Acta Oncologica, 2007; 46: 1019–1026

informa
healthcare

ORIGINAL ARTICLE

Anal carcinoma in mid-Norway 1970–2000

JO A. LUND[1,3], ARNE WIBE[2,3], STEIN H. SUNDSTROM[1,3], RUNE HAAVERSTAD[2,4], STEIN KAASA[1,3] & HELGE E. MYRVOLD[2,3]

[1]*Department of Oncology and Radiotherapy, St. Olav's University Hospital, Trondheim, Norway,* [2]*Department of Surgery, St. Olav's University Hospital, Trondheim, Norway,* [3]*Department of Cancer Research and Molecular Medicine, Norwegian University of Technology and Science, Trondheim, Norway and* [4]*Department of Circulation and Medical Imaging, Norwegian University of Technology and Science, Trondheim, Norway*

Abstract

The treatment of anal carcinoma changed from surgery to chemoradiotherapy 20–25 years ago. The aim of this observational study was to compare surgery with chemoradiotherapy with regard to side effects, local recurrence and survival during and after the implementation of a new treatment policy for anal carcinoma. The study includes all 111 patients with anal carcinoma diagnosed between 1970 and 2000 in mid-Norway. One hundred patients were treated with the intention to cure, and 11 patients received palliative treatment. Thirty-four patients were treated with surgery alone, and 57 patients with chemoradiotherapy. Among patients treated for cure, 17 patients (17%) developed local recurrence; ten patients (33%) in the surgically treated group and 4 (7%) in the chemoradiotherapy group ($p = 0.15$). Five year overall survival was 48% after surgery, compared to 78% after chemoradiotherapy ($p = 0.004$). Stage, age and treatment were all significant indicators of survival in uni- and multivariable analysis. Late side effects were moderate after combined therapy; only one patient preferred getting a stoma due to radiation damage of the anal sphincter. The change of strategy for anal cancer treatment from surgery to combined therapy has probably reduced local recurrence and improved survival. Side effects in this series of patients were minor after chemoradiotherapy compared to a permanent stoma after surgery.

Squamous cell carcinoma of the anal canal is an uncommon disease. The incidence rates are approximately 35–50 new cases each year in Norway (4.6 million inhabitants). The malignant cells originate either from squamous cells lining of the anal canal or the transitional epithelium cells at the rectoanal verge. The tumours arising from the transitional epithelium have a wide range of microscopically characteristics. During the period from 1970 to 2000 descriptive names such as cloacogenic, basaloid or transitional cell carcinomas have been used. Sub typing is now abandoned, except for anaplastic small cell carcinoma and anal carcinoma with mucinos microcycts [1].

Until the late 1970s these patients were treated with surgery alone. Abdominoperineal resection of the rectum and anus (APR) was considered the treatment of choice. The results were life-long colostomy and the 5-year overall survival rates varied from 40% to70% in different patient series. [2,3]. In 1974, Nigro et al. published a report on the use of preoperative radiotherapy and chemotherapy [4]. This report has later been followed by a number of papers that verify the benefits of chemoradiotherapy [5–11]. Two of these reports were randomised, controlled studies, reporting improved survival rates and local recurrence rates when adding chemotherapy to radiotherapy [5,10].

Also, management of lymph node metastases [12] has been investigated. Gerard et al. reported on N-stage as a negative prognostic factor for survival in anal carcinoma. Quality of life reports on anal carcinoma survivors have reported reduced quality of life after treatment, especially related to anal sphincter dysfunction [13,14]. However, long term side effects after chemoradiation for anal carcinoma

Correspondence: Jo- Asmund Lund, Department of Oncology and Radiotherapy, St. Olav's University Hospital, Olav Kyrres gt. 17, N-7006 Trondheim, Norway. Tel: +47 73 86 86 72. Fax: +47 73 86 78 21. E-mail: jo-asmund.lund@stolav.no

(Received 27 April 2006; accepted 11 December 2006)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860601166933

was evaluated by Madhu et al. [15], concluding that the side effects were not intense nor frequent enough to deter the use of chemoradiotherapy.

Although chemoradiotherapy was recommended as the gold standard 25 years ago, still some patients with early stage anal cancer were treated with surgery alone.

The present study reports on all anal carcinoma patients diagnosed in the three middle counties of Norway during the period from 1970 to 2000. Despite a thorough control regimen in which endoanal ultrasound has been routine procedure since 1983, none of the local recurrences in this patients series were detected by endoanal ultrasound alone [16].

In this retrospective study the primary outcomes were survival, local recurrence and long-term side effects according to treatment during and after the implementation of a new treatment policy for anal carcinoma. The underlying hypothesis, based on clinical experience and previous reports [5,10], was that the introduction of chemoradiotherapy had improved 5-year survival from 40 to 60%. Furthermore, improvement of long-term side effects and local recurrence rates were anticipated.

Methods and materials

The policy for treatment of a localised or a locoregional anal carcinoma in mid-Norway has been the following: Small T1N0 tumours were excised, if sphincter-preserving surgery was possible, during the entire study period. Since 1983, larger tumours, with or without glandular metastases, were treated with a combination of chemotherapy and radiotherapy. The chemotherapy was given as a continuous four-day intravenous infusion of 1000 mg/m^2/day 5-fluorouracil (5-FU) on treatment days one through four, combined with an intravenous bolus of 10 mg/m^2 mitomycin-c on day one. The radiotherapy was given with external photon beams, delivering 2 Gy fractions 5 days/week to a total dose of 40 Gy for assumed microscopic disease including the pelvis, limited cranially to the lower border of the ileosacral joints, and another 10–20 Gy booster dose to verified macroscopic disease in the anus and lymph nodes. The patients were treated without interruption, exceptions being made in case of severe acute side effects. At the end of treatment, the patients were evaluated clinically by visual and digital examination. In the cases of a suspected malignant residual tumour mass, the patients were followed closely, thus not performing "salvage" surgery for at least 2–3 months.

In the three middle counties of Norway (Møre og Romsdal, Sør-Trøndelag, Nord-Trøndelag), the surgical treatment of anal cancer patients was performed at local hospitals until 1983. In the period thereafter, oncologists and surgeons at a university hospital performed the treatment of anal carcinomas. One surgeon at St Olav's Hospital became aware of the potential benefits from chemoradiatiotherapy for these patients in the early 1980s, and referred the patients to the nearest radiotherapy department. Hence, the Norwegian Radium Hospital in Oslo treated these patients from 1983 until 1987, when the department of Radiotherapy and Oncology was established at St Olav's Hospital in Trondheim. Since 1987 the treatment of patients with anal carcinoma from these three counties has been performed at St. Olav's Hospital.

A total of 113 patients diagnosed with squamous cell carcinoma of the anus from January 1, 1970 through December 31, 2000 were identified by means of the Cancer Registry of Norway, the radiation therapy verification system and internal patient registries. This probably means that all eligible patients have been identified for inclusion. Patients' charts were evaluated in retrospect for all data collection. Patients' files were not found in two patients, because their files were transferred to an old, non-accessible archive. This left a total of 111 patients for inclusion. All patients had biopsy proven squamous cell carcinoma of the anus, although 11 specimens were described as deriving from one of the transitional cell subtypes in accordance with the guidelines previously described. One of the biopsies was described as an adenocarcinoma. This patient was perceived as having an anal carcinoma and thus included in the present analyses. Treatment choice was by doctors' preference until 1983, thereafter local and national recommendations were gradually implemented.

Staging was done according to the TNM classification system of 1997 [17]. For patients treated with abdominoperineal resection of the rectum, TNM staging was based on preoperative investigations and microscopical examination of the surgical specimen, hence resulting in a pTNM stage. For patients treated with sphincter preserving therapy, TNM staging was based on pre treatment examinations (Table I), resulting in a cTNM stage.

In the present study, patients were categorized on basis of anal cancer treatment into three groups: Patients treated with surgery alone, patients treated with a combination of chemotherapy and radiotherapy and finally, patients treated with combinations of surgery and radiotherapy, or radiotherapy without chemotherapy. This last group of patients was small and heterogeneous and thus not included in the survival analyses.

Table I. Pre – treatment investigations in 111 patients with anal carcinoma.

	Yes	No	Not known
Chest X-ray	102	7	2
Abdominal/pelvic CT	62	43	6
Ultrasound liver	42	61	8
Rectoscopy	97	12	2
Anal ultrasound	37	71	3

Survival was calculated using Kaplan Meyer estimation, and differences between treatment groups were evaluated by the log rank test. Univariable analysis on variables possibly affecting survival was performed, followed by a multivariable Cox regression analysis. Only the variables showing to be statistically significant in univariable analysis were included in the multivariable analysis. Due to a low sample size, stage was included in the univariable analysis while T, N and M stages separately were not.

The long-term side effects were graded according to the RTOG (Radiation Therapy Oncology Group)/EORTC (European Organisation for Research and Treatment of Cancer) grading system [15], and registered in the database as the worst grading for each patient later than 3 months after ending the treatment. For each patient case, grading was based on patient's files and converted into an EORTC/RTOG grade by the authors. In case of no description of side effects in a patient's file, side effects were registered as missing.

Data analysis was performed using SPSS for windows version 14.0 (SPSS Inc., Chicago Illinois, USA).

Results

All patients

The median follow-up time was three point six years (0 – 24 years). Ninety-one patients were women, 20 patients were men (ratio 4.5:1). The most common debut symptoms were pain (36%) and bleeding (31%), but itching, constipation, anal incontinence, secretion, and palpable tumour was also reported. In five patients, debut symptom was not possible to determine in retrospect. Mean time from symptom debut to the diagnosis was established, was 8.3 (range 0–56.3) months. The distribution of patients between the three counties reflected the population, Sør-Trøndelag being the largest with 49 patients.

Table II. T- and N-stage at diagnosis in 107 anal carcinoma patients without distant metastasis.

	N0	N1	N2	N3	Nx
T1	15	0	0	0	0
T2	31	5	2	2	0
T3	11	7	4	3	1
T4	10	7	4	4	1

The investigations prior to treatment varied, as shown in Table I. Thirty-seven of the patients were investigated with endoanal ultrasound prior to diagnosis; all of them were diagnosed after January 1, 1987. The results of the TNM classification are given in Table II, showing that 15 patients were classified as T1N0M0, while the remaining 96 patients were classified to stage T2N0M0 or higher. Four patients had distant metastasis at diagnosis.

One hundred patients were treated with the intention to cure, while 11 patients were treated for palliation of symptoms by surgery or radiotherapy. These 11 patients had anal carcinoma stages T2N0M0 to T4N3M1.

Thirty-four patients were treated with surgery alone, nine of these were classified as T1N0 tumours.

Fifty-three patients were treated with a combination of radiotherapy and chemotherapy, and four patients were given radiotherapy and chemotherapy after surgery, giving a total number of 57 patients treated with chemoradiotherapy (Table III). The remainder of the patients were treated as follows: Two patients had radiotherapy prior to surgery,

Table III. Treatment and results of 111 patients with anal carcinoma.

	All patients		Patients treated with a curative intent		Local recurrence	
	n	%	n	%	n	%
Surgery	34	31	30	88	10	33
Chemoradiotherapy	57	52	55	96	4	7
Preop. radiotherapy+surgery	2	2				
Radiotherapy	7	6	15	75	3	20
Surgery+post.op. radiotherapy	11	10				
	111		100		17	17

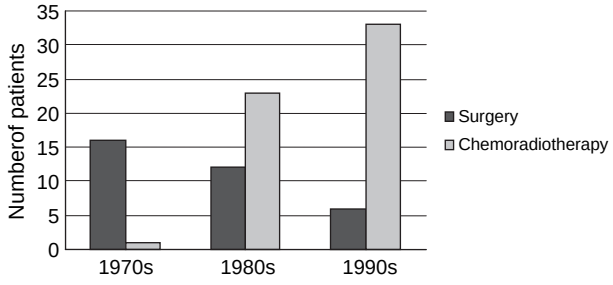

Figure 1. Number of patients with anal carcinoma treated by surgery (n = 34) or by chemoradiotherapy (n = 57) in Mid-Norway 1970–2000. Twenty patients treated by surgery and/or radiotherapy without chemotherapy not included.

seven patients had radiotherapy and 11 patients had surgery and postoperative radiotherapy.

The treatment strategy according to time period is described by Figure 1, including only patients treated by surgery alone versus patients treated by chemoradiotherapy. The treatment changed from surgery alone during the 1970s to mostly chemoradiotherapy during the 1990s.

Overall 5-year survival for the entire cohort was 60% (figure not shown). Overall 5-year survival (Figure 2) was 48% after surgery alone compared to 78% after chemoradiotherapy ($p = 0.004$). Although the two cohorts of patients were similar with respect to age and sex distribution, their TNM stages differed in that 33% of the patients treated by chemoradiotherapy were classified as T2N0M0 or lower while 62% of the patients treated by surgery were classified as T2N0M0 or lower. Anal cancer specific 5-year survival was 89% for chemoradiotherapy patients and 75% for patients treated by surgery ($p = 0.07$) (Figure 3). Anal cancer specific survival was 77% for the patients over 65 years of age and 78% for the patients at age 65 or younger ($p = 0.794$).

Univariable analysis is presented in Table IV. Patients' age at time of diagnosis, stage of disease and treatment were factors affecting their survival.

In a multivariable Cox regression, stage was the strongest indicator for survival (hazard ratio 3.094) followed by patient's age at diagnosis and treatment (Table V).

Patients treated with a curative intent

The surgical treatment was as follows: Ten patients diagnosed with stage T1N0M0 anal carcinoma were treated by local excision, while one similar patient was treated by APR. All of the 19 patients in stage T2N0M0 and higher were treated by APR.

Seventeen of the patients treated with a curative intent developed local recurrence (Table III). For one of these, the exact date of local recurrence was not possible to verify. Ten local recurrences (33%) were found amongst the 30 patients treated by surgery, while there were four local recurrences (7%) in the 55 patients treated for cure by chemoradiotherapy. The remaining three local recurrences (33%) were found in the group of ten patients treated for cure by surgery and postoperative radiotherapy. The local recurrences amongst the surgical patients were found in one of ten patients treated by local excision for T1 cancers, the reminding nine local recurrences were found amongst the 20 patients treated by APR for T2-T4 cancers.

Five-year overall survival after local recurrence for the 16 patients that were possible to include in the analysis was 15% (Figure 4).

The late side effects after chemoradiotherapy are presented in Figure 5. Follow-up time for the patients included in the analysis on side effects was 38 (3–97) months. For 39 patients in whom a late toxicity scoring was possible, 31 patients had skin

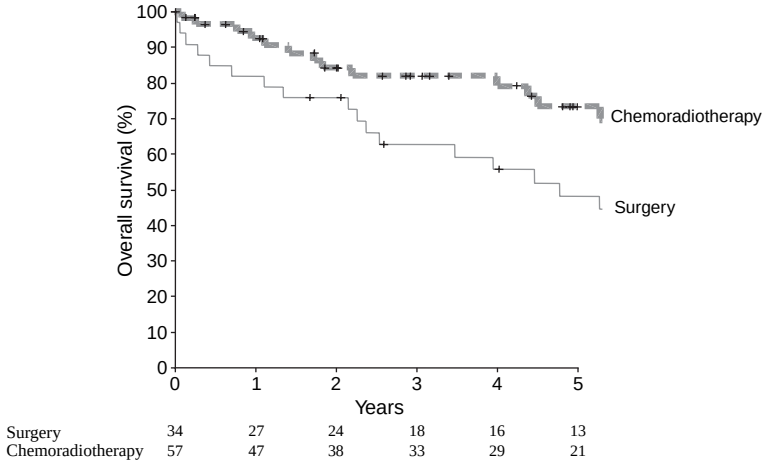

Figure 2. Overall survival according to treatment in 34 patients treated by surgery and 57 patients treated by chemoradiotherapy for anal carcinoma, not including the 20 patients treated without chemotherapy.

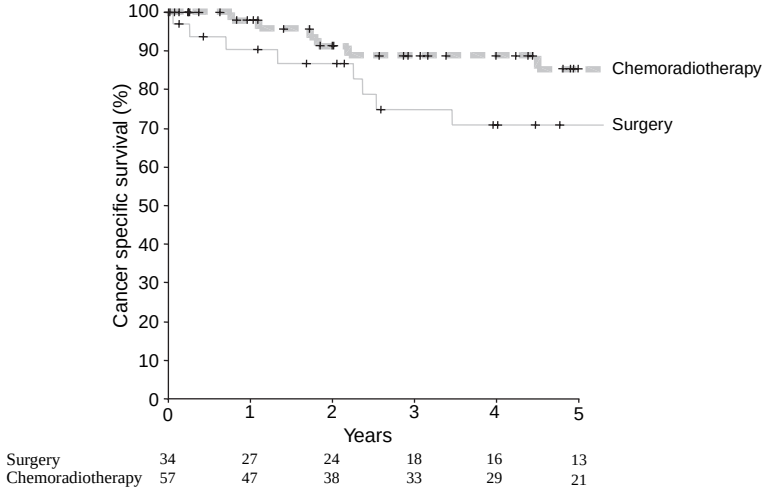

Figure 3. Cancer specific survival according to treatment for 34 patients treated by surgery and 57 patients treated by chemoradiotherapy for anal carcinoma.

and rectal toxicity grades 0-1, whereas 23 patients had grade 0-1 toxicity with regards to the anal sphincter. Two patients developed grade 4 sphincter morbidity. Only one patient chose to accept an offer of permanent colostomy due to anal incontinence.

Discussion

The treatment of anal carcinoma stage T2N0 and higher has changed since 1970. During the first 13 years of this period, patients in this region of Norway underwent abdominoperineal resection. Since 1983, a non-surgical approach has prevailed, and most of the patients have been treated with a combination of external beam radiotherapy and chemotherapy. This change of treatment has preserved the anal sphincter and probably improved overall survival.

The present report is limited by study design, and results should be considered with some caution. However, overall survival was significantly better for patients treated by chemoradiotherapy, compared to patients treated by surgery, despite the fact that patients treated by surgery had less advanced disease. Furthermore, the surgical group of patients was staged according to microscopical changes (pTNM), while the chemoradiotherapy group was staged according to clinical findings (cTNM), which may have resulted in an upstaging of the surgical group of patients in relation to the patients treated by chemoradiotherapy. Thus, keeping in mind that tumour size and lymph node involvement have been reported as poor prognostic factors [18], the difference in survival between the two groups is probably underestimated in this report. Also, this analysis included the T1N0 patients – which have been treated by local excision during the entire period. Excluding these patients further increase the survival difference between the two treatment groups (results not presented). Therefore, the present results provide support of a considerable improved survival for patients treated by chemoradiotherapy compared to surgery, probably caused by undetectable loco-regional disease not handled by surgery. Survival estimates were higher than anticipated in our hypothesis in both treatment groups. This could reflect that the hypothesis was

Table IV. Univariable survival analysis.

Variable	Variable	No of patients	Median survival	95% CI	p-value
Sex	Male	20	4.1	2.9–12.0	
	Female	91	7.4	2.7–6.0	0.2
Age	>65 years	56	4.5	3.1–5.9	
	≤65 years	55	23.1	6.4–39.8	0.000
Time to diagnosis	<6 months	62	5.5	3.2–7.9	
	≥6 months	43	16.4	3.2–29.5	0.526
Stage	Stage I and II	55	16.4	3.5–29.3	
	Stage III and IV	56	4.4	2.5–6.3	0.005
Treatment	Chemoradiotherapy	57	NR		
	Surgery	34	4.8	2.6–6.9	0.004

Table V. Multiple regression analysis.

Variable	Regression coefficient (beta)	95% CI for beta
Age >65 yrs	2.717	1.520–4.854
Surgery	1.721	1.368–2.165
Stage III & IV	3.094	1.714–5.587

based on results from prospective, randomised trials where one might expect poorer survival than in retrospective studies [10].

Furthermore, the change in treatment strategy also implies that treatment of this uncommon disease is performed at a single centre, possibly also resulting in better survival. This is in accordance with previous reports [19].

Based on the excellent survival achieved for anal carcinoma patients with modern chemoradiotherapy, one may suggest that further clinical research has to focus on reduction of acute and late side effects, for instance by intensity modulated radiotherapy, and escalation of treatment for high-risk groups, e.g. patients with large tumours and/or lymph node involvement.

In univariable analysis, patient's age, stage and treatment were all statistically significant indicators for survival. In multivariable analysis, age over 65 years at diagnosis was a strong indicator. This is not in accordance with at least one previous report [20]. In the present material, the two age groups were balanced with regards to number of patients, intent of treatment and radio/chemotherapy doses (results not presented). However, the younger patients died mainly from anal carcinoma, in that 14 of 19 deaths were due to their malignancy. In the group of older patients, 12 died from anal carcinoma while

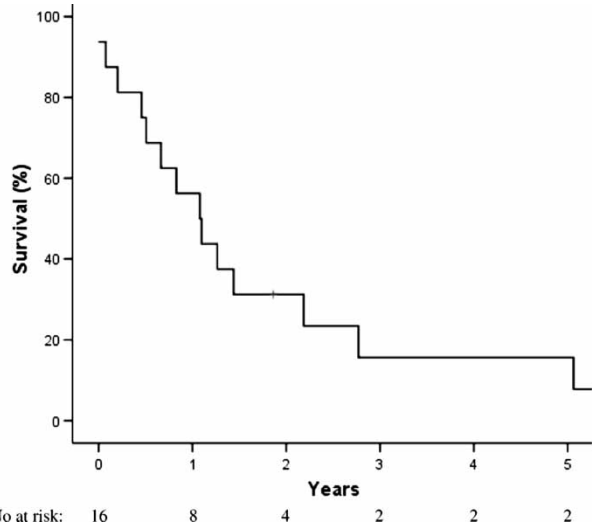

Figure 4. Overall survival in 16 patients diagnosed with a locally recurrent anal carcinoma after being treated for cure.

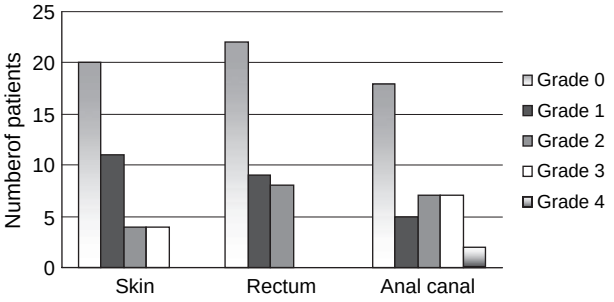

Figure 5. Late side effects in 39 patients with anal carcinoma treated by chemoradiotherapy.

22 died of other causes. Furthermore, the anal cancer specific survival in the two groups showed no significant difference. Hence, co-morbidity is important in explaining the difference in survival between the two groups.

The other findings in this analysis was in accordance with previous reports [5,12,18,21], supporting that chemoradiation is superior to surgery and that stage III and IV disease is a negative prognostic factor for survival.

Local recurrence rates were considerable lower in the chemoradiotherapy group of patients compared to the surgical group of patients. As displayed in Table III, even the patients treated by APR and postoperative radiotherapy experienced quite a few local recurrences. This indicates that chemotherapy is an important modality when treating anal carcinoma patients, in contrast to at least one previous report [6]. However, the chemotherapy in the present report was different from the chemotherapy in the report by Friberg et al., which might explain the difference in results. Furthermore, several randomised trials have demonstrated that chemoradiotherapy is superior to radiotherapy alone [5,10]. Thus, the present report supports the knowledge that chemoradiotherapy is superior to radiotherapy alone in treatment of anal carcinoma. This probably also strengthens the value of the present report, in that the results are in accordance with previous randomised trials.

In patients' stage T1N0M0, local excision is followed by a high local control rate, only one of ten such patients had local recurrence in the present report. This means that the present Nordic recommendations for treating T1N0M0 anal carcinoma are probably adequate.

Patients treated for palliation represented different TNM stages. This probably reflects that the choice of treatment intention was based on co-morbidity as well as extent of disease.

Although late side effects were present in a significant proportion of patients treated by chemoradiotherapy, these seemed to be low in intensity and

frequency. Hence, the negative effect for each patient is probably small compared to having a permanent stoma following APR. Two previous reports discuss the quality of life in anal carcinoma survivors after chemoradiation [13,14]. These reports have applied different tools for measurement of quality of life, and are difficult to compare. The present report has no quality of life measurements included. However, almost all patients in this study have chosen not to accept colostomy due to side effects, indicating that their side effects with respect to anal function were acceptable.

By using a "wait and see" approach at the end of the treatment, even if a palpable residual mass was present, most patients in this report achieved complete response. One topic discussed amongst clinicians and in the literature [22] is the treatment strategy for palpable tumour at the end of combined therapy. Some will go for early salvage surgery. In this series, a "wait and see" approach was used, and most patients avoided local recurrence. This indicates that a surgical intervention immediately after chemoradiotherapy can result in unnecessary surgery, leaving too many patients with a colostomy. This "wait and see" approach must however be performed with caution, realising that overall survival after local recurrence is poor and that degree of tumour regression has demonstrated prognostic value in a previous report [22].

In conclusion, the present report support that the shift of treatment strategy for anal carcinoma during the 1980s has improved survival and local recurrence rates. At the same time, side effects from chemoradiation seem moderate. Finally, stage of disease and patient's age seem to be negative prognostic factors for survival.

Acknowledgements

The authors would like to thank The Cancer Registry of Norway, Namsos Hospital, Levanger Hospital, Orkdal Hospital, Kristiansund Hospital, Molde Hospital, Ålesund Hospital and Volda Hospital for their co-operation in providing clinical data for this study. The study has been supported by a grant from The Norwegian Cancer Society.

References

[1] WHO classification: Pathology and Genetic. Tumors of the digestive system. IARC Press, 2000.

[2] Boman BM, Moertel CG, O'Connell MJ, Scott M, Weiland LH, Beart RW, et al. Carcinoma of the anal canal. A clinical and pathologic study of 188 cases. Cancer 1984;54:114–25.

[3] Brown DK, Oglesby AB, Scott DH, Dayton MT. Squamous cell carcinoma of the anus: A twenty-five year retrospective. Am Surg 1988;54:337–42.

[4] Nigro ND, Vaitkevicius VK, Considine B, Jr. Combined therapy for cancer of the anal canal: A preliminary report. Dis Colon Rectum 1974;17:354–6.

[5] Epidermoid anal cancer: Results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research Lancet 1996;348(9034):1049–54.

[6] Friberg B, Svensson C, Goldman S, Glimelius B. The Swedish National Care Programme for Anal Carcinoma–implementation and overall results. Acta Oncol 1998;37:25–32.

[7] Nigro ND, Seydel HG, Considine B, Vaitkevicius VK, Leichman L, Kinzie JJ. Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal. Cancer 1983;51:1826–9.

[8] Papillon J, Montbarbon JF, Gerard JP, Chassard JL, Ardiet JM. Interstitial curietherapy in the conservative treatment of anal and rectal cancers. Int J Radiat Oncol Biol Phys 1989;17:1161–9.

[9] Tanum G, Tveit K, Karlsen KO, Hauer-Jensen M. Chemotherapy and radiation therapy for anal carcinoma. Survival and late morbidity. Cancer 1991;67:2462–6.

[10] Bartelink H, Roelofsen F, Eschwege F, Rougier P, Bosset JF, Gonzalez DG, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: Results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol 1997;15:2040–9.

[11] Meyer A, Meier Zu EJ, Karstens JH, Bremer M. Chemoradiotherapy in patients with anal cancer: Impact of length of unplanned treatment interruption on outcome. Acta Oncol 2006;45:728–35.

[12] Gerard JP, Chapet O, Samiei F, Morignat E, Isaac S, Paulin C, et al. Management of inguinal lymph node metastases in patients with carcinoma of the anal canal: experience in a series of 270 patients treated in Lyon and review of the literature. Cancer 2001;92:77–84.

[13] Jephcott CR, Paltiel C, Hay J. Quality of life after non-surgical treatment of anal carcinoma: A case control study of long-term survivors. Clin Oncol (R Coll Radiol) 2004;16:530–5.

[14] Vordermark D, Sailer M, Flentje M, Thiede A, Kolbl O. Curative-intent radiation therapy in anal carcinoma: Quality of life and sphincter function. Radiother Oncol 1999;52:239–43.

[15] Madhu J, Marshall F, Nanette P. Ten-year results of chemoradiation for anal cancer: Focus on late morbidity. Int J Radiation Oncology Biol Phys 1996;34:65–9.

[16] Lund JA, Sundstrom SH, Haaverstad R, Wibe A, Svinsaas M, Myrvold HE. Endoanal ultrasound is of little value in follow-up of anal carcinomas. Dis Colon Rectum 2004;47:839–42.

[17] UICC. TNM Classification of Malignant Tumours. 5th ed. John Wiley & Sons, Inc, 1997.

[18] Peiffert D, Bey P, Pernot M, Guillemin F, Luporsi E, Hoffstetter S, et al. Conservative treatment by irradiation of epidermoid cancers of the anal canal: prognostic factors of tumoral control and complications. Int J Radiat Oncol Biol Phys 1997;37:313–24.

[19] Goldman S, Glimelius B, Pahlman L, Stahle E, Wilander E. Anal epidermoid carcinoma: A population-based clinicopathological study of 164 patients. Int J Colorectal Dis 1988; 3:109–18.

[20] Saarilahti K, Arponen P, Vaalavirta L, Tenhunen M, Blomqvist C. Chemoradiotherapy of anal cancer is feasible in elderly patients: Treatment results of mitomycin-5-FU combined with radiotherapy at Helsinki University Central Hospital 1992–2003. Acta Oncol 2006;45:736–42.

[21] Chapet O, Gerard JP, Mornex F, Goncalves-Tavan S, Ardiet JM, D'hombres A, et al. Prognostic factors of squamous cell carcinoma of the anal margin treated by radiotherapy: The Lyon experience. Int J Colorectal Dis 2006.

[22] Chapet O, Gerard JP, Riche B, Alessio A, Mornex F, Romestaing P. Prognostic value of tumor regression evaluated after first course of radiotherapy for anal canal cancer. Int J Radiat Oncol Biol Phys 2005;63:1316–24.