

Management of Epidermoid Carcinoma of the Anus

Lars Pählman,¹ Bengt Glimelius² and Sven Goldman³

Departments of ¹Surgery and ²Oncology, University Hospital, Uppsala, and ³Department of Surgery, Södersjukhuset, Stockholm, Sweden

ABSTRACT

In two unselected, consecutive and population-based patient materials from two regions in Sweden, different treatment modalities in patients with epidermoid carcinoma of the anus have been evaluated. By using a primary radiotherapeutic approach, combined with surgery in patients with large and/or less radiosensitive tumours, considerably more surviving patients can be disease-free in the long term compared with a primarily surgical approach. In addition, several patients will have preserved anal function. Based upon these data together with the experience described in the literature, we conclude that surgery is no longer the primary treatment of choice in patients with anal carcinoma.

INTRODUCTION

Until the past 10-15 years, most patients with anal epidermoid carcinoma have been treated with the same surgical procedure as those with a tumour in the lower part of the rectum, i.e. with an abdominoperineal resection. A sphincter-saving local excision is only possible in a minority of patients (less than 10-15 %). Previously only patients with an unresectable tumour and those not operable because of a high age and/or poor general condition have been referred for radiotherapy, and then mostly for palliative treatment only. During the last decade, the experience with non-surgical treatment modalities, especially radiotherapy, has increased. However, the majority of presented series are small, owing to the rarity of the disease, and the extent of patient selection is not always known in these treatment series. Furthermore, the radiation has varied considerably, both with respect to dose level and target volume. It has often been combined with different chemotherapy schedules, making it difficult to evaluate this new treatment modality. An essential question is whether this new approach, with its advantage of being sphincter-preserving, results in the same long-term outcome or even improves the prognosis compared with surgery alone in the treatment of anal epidermoid carcinoma.

CLASSIFICATION AND HISTOPATHOLOGY

Anal carcinomas are usually into those growing perianally and those situated in the anal canal. The border between the anal canal and the perianal region is at the anal verge. The upper border of the anal canal lies at the anorectal junction and the outer limitation of the perianal region is usually set at 6 cm from the anal verge. The prognosis for perianal tumours is considerably better than for those in the anal canal (16).

Anal carcinomas usually spread directly towards surrounding organs or to regional lymph nodes. Distant metastases are only found in 10 % of the patients at diagnosis (9, 16). The upper part of the anal canal is mainly drained to the perirectal lymph nodes, the middle part mostly laterally to lymph nodes at the obturator foramina and the distal part of the anal canal and the perianal area predominately to the inguinal nodes. Groin metastases are present in 15-20 % and intrapelvic metastases in 20-25 % of the cases at diagnosis (9, 15). Lymph node metastases are more common in patients with a large tumour, but can also be present in those with even very minute tumours.

Two main histopathologically identifiable types are suggested, namely the squamous cell type derived from the squamous epithelium and the cloacogenic carcinoma type derived from the transitional epithelium in the anal canal just above the dentate line. There is no clearcut difference between these two major types and mixtures are common (9, 12). The question whether this subdivision is of prognostic importance has been discussed. A recent analysis rather suggests that the degree of differentiation is more discriminatory than the type of differentiation (9). Also there is no apparent clinical reason to separate the different types histologically, since treatment appears to be the same.

TREATMENT

Surgery alone:

In cases where a local excision is possible, the tumour is removed with a margin of normal tissue, leaving the rectum and the greater part of the anal canal intact. This surgical procedure is only applicable to lesions of small size located perianally or in the lower part of the anal canal. As shown in Table 1 there are considerable discrepancies between reported results obtained after local excision, with a recurrence rate ranging from 0 to 75 %, average 50 %. This high recurrence rate indicates that local excision is not a suitable approach in any but highly selected cases. The reason for this is probably a combination of difficulty in achieving local radicality without interference with the sphincter function and lymphatic spread to the pelvis

and inguinal nodes, which may occur even in patients with a small tumour.

The results of radical surgery, i.e. abdominoperineal resection with a wide perianal excision, are neither impressive (Table 1). Although several of these series probably also include large tumours that are primarily not suitable for surgery, the results are poor, with a high recurrence rate - leading to a low five-year survival rate (average 45 %). Moreover, this treatment results in a permanent colostomy.

Table 1. Results of surgical treatment (T₁₋₄ N₀ M₀,¹⁹)

Institutions	Local excision		Abd.per. resection	
	No. of cases	Recurr. rate	No. of cases	Recurr. rate
Malmö, Sweden ²	5	60 %	13	46 %
Denmark (national) ¹⁴	51	65 %	48	31 %
St. Mark's Hospital, UK ^{10,17}	10	0 %	92	48 %
Mayo Clinic, US ³	19	11 %	118	40 %
Cleveland Clinic, US ¹	10	50 %	-	-
Roswell Park, US ⁵	9	73 %	17	71 %

Radiotherapy:

During the last 10-15 years, several series of patients treated with radiotherapy either without or - usually - with additional chemotherapy have been reported in the literature. The results appear considerably better than in surgical series, although patient selection, with more favourable cases in the irradiated groups of patients, may have occurred.

An essential point in discussing radiotherapy is the dose level. Experimental and clinical data have shown that the minimal dose level required to kill micrometastases with a high degree of probability is about 45 Gray (Gy) given with conventional fractionation, i.e. 1.8 - 2 Gy daily for four to five weeks (7). To compare the results of different trials using different irradiation schedules, an estimation of the relative biological effect on the irradiated area is therefore important. As proposed by Kirk et al., one mode of estimation is by means of the cumulative radiation effect (CRE) concept (11). With this concept, although the estimation is made on normal cells, the dose at each fraction, the total dose and the duration of treatment are taken into account. A dose of 45 Gy delivered with conventional fractionation corresponds to a CRE value of 14.5.

The results from reported series treated by irradiation without surgery or with additional surgery in cases where the tumour was not completely eradicated by the radiotherapy, are listed in Table 2. The results seem to be

superior to those surgery alone. It should be remembered, however, that the follow-up in several of these series was comparably short. When reported, the five-year survival rates ranged between 75-90 %. An interesting finding is that even in series where a relatively moderate dose level was used, the results were better than those of surgery alone, indicating that anal epidermoid carcinomas are extremely radiosensitive. Another indication of this is the observation in several series that no viable cancer cells were found in the resected specimen after "preoperative" radiotherapy.

Table 2. Results of radiotherapy +/- surgery (T₁₋₄ N₀ M₀)

Institutions	Dose level		No. of cases	Recurr. rate
	Gy	CRE		
Uppsala, Sweden ⁸	40-65	>16.0	28	11 %
Lyon, France ¹⁶	55-60	>16.0	72	18 %
Rochester, N.Y., US ¹⁸	45-60	>14.0	18	0 %
Toronto, Canada ⁶	45-60	>14.0	40	10 %
Detroit, US ¹⁵	30-35	>12.0	26	19 %
New York, US ¹³	30	>12.0	27	15 %

The effect of a combination of chemotherapy and irradiation is still not clear. Experimental data have shown that when combined, these two treatment modalities have synergistic effects (4). Almost all treatment regimes have therefore included some form of combination of radiotherapy and chemotherapy. However, no randomized trial has been carried out with the aim of evaluating the true benefit of additional chemotherapy, although both Cummings et al. and Papillion et al. claim that their data indicate a favourable effect (6, 16). In the trial by Cummings et al., toxicity was increased substantially in the group of patient receiving chemotherapy. On the other hand, in randomized trials in head and neck tumours, a combination of irradiation and Bleomycin or irradiation plus 5FU and Mitomycin C, the most commonly used combinations in the treatment of anal carcinoma, appeared to give no benefit of survival rates. For this reason, the use of different chemotherapy schedules has not been taken into account in Table 2 in the comparison of different trials.

UPPSALA-STOCKHOLM MATERIAL

Material and methods:

In order to obtain an unselected, representative and population-based material, data for all patients with diagnosed epidermoid carcinoma of the anus who were resident in the Uppsala and Stockholm regions between 1978 and 1984 were gathered from the diagnostic files of all Departments of Surgery of these regions and from the Swedish Cancer Registry. In this way, a total of 141 patients with an anal epidermoid carcinoma primarily in the anal canal

were found. Their mean age was 69 years (range 34-93). One hundred and six patients had no signs of groin metastases or distant metastases at diagnosis and were therefore considered potentially curable. One patient died before treatment started, giving a total of 105 patients treated with curative intent. No patients have been lost to follow-up.

Treatment and results:

In the Uppsala region most patients were admitted to the Department of Oncology of the University Hospital, Uppsala and treated in a prospective manner according to a protocol which is described elsewhere (8). Briefly, all patients received radiotherapy (with or without Bleomycin) to a dose level of 40-45 Gy during a period of 4-5 weeks, giving a total dose of 10 Gy/week. After a split of 3 weeks, radiotherapy was started again and delivered to a total target dose of 60-65 Gy provided that no residual tumour bulk was found at the end of the split. If residual tumour was present at the end of the first irradiation period the patient was referred for surgery, usually an abdomino-perineal resection.

No single treatment protocol was followed in the Stockholm region. At the beginning of the study the patients in this region were treated with surgery alone or surgery preceded by a period of preoperative irradiation to a low or moderate dose level. At the end of the period almost all patients in this region were admitted to Södersjukhuset and treated according to the same protocol as in Uppsala. Since both materials are each individually population-based and since no selection was made, the two materials and the results of the different treatment policies can be compared. The projected five-year survival rate is higher in the Uppsala region than in the Stockholm region (all patients, 58 % versus 42 %; initially non-disseminated patients, 76 % versus 51 %). The proportion, of patients with disseminated disease and other prognostic variables were equally distributed in the two materials.

As shown in Table 3, patients initially treated with radiotherapy, with or without surgery, did better than those treated with surgery alone. The overall radiotherapy results are not as good, however, as in those published from individual institutions. One explanation for this is that all patients who had received radiotherapy to any dose level (and irrespective of whether this treatment was given alone) pre- or postoperatively were analysed together. Among patients who have received radiotherapy to a higher dose level (CRE above 15), only 15 % (5/33) have had a recurrence. Two of them have been retreated successfully with surgery and are still alive with no signs of recurrent tumour; one had groin metastases and one had a local relapse.

Table 3. Epidermoid carcinoma of the anal canal (T₁₋₄ N₀ M₀), combined Uppsala-Stockholm material.

Treatment	Tumour stage					
	T ₁₋₂		T ₃		T ₄	
	No. of cases	Recurr. rate	No. of cases	Recurr. rate	No. of cases	Recurr. rate
Local excision	9	78 %	-	-	-	-
Abdominoper. res.	7	57 %	10	80 %	-	-
Irrad. +/- surgery	30	13 %	44	52 %	5	80

CONCLUSIONS

Using a primary radiotherapeutic approach in the treatment of anal epidermoid carcinoma, considerably more surviving patients can be disease-free in the long term with preserved anal function. The quality of life of the patients will thus be higher and in addition, survival appears to be improved by this approach. From the data found in the comparison between the two population-based materials in Sweden, together with the excellent short-term survival figures reported from hospital-based series, we conclude that surgery is no longer the mainstay in the treatment of this rare disease. The optimal radiotherapeutic dose level in this apparently radiosensitive tumour and the possible benefit of chemotherapy as an addition to irradiation have not yet been established.

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Address for reprints:
 Lars Pahlman M.D.
 Department of Surgery
 Uppsala University
 Akademiska Sjukhuset
 S-751 85 Uppsala
 Sweden