The Swedish National Care Programme for Anal Carcinoma

Implementation and Overall Results

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The Swedish National Care Programme for Anal Carcinoma (SNCPAC) was instituted in order to create a uniform handling policy for anal cancer and thus to accrue a population-based material allowing unbiased analyses. This study evaluates the degree of implementation of the SNCPAC guidelines, and presents overall treatment results in a total of 356 patients with epidermoid cancer of the anus and the perianal region diagnosed in Sweden between 1985 and 1989. Primary treatment according to the guidelines was irradiation up to 40 Gy. Bleomycin was administered intramuscularly before the first 18 fractions. After a 3-week pause, radiotherapy was to be continued up to a dose of 60–64 Gy, if at least an almost complete response was achieved. Otherwise, the patient was recommended surgery within a week. The guidelines were applied in 90% of cases where such treatment was possible. The 5-year tumour-specific survival rate was 72%. The survival rate was more favourable in perianal tumours (90%) than in anal canal tumours (68%, $p < 0.01$). The 5-year probability of having a preserved anus was 64% (anal canal/perianal 58%/91%, $p < 0.001$). Bleomycin did not appear to have any effect on treatment results. The care programme has had a rapid and almost complete nation-wide penetration, and h as created the desired uniformity allowing proper analyses. The treatment results also appear comparable with specialised referral centres.

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Epidermoid cancer of the anus (the anal canal and the perianus, the latter defined as an area within a 5-cm radius from the anal orifice) is relatively uncommon, with at present approximately 90 new cases per year in Sweden (population of 8.6 million) (1). This constitutes less than 2% of all colorectal malignancies. The age-standardised incidence rate has increased considerably during recent decades, particularly in women (2, 3). Cancer of the anal canal has a female preponderance by a factor of 3:1, whereas perianal carcinoma is evenly distributed between the sexes (2–6).

Surgery, usually an abdominoperineal resection (APR), was formerly regarded as the treatment of choice. During the 1970s and early 1980s, a number of publications reported favourable results using radiotherapy (RT) alone or in combination with chemotherapy (7–12). In a substantial proportion of cases, cure was achieved with preservation of anal sphincter function. Because of this, and to establish a nation-wide uniformity in handling policy in order to be able to evaluate the treatment principles in a population-based material, The Swedish National Care Programme for Anal Cancer (SNCPAC) was proposed and accepted in 1984. It contains guidelines for staging, treatment, and follow-up of all incident cases. Based upon favourable experience of using RT in combination with bleomycin in various epidermoid cancers including anal (13), head-neck (14), and lung (15) cancer, respectively, this combination was recommended as primary treatment. The objectives of this study were to describe the extent to which the guidelines in the SNCPAC have been implemented in the Swedish population of patients diagnosed with epidermoid cancer of the anus between 1985 and 1989, and to analyse the overall treatment results.

MATERIAL AND METHODS

Patients

In Sweden, notification to the National Cancer Registry of all cases of cancer is mandatory, both by the clinician responsible for the care of the patient and by the pathologist or cytologist who has confirmed the diagnosis, result-

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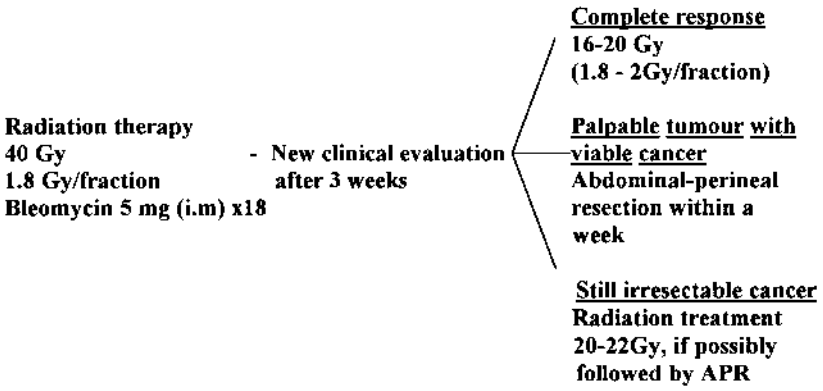

Fig. 1. An overview of the recommended treatment policy for epidermoid carcinoma of the anus.

ing in an almost complete registration, with an overall deficit of less than 2% (16). All patients diagnosed with epidermoid cancer of the anus were identified from the six different regional cancer registers. A total of 372 cases was found. In 10 of these cases, the diagnosis was found to be incorrect and in 6, the patient records could not be retrieved. The remaining 356 tumours were all histopathologically verified.

Tumour classification

All tumours were originally classified according to the third revision of the UICC TNM classification. Retrospectively, a reclassification was done according to the fourth revision (17). Tumours found in both the anal canal and in the perianus were regarded as originating from the anal canal. Lymph node staging was simplified, however, in the absence (N_-) or presence (N_+) of pathologic lymph nodes. Histologically, the tumours were classified as squamous cell carcinoma or basaloid (cloacogen). No re-evaluation of the original histopathological diagnosis was made.

Treatment recommendations

The primary treatment recommended to most of the patients was RT in combination with bleomycin. For those patients with peripherally located (i.e. preferentially perianal tumours), small (< 2 cm), and well-differentiated tumours, primary surgery was optional, provided a local surgical procedure with adequate margins was possible.

After a cumulative radiation dose of 40 Gy followed by a 2–3 week pause, surgery, usually an APR, was to be performed if there was not at least a clinically nearly complete tumour regression. Otherwise, RT was to be continued up to a total dose of 60–64 Gy. In the event of residual tumour after conclusion of full-dose RT, salvage surgery was recommended if possible. An overview of the recommended treatment policy is presented in Fig. 1. Previously irradiated patients were usually treated with surgery, although limited radiotherapy was given to some patients if this was considered possible.

Radiation treatment

For tumours of the anal canal, the clinical target volume (CTV), during the first radiation course up to approximately 40 Gy, included the primary tumour, medial inguinal, perirectal, and iliacal lymph nodes. The inguinal nodes were not included in the CTV if the tumour was entirely located above the dentate line. If the tumour extended perianally, or lymph node metastases were coexistent, the lateral inguinal nodes were also included. In practice, this usually meant that for cancers of the anal canal, the cranial limit of the CTV was at the lower border of the fifth lumbar vertebra, the lower limit was 1 cm below the perineum, and the lateral limits were approximately at the mid-point of the inguinal ligament. For perianal tumours, the cranial limits were at the S2–S3 level, and laterally the beams included all inguinal lymph nodes. During the second course, the CTV was reduced to include only the primary tumour with a 3 cm margin in all directions.

The treatment technique during the first course was usually parallel opposing AP and PA rectangular beams with the patient in the supine position. If the inguinal nodes were not included, a 3-beam treatment technique was utilised (18). One hour before RT, 5 mg bleomycin was administered as an i.m. injection at 18 fractions. Bleomycin should not be given in the presence of pulmonary disease. A pulmonary x-ray was performed in all patients as part of the staging procedure. When bleomycin was administered, the minimum fraction target dose was

1.8 Gy, otherwise 1.8–2.0 Gy. The cumulative target dose at the end of the first course of RT was approximately 40 Gy.

During the second course, a 3-beam treatment technique was used for cancers of the anal canal. For perianal tumours, the second course was often administered with an electron beam to the perianal region. The minimum fraction target dose was specified to 1.8–2.0 Gy. No bleomycin was given during the second course.

Data collection

The SNCPAC requested all centres to record necessary data on special forms in order to make a subsequent evaluation of treatment results possible. For those cases where the forms had not originally been completed, this was done retrospectively using the patient records. The mean follow-up period was 99 months for patients still alive (range 49–139).

Statistical methods

Statistical evaluation of the results with respect to overall and tumour-specific survival, freedom from residual or recurrent tumour, and preservation of sphincter function was carried out using the Kaplan-Meier life-table analysis (19, 20). Time intervals were computed with respect to the date of diagnosis. Tests of homogeneity and trend were made with the Peto-Wilcoxon statistics (21, 22). Cox multiple logistic regression analyses were made in order to find significant determinants of risk for the above endpoints (23).

RESULTS

Patient characteristics

Of the 356 identified cases, 283 (79%) were located in the anal canal (38 patients had both anal and perianal location and were regarded as anal canal tumours), and 73 (21%) in the perianal region. Two hundred and fifty-three patients were females (71%). The female:male ratio for cancers of the anal canal was 3:1, whereas for perianal tumours it was 1:1. The mean age at the time of diagnosis was 66 years for females and 65 for males, with similar age distributions in both anal and perianal location (see Table 1).

Table 1

Patient characteristics at diagnosis

Age, sex, histology	Anal canal	Perianal	Total
Age, females mean (range)	67 (29–95)	64 (36–92)	66 (29–95)
Age, males mean (range)	65 (33–90)	64 (31–83)	65 (31–90)
Age, all	66 (29–95)	64 (31–92)	66 (29–95)
Sex female/male	215/68	38/35	253/103
Squamous/ cloacogenic	188/95	63/10	251/105
Stage	n (%)	n (%)	n (%)
Total	283 (79)	73 (21)	356 (100)
T1–4 N0M0	218 (77)	65 (89)	283 (79)
T1	32 (15)	24 (36)	56 (20)
T2	101 (46)	32 (50)	133 (47)
T3	47 (22)	8 (12)	55 (20)
T4	38 (17)	1 (2)	39 (14)
T1–4 N+M0	52 (18)	6 (8)	58 (16)
T1	1 (2)	0 (0)	1 (2)
T2	17 (33)	3 (50)	20 (34)
T3	21 (40)	1 (17)	22 (38)
T4	13 (25)	2 (33)	15 (26)
M+	13 (5)	2 (3)	15 (4)

Histologically, 105 (29%) of the tumours were classified as basaloid (cloacogen), and 251 (71%) as squamous cell carcinoma (Table 1). For anal canal tumours, 34% were classified as basaloid, and for perianally located tumours the proportion was 14%. Distributions of tumours according to TNM-stage for the total patient material and for anal canal and perianal cancers separately are presented in Table 1. There were no gender differences according to stage (data not shown).

Treatment

Three hundred and eleven patients (87%) were treated with curative intent. This proportion was similar for tumours

Table 2

Treatment according to tumour localization

	Anal canal n (%)	Perianal n (%)	Total n (%)
Total	283	73	356
Treatment with curative intent	245 (87)	66 (90)	311 (87)
Treatment according to SNCPAC	216 (88)	54 (81)	270 (87)
Primary surgery	0 (0)	13 (25)	13 (5)
RT	158 (73)	28 (51)	185 (68)
RT <46 Gy+surgery	47 (22)	6 (11)	53 (20)
RT >46 Gy+surgery	11 (5)	7 (13)	18 (7)
Treatment with curative intent, but not to SNCPAC	29 (12)	12 (19)	41 (13)
Primary surgery	19 (66)	10 (83)	29 (71)
Primary surgery, due to earlier RT	10 (34)	2 (17)	12 (29)
Palliative treatment	38 (13)	7 (10)	45 (13)

Table 3

Actuarial 5-year treatment results in the entire material and selected subgroups (%)

Total material	(n)	Overall survival	Tumour-specific survival	Recurrence free	Intact anal sphincter
Ac+Pa	(356)	53	65	49	64
Ac	(283)	49	60	45	58
Pa	(73)	66	82	70	89
Curative treatment					
All	(311)	59	70	56	63
SNCPAC–All	(270)	61	72	59	64
SNCPAC–Ac	(216)	57	68	54	58
SNCPAC–Pa	(54)	74	90	83	91
Bleomycin					
RT+bleomycin	(159)	63	72	59	60
RT−bleomycin	(57)	48	68	56	68
Primary surgery/RT					
RT ± surgery (Ac T1–2 N0)	(103)	77	85	67	69
Primary surgery ± RT (Ac T1–2 N0)	(23)	45	61	40	59
Primary surgery+RT (Pa T1–2 N0)	(23)	92	100	92	92
Primary surgery−RT (Pa T1–2 N0)	(13)	74	82	61	96

Ac = anal canal; Pa = perianal

located in the anal canal and in the perianal region (Table 2). Thirty-eight anal canal and 7 perianal tumours received only palliative treatment. Reasons for giving palliative treatment were distant metastases (15 patients), very advanced loco-regional disease, advanced age, patient negative to treatment, and other debilitating illnesses precluding intensive oncological treatment.

Twenty (8%) patients of all 253 female patients had a history of previous pelvic irradiation for a cervical carcinoma. Seventeen of these were treated with a curative intent but further RT was considered possible for only 5 of them. The remaining 12 were treated with surgery. Consequently, 299 patients could be treated with curative intent according to the recommendations. Of these, 270 (90%) were treated in accordance with the SNCPAC guidelines, 216 anal canal and 54 perianal (Table 2).

Overall treatment results

In the entire material, a 5-year actuarial crude survival rate of 53% and a tumour-specific survival rate of 65% were found. The corresponding figures for the 311 patients treated with a curative intent were 59% and 70%, respectively (Table 3).

For patients treated with curative intent according to the guidelines, the overall 5-year survival rate was 61%, while the tumour-specific survival rate was 72%. For the subset of patients who did not have lymph node metastasis at diagnosis (any TN_0M_0), these figures were 68% and 78%, respectively (data not shown). Of the 270 patients treated according to the guidelines, 59% (anal canal 54%, perianal 83%) were recurrence free at 5 years. The results in the various treatment groups are presented in Table 3. Palliatively treated patients had a poor outcome with a median survival of 9 months and a 5-year crude survival rate of 4% (not shown).

Effect of bleomycin in addition to radiotherapy

Of 216 patients with tumour in the anal canal who had been irradiated with curative intent, 57 (26%) did not receive bleomycin. In general, bleomycin was not administered to patients who were very old, had concurrent pulmonary disease, or when the physician considered that such treatment would be too toxic for the patient. Those who had received bleomycin had a significantly better crude survival rate at 5 years, 63% vs. 48% ($p < 0.01$) (Table 3). This difference was not seen, however, for tumour-specific survival rate, 72% vs. 68% (p = N.S.), freedom from recurrence, or probability of sphincter preservation. Owing to the limited number of patients, no separate analysis for perianal tumours has been made.

Surgery vs. radiation as primary treatment

Twenty-nine patients with a tumour in the anal canal underwent surgery as initial therapy (13 local surgery and 16 APR). Twenty-three (8 previously irradiated) of these were in stages T1–T2N0, 4 (2 previously irradiated) in stage T3N0, and 2 in stage T4N0 (none previously irradiated). In order to achieve a more unbiased comparison

Table 4

Cox multivariate analyses of determinants of risk overall, tumor specific survival, for residual or recurrent tumour and loss of sphincter

Variable	B	Exp(B)	S.E.(B)	B/SE	p
Overall survival					
Age	0.03	1.04	0.01	4.68	0.000
Female/male	−0.48	0.62	0.19	−2.47	0.01
Nodal status N_+/N_-	0.69	2.00	0.20	3.51	0.001
Bleomycin (±)	−0.27	0.77	0.18	−1.48	0.13
Tumor site Ac/Pa	0.46	1.60	0.25	1.86	0.06
Stage T = T2	0.25	1.29	0.29	0.88	0.38
Stage T = T3	0.81	2.25	0.31	2.62	0.01
Stage T = T4	1.22	3.41	0.32	3.84	0.000
Tumor specific survival					
Age	0.03	1.03	0.01	2.79	0.005
Female/male	−0.45	0.64	0.24	−1.83	0.07
Nodal status	0.85	2.34	0.23	3.72	0.000
Bleomycin (±)	−0.25	0.78	0.22	−1.09	0.28
Tumor site Ac/Pa	0.60	1.82	0.34	1.76	0.08
Stage T = T2	1.07	2.91	0.53	1.99	0.05
Stage T = T3	1.81	6.11	0.55	3.34	0.001
Stage T = T4	2.09	8.06	0.56	3.76	0.000
Residual or recurrent tumour					
Age	0.01	1.01	0.01	1.96	0.05
Female/male	−0.16	0.84	0.20	−0.78	0.43
Nodal status N_+/N_-	0.61	1.83	0.21	2.94	0.005
Bleomycin (±)	−0.28	0.76	0.18	−1.52	0.13
Tumour site Ac/Pa	0.43	1.54	0.26	1.65	0.10
Stage T = T2	0.53	1.70	0.31	1.69	0.10
Stage T = T3	0.81	2.25	0.34	2.40	0.01
Stage T = T4	1.18	3.24	0.35	3.32	0.001
Loss of sphincter					
Age	−0.02	0.98	0.01	−2.33	0.02
Female/Male	0.07	1.07	0.22	0.32	0.75
Nodal status N_+/N_-	−0.01	0.99	0.23	0.32	0.75
Bleomycin (±)	−0.24	0.78	0.21	−1.18	0.24
Tumour site Ac/Pa	0.91	2.49	0.34	2.63	0.01
Stage T = T2	1.00	2.73	0.41	2.44	0.01
Stage T = T3	1.80	6.04	0.42	4.21	0.000
Stage T = T4	1.61	5.03	0.32	5.12	0.000

Ac = anal canal, Pa = perianal

with primarily irradiated patients, only those in stages T1–T2N0 were included in an analysis of treatment results. One hundred and three patients in these stages had received primary RT. Five-year crude/tumour-specific survival rates were 77%/85% for the RT group and 45%/61% for those surgically treated. The differences were statistically significant (overall survival $p < 0.01$, tumour-specific survival $p < 0.05$). For perianal tumours (T1–T2N0) treated only with primary surgery (13 patients), the 5-year overall and tumour-specific survival rates were 74% and 82%, respectively. These results were significantly inferior to those seen in patients ($n = 23$) who also were irradiated (92%, $p < 0.05$ and 100%, $p < 0.01$, respectively). Survival data for the different subgroups are presented in Table 3. No significant difference in survival between previously irradiated and non-irradiated women was seen (data not shown).

Preservation of the anus

In the total material, the actuarial probability of having a preserved anus at 5 years was 64%. For those treated according to the SNCPAC, it was also 64%. The corresponding results for anal canal vs. perianal location were 58% and 91%, respectively ($p < 0.05$) (Table 3).

Multivariate analyses (curatively treated patients)

The parameters included in the multivariate Cox-analyses of possible determinants of risk for overall and tumour-specific survival, residual or recurrent tumour, and loss of sphincter function were age, gender, tumour site (anal, perianal), tumour stage, nodal status and bleomycin (±) (Table 4). Increasing age was a statistically significant determinant of risk. Females had a significantly better prognosis than males with regard to crude survival. Tumour location was not a statistically significant determi-

nant of risk, except for sphincter loss. Tumour stage and nodal status were the most important variables for all endpoints. No significant positive effect of bleomycin could be shown. In a separate multivariate analysis also including the health care region, there were no significant differences in results between the regions (data not shown).

Late treatment-related toxicity

Late toxicity, defined as possibly RT-associated symptoms still present more than six months after conclusion of therapy, was moderate. For 78% of all patients treated with RT and followed for more than 2 years, no side effects related to the anus–rectum were registered. For the urinary tract, the figure was 94%. The corresponding data for those primarily operated were 88% and 87%, respectively. The most common complaints were diarrhoea and urgency. Sixteen patients (5%) showed signs of light incontinence, soiling, or incontinence for gas. Seven patients could not hold their faeces, three of those patients have been given a sigmoidostomy. A general impression was that patients who had an APR after full-dose RT (60–64 Gy) experienced a prolonged healing period in the perineum. This was not the case for patients who had surgery after a lower 'preoperative' dose (40–44 Gy).

DISCUSSION

The first positive experiences of using RT were reported in the mid-70s (10, 12). In Sweden, this led to an increased interest in a change from primary surgery, but apart from occasionally advanced cases referred to the radiotherapy departments, a more systematic change in treatment policy initially occurred in only two health care regions (Uppsala and the Southern region).

In the early 1980s, confirmatory studies, some also with longer follow-up, were published (7, 9, 11). Positive experiences were also reported from one of the Swedish centres (13), but a general change in treatment routines had not taken place. After a local initiative, and after discussions within the Swedish Medical Societies for Surgery and Radiotherapy, it was decided that a 'Care programme' providing recommendations for diagnosis, staging, treatment, and follow-up should be worked out in order to secure rapid acceptance and implementation of a new and potentially superior treatment strategy. During 1983 and 1984, a smaller group, with representatives from several health care regions, made a proposal for a care programme that was discussed extensively among pathologists, surgeons and oncologists country-wide. This process, which took about a year, may be one explanation for the rapid and general acceptance of the principles. In the first five years after establishing the care programme, 90%, for whom curatively intended RT was deemed feasible, were treated according to the guidelines. Radiation therapy, often in combination with chemotherapy, is now widely accepted as the primary treatment of anal epidermoid carcinoma. However, a wide range of radiation and chemotherapy regimens are being used (6, 9, 11–13, 24–32).

This study presents the treatment results for the entire population of patients in Sweden who were diagnosed during the period 1985–1989. This precludes any bias in the results caused by selection mechanisms, which is important to bear in mind when comparisons are to be made with other studies. Yet the treatment results in this study appear similar to those of most previously published hospital-based studies on RT-based regimens (4, 6–9, 24–32).

A comparison of patients treated with primary surgery with those treated with irradiation showed significant survival differences in favour of those irradiated. This was seen both for anal canal tumours and for those located beyond the anal margin. Since these results are not achieved in a randomised study, the observations cannot be regarded as proof of the superiority of a non-surgical approach. The patients treated with primary surgery must be regarded as a negative selection with respect to a history of previous and possibly radiation-induced malignancy in a proportion of the patients. Goldman et al. (33) have previously made a comparison between two Swedish health care regions with different treatment policies, and found significantly better treatment results in the region with primary irradiation for most patients than in the region where surgery was predominant. Without a randomised comparison, these are the best estimates for a survival benefit of using radiotherapy as opposed to surgery as an initial treatment.

From 1985 until now, many centres have reported on their positive experience using RT, usually, but not always, combined with chemotherapy as primary treatment for anal cancer. Since the start of the care programme in 1985 up until the present time no new treatment policies, with the exception of the choice of chemotherapy, have been reported that can challenge the basic principles in the programme. Thus, even if none of the studies has questioned the primary RT approach, the relevance of using chemotherapy, most frequently 5-FU + mitomycin C (MMC) (6, 24, 28, 30, 34–36) in addition to RT has been extensively discussed. Several comparisons using historical controls have been made (6, 28, 30), but only two randomised trials, one in the UK and one within the EORTC, comparing RT alone with RT in combination with 5-FU + MMC have been performed. Results from both the UKCCCR trial and the EORTC trial (34, 35) demonstrated that the addition of 5-FU and MMC reduced local failure rates, and hence radical surgery and colostomy. The tumour-specific survival was also significantly higher for those who had received 5-FU and MMC. After a median follow-up of 42 months in both trials, no effect on crude survival was noted. Finally, in a randomised trial performed in the US (36), local control rates, colostomy-

free survival and disease-free survival were significantly higher in patients treated with 5-FU and MMC in addition to RT than in those treated with RT and 5-FU alone. No significant difference in overall survival was observed at 4 years. The importance of MMC was also suggested in a prospective, but non-randomized study by Cummings et al. (37). Taken together, these trials thus show that not only the addition of chemotherapy but also the type of chemotherapy can influence treatment outcome. Whether other drug combinations will result in further improvements is currently being studied. It is likely, however, that RT with respect to, for example, dose, schedule, choice of target volumes, and quality, is also of great importance. This has not been subject to any randomised trials. Inter-study comparisons of treatment results are also notoriously difficult to assess because of patient selection.

Previous studies have shown good treatment results for the combination of RT and bleomycin (5, 13, 18). This study is no exception, but there are no conclusive data concerning to what extent the results are attributable to bleomycin. In this study the patients were not randomly assigned to treatment with or without bleomycin and those who did not receive bleomycin, constituted a negative selection, (e.g. old age, pulmonary disease), which can explain the superior crude survival seen for patients treated with bleomycin. For tumour-specific survival, and freedom from recurrence, no significant differences were seen. Furthermore, the multivariate analyses failed to show any significant difference in favour of bleomycin, which further supports our notion that bleomycin is probably of no benefit. Only a properly controlled clinical trial can disclose whether the addition of bleomycin results in any therapeutic advantage.

During the 1990s, reports have emphasised the rather poor results in loco-regionally advanced cases (T3–T4, or N_+), and neo-adjuvant chemotherapy has been piloted (38, 39). Although positive results have been indicated, no firm conclusions can be drawn, since the numbers of patients have been small, follow-up short and the design uncontrolled.

Epidemiologic studies have indicated an association between cervical and anal neoplasias (40). In this population-based material, 8% (20/253) of the female population had a previous history of radiotherapy for cervical carcinoma. Treatment results for anal carcinoma patients previously irradiated have, to our knowledge, never been reported before. Seventeen (85%) of the 20 patients with a previous history of RT were treated with curative intent. The treatment results in these patients did not significantly differ from the previously non-irradiated females. Since this is not a controlled study and the number of patients limited, no firm conclusions can be drawn, but the results suggest that anal carcinomas arising in patients previously irradiated for cervical cancer do not behave differently with regard to tumour control and long-term survival.

During the period 1985–1989, only a small number of patients were not treated in accordance with the programme's guidelines. It can be assumed that a standardised treatment protocol for a relatively rare disease can be of value for obtaining good clinical results. It can likewise be assumed that the development of the care programme and the programme itself precipitated surgeons' awareness of the advantages of radiation as primary treatment. A care programme in all likelihood results in greater uniformity than would otherwise be the case. Uniformity in staging and treatment facilitates evaluation of treatment results, but can in itself not be a primary aim unless it reaches the highest possible standard.

When the programme was developed in 1984, it was based upon positive experiences from a few centres in Sweden, and an extensive literature review, and was thus likely to meet the desired high-quality criteria. With time, however, there is a risk that a care programme may conserve a treatment strategy that does not develop alongside progress made at other centres.

Besides the use of bleomycin, which may have no or only limited therapeutic benefit, we conclude that the recommendations are still basically sound, yielding good treatment results also in an international perspective. During the mid-1990s, a continuous discussion about the treatment principles has resulted in a gradual change in some of them. We no longer advocate the use of bleomycin, and neo-adjuvant chemotherapy with either cisplatin or carboplatin together with 5-FU is increasingly used in loco-regionally advanced cases, despite its yet unproven value in anal cancer.

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REFERENCES

1. Cancer incidence in Sweden. National board of health and welfare, the Cancer registry. Socialstyrelsen 1994.
2. Goldman S, Glimelius B, Nilsson B, Påhlman L. Incidence of anal epidermoid carcinoma in Sweden 1970–1984. Acta Chir Scand 1989; 115: 191–7.
3. Melbye M, Rabkin C, Frisch M, Biggar RJ. Changing patterns of anal cancer incidence in the United States 1940–1989. Am J Epidemiol 1994; 139: 772–80.
4. Goldman S, Glimelius B, Påhlman L, Ståhle E, Wilander E. Anal epidermoid carcinoma, a population-based clinico-

pathological study of 164 patients. Int J Colorect Dis 1988; 3: 109–18.
5. Svensson C, Goldman S, Friberg B. Radiation treatment of epidermoid cancer of the anus. Int J Radiat Oncol Biol Phys 1993; 27: 67–73.
6. Touboul E, Schlienger M, Buffat L, et al. Epidermoid carcinoma of the anal canal. Results of curative-intent radiation therapy in a series of 270 patients. Cancer 1994; 73: 1569–79.
7. Cummings BJ. The place of radiation therapy in a treatment of carcinoma of the anal canal. Cancer Treat Rep 1982; 9: 125–47.
8. Papillon J. Rectal and anal cancers. Conservative treatment by irradiation. An alternative to radical surgery. Berlin, Heidelberg, New York: Springer Verlag, 1982.
9. Papillon J, Mayer M, Montbarbon J, Gerard J, Chassard J, Bailly C. A new approach to the management of epidermoid carcinoma of the anal canal. Cancer 1983; 51: 1830–7.
10. Nigro MD, Vaitkevicius VK, Considine BJ. Combined therapy for cancer of the anal canal. A preliminary report. Dis Colon Rectum 1974; 17: 354.
11. Nigro MD, Vaitkevicius VK, Buroker T, et al. Combined therapy for cancer of the anal canal. Dis Colon Rectum 1981; 24: 73–5.
12. Papillon J. Radiation therapy in the management of epidermoid carcinoma of the anal region. Dis Colon Rectum 1974; 17: 184–7.
13. Glimelius B, Graffman S, Påhlman L, Wilander E. Radiation therapy of anal carcinoma. Acta Radiol Oncol 1983; 22: 273–9.
14. Shanta V, Krishnamurthi S. Combined bleomycin and radiotherapy in oral cancer. Clin Radiol 1980; 31: 617.
15. Chan PY, Byfield JE, Kasan AT, Aronstam EM. Unresectable squamous cell carcinoma of the lung and its management by combined bleomycin and radiotherapy: a clinical study of the enhanced results. Cancer 1976; 37: 2671.
16. Mattson B, Wallgren A. completeness of Swedish Cancer Registry. Non-notified cancer cases on death certificates in 1978. Acta Radiol Oncol 1984; 23: 305–13.
17. Hermanek P, Sobin LH, eds. Union Internationale Contre le Cancer. TNM Classification of Malignant Tumours, 4th ed. Berlin: Springer Verlag, 1987; 50–2.
18. Glimelius B, Påhlman L. Radiation therapy of anal epidermoid carcinoma. Int J Radiat Oncol Biol Phys 1987; 13: 305–12.
19. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457–81.
20. Peto J. The calculation and interpretation of survival curves. In: Buyse M, Staquet M, Sylvester RJ, eds. Cancer clinical trials: methods and practice. Oxford: Oxford University Press, 1988: 361–80.
21. Peron RE. Test for trend in life-table analyses. Biometrics 1975; 62: 679–82.
22. Tarone RE, Ware J. On distribution-free tests for equality of survival distributions. Biometrica 1977; 64: 156–9.
23. Breslow NE, Day NE. Statistical methods in cancer research. Vol 1. The analyses of case control studies. Lion IARC 1980; 21: 1115–25.
24. Cummings BJ, Keane TJ, O'Sullivan B, Wong CS, Catton CN. Epidermoid anal cancer: treatment by radiation alone or by radiation and 5-fluorouracil with and without mitomycin C. Int J Radiat Oncol Biol Phys 1991; 1115–25.
25. Papillon J, Montbarbon JF. Epidermoid carcinoma of the anal canal. A series of 276 cases. Dis Colon Rectum 1987; 30: 324–33.
26. Nigro ND, Vaitkevicius VK, Herskovic AM. Preservation of function in the treatment of cancer of the anus. In: De Vita VT, Hellman S, Rosenberg SA, eds. Important advances in oncology. Philadelphia: JB Lippincott, 1989: 161–77.
27. Cummings BJ. Current management of epidermoid carcinoma of the anal canal. Gasteroenterol Clin N Am 1987; 16: 125–42.
28. Grabenbauer GG, Schneider IH, Gall FP, Sauer R. Epidermoid carcinoma of the anal canal: treatment by combined radiation and chemotherapy. Radiother Oncol 1993; 27: 59–62.
29. Tanum G, Tveit K, Karlsen KO, Hauer-Jensen M. Chemotherapy and radiation therapy for anal carcinoma. Cancer 1991; 67: 2462–6.
30. Tanum G. Diagnosis and treatment of anal carcinoma. Acta Oncol 1993; 31: 513–8.
31. Wagner JP, Mahe MA, Romeestaing P, et al. Radiation therapy in the conservative treatment of carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 1994; 29: 17–23.
32. Touboul E, Schlienger M, Buffat L, et al. Conservative versus nonconservative treatment of epidermoid carcinoma of the anal canal for tumors longer than or equal to 5 centimeters. A retrospective comparison. Cancer 1995; 75: 786–93.
33. Goldman S, Glimelius B, Glas U, Lundell G, Påhlman L, Ståhle E. Management of anal epidermoid carcinoma, an evaluation of treatment results in two population-based series. Int J Colorectal Dis 1989; 4: 234–43.
34. Arnott SJ, Cunningham D, Gallagher J, Gray R, Hardcastle J, Houghton J. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. Lancet 1996; 348: 1049–54.
35. Bartelink H, Roelofsen F, Eschwege F, et al. Concomittant 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 EORTC radiotherapy and gastrointestinal tract cooperative groups. J Clin Oncol 1997; 15: 2040–9.
36. Flam M, John M, Pajak TF, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definite nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. J Clin Oncol 1996; 14: 2527–39.
37. Cummings BJ, Keane TJ, O'Sullivan, et al. Mitomycin in anal canal carcinoma. Oncology 1993; 50: 63–69.
38. Brunet R, Sadek H, Vignoud J, et al. Cisplatin (P) and 5 fluorouracil (5FU), for the neoadjuvant treatment (Tt) of epidermoid anal canal carcinoma (EACC). Proc ASCO 1990; 9: 402.
39. Svensson C, Kaigas M, Goldman S. Induction chemotherapy with carboplatin and 5-fluorouracil in combination with radiotherapy in loco-regionally advanced epidermoid cancer of the anus—preliminary results. Int J Colorect Dis 1992; 7: 122–4.
40. Melbye M, Springel P. Aetiological parallel between anal cancer and cervical cancer. Lancet 1991; 338: 657–9.