PR is thought to be the best time to obtain the maximum regression of the tumour and healing of the proper tissues (9).

When dealing with a locally advanced tumour T3 or T4 and metastases to the local lymph glands N1, the pre-operative radiotherapy is treated as part of the "sandwich" radiotherapy, i.e. pre- and post-operative radiotherapy. However, combined PR and chemotherapy are more often treated as pre- and/or post-operative procedures. About a week preceding the operation MRI of the pelvis or transrectal USG are performed in each patient in order to assess the effects of PR and/or PR combined with chemotherapy (6,13,14).

As refers to the so called "short PR courses", recent tests proved positive results in every patient with advanced carcinoma (according to Dukes' staging classification) who was exposed to 15-25 Gy over 4-5 days before the operation. Nevertheless, this procedure seems less reliable when compared to the planned pre-operative radiotherapy. It results from the necessity of extremely precise following the irradiation principles (the multifield techniques are so modified to limit irradiation doses for the small intestine) and detailed histopathological assessment of a tumour. Sometimes the size of a tumour is not very large (T1) but its histopathological differentiation suggests careful planned PR.

The possible "mapping" of the irradiated skin borders may facilitate achieving full oncologic radicality. This procedure is immensely important in further healing of the post-operative wound. It is commonly known that the irradiated tissues are more difficult to heal up than the potentially healthy tissue (8).

In our conservatively treated patients the 5-year overall survival rate was 74% while the 5-year disease-free survival rate was 61%. In the international reports the 5-year overall survival rate goes even as high as 85%. In the group of the patients subject to the surgical treatment the results were 66% and 66% respectively. One hundred per cent of the patients had colostomy, whereas the Japanese authors claim that the conduit can be avoided even in 97% of the patients. Additionally, no difference could be observed in the 5-year survival rate in the patients who underwent only radiotherapy and those after radiochemotherapy (13).

The fact that carcinoma can often be associated with HIV infection should also be considered (4,15,16). The



Figure 1. Anal squamous cell carcinoma



Figure 2. Anal squamous cell carcinoma after 2 radiotherapy courses – before planned surgery



Figure 3. Post-operative specimen of the resected squamous cell carcinoma and rectum



Figure 4. Post-operative perianal wound 6 months after APR due to anal squamous cell carcinoma

Table 1. Complications after APR of the rectum due to anal squamous cell carcinoma

L.p.	Complication	n	%
1	Wound infection	2	66
2	Wound haematoma	1	33
3	Urinary disorder	1	33
4	Hernia in cicatrix	1	33
5	Temporary pain in the abdomen	2	66

authors from Greece suggest cytology of the anal canal as one of the diagnostic methods. The researchers recognised an injury of the endothelium with a concurrent HIV infection in 40 out of 116 cases, out of which 17 revealed squamous cell carcinoma (17).

The group of the patients who did not respond to tele-radiotherapy underwent the abdomino-perineal resection of the rectum. Each of the tumours was located on the margin

of the anus (Fig. 1). The vast extent of the resection (the large size of the material) hampered the closure of the perineal wounds with sutures, which consequently prolonged the process of the granulation tissue growth (Fig. 2). The perineum healing process lasted 9 months on average (7-12). The shape of the wound after a 6-month healing process is shown in Fig. 3. The complications we had to deal with are presented in Table 1. The longest follow-up after the operation lasted 74

months and the patient finally died due to other than neoplastic causes.

The pre-operative radiotherapy in the large intestine cancer, independently on how it is performed, can decrease the tumour size and its infiltration on the intestinal wall, as well as it can fully eradicate the tumour histopathologically (not biologically). PR can be used directly before a surgical procedure, but it is far more effective when planned. This method may influence the way the operation is performed, e.g. LAR instead of APR and/or further post-operative adjuvant treatment. At present, there is no evidence that properly applied PR may induce undesirable effects such as possible disorders of intestinal anastomosis. PR may only cause a chronic dysfunction of the sphincters after LAR surgery. Nevertheless, it should not conceal the fact that PR could help to decrease immensely the number of local relapses as well as lengthen the mean survival rate after surgical resections of anal squamous cell carcinoma.

Conclusions

- Teleradiotherapy over 30-35 days with a maximum daily dose of 2 Gy is a standard procedure in anal squamous cell carcinoma.
- In advanced cases, which do not respond to radiotherapy, surgical treatment should be taken into account.
- The abdomino-perineal resection of the anus can be responsible for numerous complications but this therapeutic procedure may prove essential in some cases.
- A life-saving surgical procedure should be considered in every case that is resistant to radiant energy therapy.

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