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Treatment of epidermoid anal canal carcinoma

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During the last two decades, the role of surgery in anal cancer treatment has been changing continuously. Nowadays, surgery is applied only in treatment of (recurrent) radio-and chemoresistant disease. At present, anal function-conserving radiation therapy (45-60 Gy) and concomitant chemotherapy with 5-FU and MMC are considered to be standard therapy methods applied in locally advanced tumours, whether N0 or N+. In small tumours (T1N0), chemotherapy can be omitted without jeopardizing the outcome. In future, the role of induction chemotherapy will have to be evaluated in order to see whether some other drug would contribute better to the improvement of the already favourable results.

Key words: rectal neoplasms; combined modality treatment

Introduction

Epidermoid cancer of the anus is a rare disease comprising 1-4% of malignant colorectal cancers, though 30% of all ano-rectal cancers are anal cancers. About 75% of anal cancers are anal canal cancers and are more common in women than in men (ratio 3:2 - 5:1) (Quan 1978, Beahrs 1979, Eschwege *et al.* 1985). Histologically, most cancers are of the squamous cell type of different keratinization. The lymphatic spread is mainly in three directions. The anal margin drains in the inguinal superficial region, anal canal tumours primarily in lymph nodes along the great vessels (A. mesenterica inferior, A. iliaca) and perirectal/anal lymph nodes.

Treatment of anal canal cancers is mainly a locoregional problem, distant metastases being uncommon. The age of patients has a wide range from 25 to 80 years, with a median age of about 60 years. About 75% patients have uncharacteristic symptoms with haemorrhoids, fistulas, pruritus or leucoplakia which may delay the correct diagnosis.

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Treatment

The role of surgery as primary treatment modality has gradually decreased during the last 30 years and has now been abandoned by most centres. Only very small tumours could be treated by conservative, sphincter saving surgery, and the local recurrence rate was high in these cases. Major abdomino-perineal resection and permanent colostomy was the option for most patients undergoing surgery. In spite of major surgery, the survival results were far from acceptable. Tables 1 and 2 show the results of surgery for anal canal cancer.

In Europe, radiation therapy has always played a more important role in the therapy of these tumours, compared with North America where surgery was often preferred as initial therapy. Radiotherapy was abandoned in some centres during the early decades of this century because of severe side effects. With the introduction of modern, high voltage machinery, improved brachytherapy methods and more knowledge about the natural history of this disease, the treatment results of irradiation of anal tumours gradually improved. Table 3. shows the results of primary radiation therapy for anal canal cancers.

Following the introduction of combined radiotherapy and concomitant administration of chemotherapy

(Mitomycin C and 5-Fluorouracil) by Nigro *et al.* 1974, this combination was widely adopted as the primary treatment of choice for anal cancers. This combined treatment was first used as preoperative treatment and resulted in over 60% tumour-free cases after a radiation dose of only 30 Gy (Nigro *et al.* 1981, Wanebo *et al.* 1981, Meeker *et al.* 1986). Following these encouraging results, surgery was gradually replaced by an increased radiation dose. The increased toxic effect of Mitomycin C (MMC) on hypoxic cells and on extracellular acidic environment is a clear benefit in large squamous cell cancers with considerable hypoxic regions being less sensitive to radiation (Rauth *et al.* 1983 Rockwell 1982, Dobrowsky & Dobrowsky 1995). 5-Fluorouracil (5-FU) was attributed a role of a radiosensitizing agent when administered after irradiation for longer time periods and was reported to be interacting in a supraadditive way with MMC *in vitro* (Byfield *et al.* 1982, Nakajima *et al.* 1979, Dobrowsky *et al.* 1992). It has been used in the clinic for many years in combination with radiation therapy. Table 4 shows some results from chemoradiation with MMC and 5-FU.

Table 1. Local excision for anal canal cancer - 5-year survival and local relapse rate

Author	No. of patients	Survival	Local recurrence rate
Kuehn *et al.* 1968	26	75%	8%
Stearns & Quan 1970	30	66%	63%
Beahrs 1979	21	85%	42%
Klotz *et al.* 1967	33	61%	33%
Boman *et al.* 1984	19	84%	11%
Frost *et al.* 1984	20	66%	60%

Table 2. Major surgery for anal cancer - 5-year survival

Author	No. of patients	Survival
O Brien *et al.* 1950	45	32%
Grinell 1954	13	46%
Klotz *et al.* 1967	194	50%
Kuehn *et al.* 1964	83	47%
Greenall *et al.* 1985	103	55%
Boman *et al.* 1984	114	71%

Table 3. Radiation therapy for anal cancer

Author	No. of patients	Survival	Local recurrence
Green *et al.* 1980	16	81%	25%
Cummings *et al.* 1982	51	59%	43%
Eschwege *et al.* 1985	64	46%	19%
Papillon 1982	88	68%	14%
Dobrowsky 1987	14	79%	14%

Table 4. Chemoradiation with MMC and 5-FU for anal cancer

Author	Primary tumour control	Survival
Leichman *et al.* 1985	86%	80%
Sischy *et al.* 1989	71%	73%
Papillon & Montbarbon 1987	81%	
Cummings *et al.* 1991	87%	65%
Dobrowsky *et al.* 1996	95%	73%

Other groups tested the combination of bleomycin and radiation, but it was stated that the benefit of bleomycin administration was of questionable value (Glimelius & Pahlman 1987, Svensson *et al.* 1993).

Most reports have dealt with single institutional experiences and there have not been any randomized trials until recently. Three major trials tested the effect of different chemotherapy regimens administered simultaneously with radiation therapy. An intergroup study tested whether or not the addition of MMC to 5-FU chemotherapy administered with radiation therapy was of benefit (Flam *et al.* 1996). At 4 years, colostomy rates were lower (9% vs 22%; p=0.002), colostomy-free survival higher (73% vs 59%; p=0.014) and disease-free survival higher (73% vs 51%; p=0.0003) in the MMC arm. Overall survival was not significantly different in the two arms and the MMC arm showed significantly higher toxicity.

The British UKCCCR Study made a comparison between radiation therapy with radiation therapy and concomitant chemotherapy (MMC and 5-FU) in a randomized trial in which 856 patients were treated (UKCCCR 1996). The group found a 46% reduction in local recurrence (p<0.0001) for patients treated by combined therapy. The risk of death from anal cancer was significantly reduced, but overall survival was not significantly different in the two treatment groups.

The EORTC also tested the addition of chemotherapy to radiation therapy (Bartelink 1996). After randomization of 110 patients, a higher local tumour control was reported after chemoradiation (local recurrence 9 vs 15, local recurrence and distant relapse 9 vs 10 for rt+ct vs rt, respectively; significant improvement in local tumour control: p<0.02). Overall survival was not significantly different in the two groups.

Although combined modality therapy is accompanied by an increased local toxicity and moderate haematological toxicity, it is believed to be justi-

fied by the excellent results obtained with regard to local tumour control and colostomy free survival.

In conclusion, the standard therapy for anal canal cancers consists of radiation therapy and concomitant chemotherapy with the use of 5-FU and MMC. This is the best treatment for advanced tumours, whether N0 or N+. All cases, even unresectable should be considered for this regimen. In small tumours (T1N0) chemotherapy can be omitted without jeopardizing the outcome with regard to response rate and survival. The future will show if induction chemotherapy will keep its role, or if a change of chemotherapeutic drugs (cisplatin or carboplatin and 5-FU) will further improve the already very favourable results obtained by the present therapy in this rare disease.

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