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Combined radiation and chemotherapy for squamous cell carcinoma of the anal canal: Results and prognostic variables in a multiinstitutional series of 173 patients

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Purpose: This retrospective multicenter study was aimed to asses the effect of combined modality therapy in patients with squamous cell carcinoma of the anal canal, stage T1-4 N0-3 M0.
Patients and methods: Between 1985 and 1994, 173 patients underwent treatment by combined radiation and chemotherapy. A median total dose of 50 Gy was delivered to the primary, perirectal, presacral and inguinal nodes, followed by a local boost in selected cases. 5-Fluorouracil was scheduled as a continuous infusion of 1000 mg/m²/24 h on days 1-5 and 29-33, and mitomycin C as bolus of 10 mg/m² on days 1 and 29.
Results: Cancer related survival (OS), NED-survival and local control rates at 5 years were 71±5%, 59±4% and 67±4%, respectively. Anorectal function was preserved in 91% of the patients in whom the primary was controlled. Only 9.6% experienced severe late toxicity requiring surgery. In univariate analysis, T category (T1/2 vs. T3/4) was predictive for OS (83±4% vs. 53±9%, p=0.01), NED-survival (75±4% vs. 36±7%, p<0.0001) and local control (81±4% vs. 46±7%, p<0.0001). N category (N0 vs. N1-3) influenced NED-survival (66±5% vs. 33±12%, p=0.004) and local control (76±4% vs. 37±13%, p=0.003). Treatment technique (>2 fields vs. 2 fields) was found to be of prognostic value for NED-survival (70±6% vs. 50±6%, p=0.016) and local control (77±6% vs. 58±6%, p=0.018). Only in T3/4 cases the total RT-dose (< 45 Gy vs. 45 Gy) had an impact on NED-survival (42±7% vs. 23±13%, p=0.01) and local control (52±8% vs. 45±15%, p=0.03). In multivariate analysis, the T category (UICC 1992) remained the only significant variable with impact on survival (p=0.04), NED-survival (p<0.001) and local control (p=0.003).
Conclusion: Treatment with a combination of radiotherapy and chemotherapy is safe and effective for patients with anal canal carcinoma. The improvement of results in advanced stages is warranted.

Key words: rectal neoplasms; radiotherapy; chemotherapy; treatment outcome

Introduction

The potential curative effects of radiation therapy (RT) alone or radio-chemotherapy (RCT) in the preservation of anal function has been well established in squamous cell carcinoma of the anal canal.[1-12] The abdomino-perineal resection (APR) is reserved for patients with residual or recurrent carcinoma after primary RT or RCT.

As squamous cell carcinoma of the anal canal is relatively rare, it is difficult to assemble a larger series of patients treated by a single protocol so that survival rates, primary tumor control rates, patterns

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of failure as well as acute and late treatment-related toxicity can be evaluated. This paper gives the results after treatment of 173 patients with carcinoma of the anal canal treated in eight German centers.

Patients and methods

Between January 1985 and May 1994, 173 patients underwent radical treatment by combined RCT and form the study group. Patient's age, gender and histological type of the tumors are shown in Table 1. Prior to treatment all patients underwent clinical examinations including sigmoidoscopy and biopsy. Chest X-ray, laboratory tests, abdominal ultrasound and CT- scans of the abdomen and pelvis were performed routinely. On the basis of these findings tumor stages were assigned according to the UICC-system of 1987.[13] Data on cancers treated between 1985 and 1987 were revised to conform with these criteria. T and N categories are listed in Table 1. The standard treatment protocol is shown in Figure 1.

Radiotherapy

The primary tumor region including perirectal, internal-iliac and inguinal lymph nodes was irradiated using parallel opposed anteroposterior-posteroanterior fields in the early years of the study (1985-1988) and later using a 3- or 4-field box technique. External RT was delivered with megavoltage equipment (mostly 6-10 MV-photons) and single fractions between 1.6 and 2.0 Gy (median 1.9 Gy) in an uninterrupted course up to a median total dose of 49.5 Gy. The radiation dose was specified to the isocenter using multiple field techniques or to the midplane for parallel opposed fields. Otherwise specified doses were retrospectively assigned to the reference point according to the ICRU 50 guidelines. Forty-five patients received an additional boost of external RT, 31 patients using interstitial brachytherapy (BT), 12 patients Iridium-192 low-dose-rate, 11 patients Au-198 and 8 patients Iridium-192 high-dose-rate. Table 1 gives the dosages of external RT and of the Ir-192-BT for all 173 patients. Dosimetric details of the Au-198-BT patients were reported elsewhere.[14]

Chemotherapy

One-hundred and seventy-three patients received concomitant chemotherapy. 5-Fluorouracil (5-FU) was scheduled as a continuous intravenous infusion for 120 hours (1000 mg/m²/24 h) to a maximum of 1800 mg/24 h on days 1-5 and 29-33. Mitomycin C (MMC) was administered on days 1 and 29 as a single bolus intravenous injection with a dosage of 10 mg/m². The second course of chemotherapy was adjusted according to the extent of treatment related hematologic, gastrointestinal and cutaneous toxicity. A summary of the dosage of 5-FU and MMC is given in Table 1.

Table 1. Patients characteristics

Number of patients	173
Median age (range)	61 years (26–82)
Histological type	
Squamous cell carcinoma	127 (73%)
Cloacogenic carcinoma	46 (27%)
T category (UICC 1992)	Patients (%)
T1	28 (16)
T2	77 (45)
T3	46 (27)
T4	19 (11)
TX	3 (1)
N category (UICC 1992)	
N0	115 (66)
N1-3	28 (17)
NX	30 (17)
Grading (UICC)	
G1	21 (12)
G2	74 (43)
G3	49 (28)
G4	2 (1)
GX	27 (16)
External RT	
30-44 Gy	45 (26)
45-50 Gy	59 (34)
51-55 Gy	25 (14,5)
56-60 Gy	25 (14,5)
61-66 Gy	19 (11)
Ir-192 low-dose-rate	12 (7)
12 Gy	5 (3)
15-16 Gy	7 (4)
Ir-192 high-dose-rate	8 (5)
7-18 Gy	4 (3)
20-26 Gy	4 (3)
Au-198	11 (6)
5-FU (mg/m²)	
3000-4000	61 (35)
4500-8000	84 (49)
8200-12000	28 (16)
MMC (mg/m²)	
7-10	67 (38)
11-20	81 (47)
24-35	17 (10)
none	8 (5)

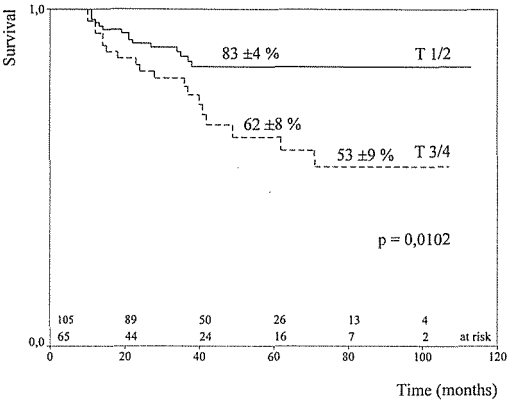

Figure 1. Cancer related survival according to T category (UICC 1992)

Follow-up assessment

Two months after the completion of therapy all patients were reassessed by digital examination, sigmoidoscopy and CT scans of the pelvis. In case of residual mass or suspicious ulcers multiple biopsies were taken under general anesthesia. Histologically verified lesions in the anal canal were counted as local disease, positive perirectal, iliac or inguinal nodes as regional disease. After negative biopsies patients were followed up at 3-month-intervals for two years from treatment and at 6-month-intervals thereafter. Median follow-up was 40 months with a range between 3 and 130 months. No patients were lost to follow-up. All events prior to May 1996 were included in the analysis. For calculating survival rates only cancer related deaths were counted (adjusted survival rate). The rates of survival, NED (no evidence of disease)-survival and locoregional tumor control were determined according to Kaplan and Meier.[15] Differences between patient groups were assessed by the log-rank-test, multivariate analysis was performed according to the Cox-regression-model.[16]

Results

Cancer related survival-, NED-survival- and loco-regional tumor control rates were 71±5 %, 59±4 % and 67±4 % at 5 years. 34 patients died of anal cancer, 14 of intercurrent disease. The survival rate for patients with T1/2-tumors was 83±4 % compared to 53±9 % in patients with T3/4-tumors (Figure 2, p=0.0102). Significant prognostic factors for all three endpoints are shown in Table 2. Only the T- and N category had a highly significant prognostic impact on NED-survival. For T3/4-tumors a total RT-dose of less than 45 Gy led to a significantly inferior NED-survival being 23±13% at five years compared to a survival rate of 42±7% following higher doses (p=0.01). Multiple field arrangements were associated with a better NED-survival of 70±6% in comparison to parallel opposed fields leading to survival rates of 50±6% (p=0.016).

Primary and regional tumor control

Two months after completion of therapy 134 (77%) patients had a clinical complete remission, 38 (22%) patients a partial remission, one patient no change. All patients with partial remission had positive biopsies, either performed as local excisions (12 patients) or multiple needle biopsies (14 patients). Significant prognostic factors for the loco-regional tumor control are shown in Table 4. Patients with smaller lesions up to a maximum diameter of 5 cm (T1/2) had a loco-regional tumor control rate of 81±4% (Figure 3) as compared to patients with larger tumors (T3/4), in whom a control rate of 46±7% was achieved (p<0.0001). Positive regional lymphnodes were associated with a poor loco-regional tumor control rate of 37±13% (Figure 4). By contrast a 76±4%-loco-regional control rate was noted in N0-cases (p=0.003). For patients with larger primaries (T3/4) a total RT-dose of less than 45 Gy led to a significantly lower tumor control rate of 45±15% as compared to 52±8% for doses above or equal to 45 Gy (p=0.03). Tumor control was also influenced by the treatment technique. The use of parallel opposed anterior and posterior fields was associated with a control rate of 58±6% which was significantly inferior to the results following treatment with multiple fields leading to a control rate of 77±6% (p=0.018).

Patterns of failure

Forty-nine (28 %) of the 173 patients experienced a local and/or regional tumor recurrence. In 26 cases there was an isolated local failure, in 7 cases a combined loco-regional failure and in another 8 cases a regional failure alone. Recurrences were noted after a time interval between 2 and 58 months (median 12 months). Twenty-six (15 %) patients experienced distant metastases between 1 and 35 months after completion of therapy. Distant metastases were combined with a local and/or regional failure in 9 cases.

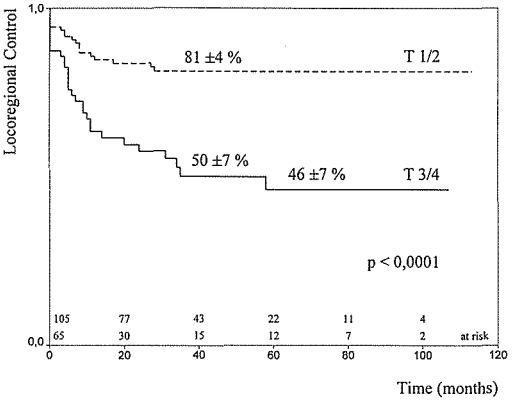

Figure 2. Locoregional tumor control according to T category.

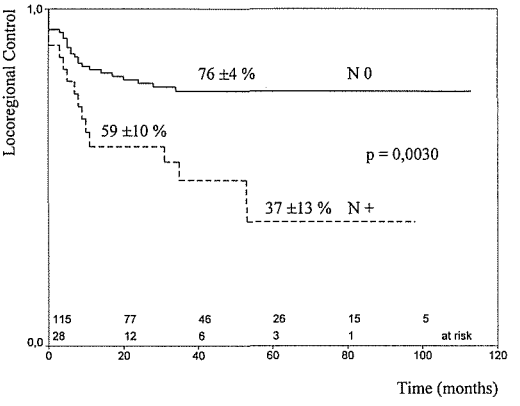

Figure 3. Locoregional tumor control according to N category.

Table 2. Significant prognostic factors for survival, NED-survival and locoregional tumor control at 5 years.

Factor	Overall survival	NED-survival	Tumor control
T category			
T1/2	83±4%	75±4%	81±4%
T3/4	53±9% (p=0.0102)	36±7% (p<0.0001)	46±7% (p<0.0001)
N category			
N0	73±5%	66±5%	76±4%
N1-3	66±11% (n.s.)	33±12% (p=0.004)	37±13% (p=0.003)
RT Dose (T3/4)			
≥45Gy	57±9%	42±7%	52±8%
<45Gy	67±16% (n.s.)	23±13% (p=0.01)	45±15% (p=0.03)
RT/CT Dose			
≥45Gy, >6g 5-FU	73±6%	61±6%	67±6%
<45Gym <6g 5-FU	69±14% (n.s.)	45±11% (p=0.042)	54±12% (p=0.11)
Treatment technique			
>2 fields	74±9%	70±6%	77±6%
2 fields	71±6% (n.s.)	50±6% (p=0.016)	58±6% (p=0.018)

n.s. not significant

Table 4. Multivariate analysis on prognostic factors for cancer related suvival, NED survival and local tumor control.

Cancer related survival				
Variable Beta	95% C.I.	Exp (Beta)		P
T category	−0,2992	0,5546-0,9910	0,7414	0,043
Technique	−0,0562	0,6880-1,2990	0,9457	0,72
RT-dose	0,0116	0,0759-1,0487	1,0016	0,53
MMC-dose	−0,0265	0,9264-1,0237	0,9738	0,29
NED-survival				
T category	−0,5591	0,4397-0,7434	0,5717	0,001
Technique	0,1781	0,9004-1,5869	1,1954	0,217
RT-dose	−0,0228	0,9447-1,0114	0,9775	0,19
MMC-dose	−0,0164	0,9436-1,0256	0,9837	0,44
Local tumor control				
T category	−0,5458	0,4302-0,7804	0,5794	0,003
Technique	0,2674	0,9436-1,8090	1,3065	0,10
RT-dose	−0,0100	0,9530-1,0285	0,9901	0,60
MMC-dose	−0,0046	0,9503-1,0427	0,9954	0,84

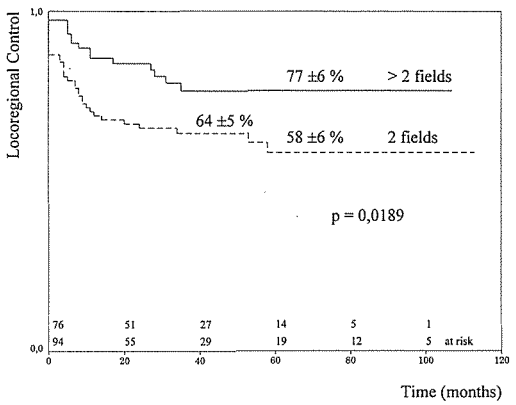

Figure 4. Locoregional tumor control according to treatment technique.

Toxicity

The various levels of acute toxicity were classified as stated by the WHO17 and are shown in

Table 3. Acute toxicity (WHO) and late treatment related toxicity (Eschwege) among 124 patients* following radiochemotherapy of anal canal carcinoma.

Grade	Dermatitis	Diarrhea	Anemia	Leucopenia	Thrombocytopenia	Late Toxicity
0	10 (6%)	20 (11%)	99 (56%)	59 (33%)	93 (53%)	77 (62)
1	13 (7%)	28 (15%)	18 (10%)	21 (12%)	19 (11%)	9 (7)
2	42 (24%)	45 (25%)	7 (4%)	27 (15%)	7 (4%)	26 (21)
3	56 (32%)	31 (18%)	0	16 (9%)	3 (2%)	12 (10)
4	3 (2%)	1 (1%)	0	1 (1%)	2 (1%)	

* Data on toxicity from one center not available

Table 3. The frequency of severe hematological toxicity (grade 3/4) was 22/124 patients (18%). Thirty-four percent and 19% of the patients experienced a dermatitis and enteritis of at least grade 3 (WHO), respectively. Late toxicity was scored according to Eschwege *et al.* (1985) and is shown in Table 5. Only 12 of 124 patients (9.6%) had late sequelae of grade 3, requiring surgery. The use of interstitial BT using Ir-192 high-dose-rate and Au-198 in two centers had a significant negative impact on survival without grade 3 toxicity, which was 92% without and 74% with interstitial BT of this type.

Preservation of anorectal function

A major objective of the conservative treatment of anal carcinoma by RCT or RT is the preservation of anorectal function. APR was performed in 51 (29%) of the patients, in 41 patients after local recurrence and in 10 patients for other reasons. The remaining 12 patients were scored as being partially incontinent. Thus a functioning anorectal sphincter was preserved in 110 of 173 patients (64%), and in 110 of 121 patients (91%) in whom the primary tumor was controlled by RCT.

Multivariate analysis

The following variables were included in the analysis: Total RT dose, total dose of MMC (continuous variables), treatment technique, T category (T1/2 vs. T3/4) and N category (N0 vs. N1-3), as categorial variable. The only independent and significantly related factor for survival, NED-survival and loco-regional tumor control was the T category with a p-value of 0.04, 0.001, and 0.003, respectively (see alsoTable 4).

Discussion

Carcinoma of the anal canal tends to cause sphincter muscle invasion in the early course of the disease. Adequate local excision is therefore not feasible under the prerequisite of preserving an intact anal sphincter. Local excision as a treatment strategy appears to be only appropriate for small lesions (< 2 cm) involving the anal margin and the perianal skin.[18] APR was the standard treatment for anal cancer in many centers until the mid-eighties. Five-year-survival-rates between 40% and 70% have been reported. Obvious disadvantages of the APR include the permanent loss of the anal sphincter function, a significant postoperative morbidity and mortality as well as impotence.[19-23]

Treatment options, results and late effects

It has been the ongoing and continuing policy of several French centers to use RT alone or in combination with interstitial BT for conservative treatment of anal cancer with excellent results.[1,3,10-12,18,24,25] RT alone proved to be very effective for small lesions of less than 4 cm in diameter: Local tumor control rates between 76% and 91% were reported.[3,9] For adequate local control of larger primaries, however, relatively high total doses between 60 and 65 Gy had to be applied.[3,10,11] Consequently late treatment related toxicity was noted more frequently (9-13% grade 3 according to Eschwege) requiring APR for the control of distressing symptoms. In a series reported by Touboul *et al.* only 65% of the patients with no evidence of local tumor had an intact anal sphincter.[11] By contrast, local complication rates as low as 3% together with local tumor control rates of 88% (23,24) were reported by centers using RCT with and without interstitial BT.[2,5,6,27] Nigro *et al.* (1974) pioneered in the clinical use of concomitant RCT as a neoadjuvant treatment strategy for downstaging of anal carcinoma. After 30 Gy total dose and one course of MMC/5-FU histologically negative resection specimens were obtained in almost 60% of the patients. During the following years numerous phase-II studies were conducted.

Our results of 173 patients treated between 1985 and 1994 in eight Radiation Centers compare very favorably with the literature data on survival-, NED-survival- and loco-regional control rates at of 71%, 59% and 67%, respectively. The anal sphincter function was preserved in 110 of 121 patients (91%) in whom the local tumor was permanently controlled by RCT. Noteworthy is the fact that in other series using RCT the sphincter preservation rate was as high as 80%[5,12,18] in comparison to the results following RT alone.[10,11,24]

A recent randomized EORTC study provided preliminary data concerning the issue whether RCT is superior to RT alone in advanced anal carcinoma (either node positive or > 4 cm). Both locoregional tumor control and colostomy-free survival were significantly improved in the concomitant arm.[26] In an RTOG/Intergroup study the value of additional MMC as part of the concomitant chemotherapy was investigated.[4] As has been pointed out earlier in a retrospective series by Cummings *et al.*[27] NED-survival and local tumor control rates were significantly lower after regimens omitting MMC, but using RT and 5-FU alone.

Prognostic factors

Our results clearly demonstrate that the tumor volume represented by the T category (UICC 1992) remained the only independent significant prognostic factor for survival, NED-survival and local tumor control. This was also noted in a larger series of 242 patients treated with RT alone.[10] In patients treated by RT alone and studied by multivariate analysis the size of the primary tumor was predictive for both survival and local control.[10,28,29] Local tumor control rates of 91% and 89% for tumors of less than 4 cm in diameter versus control rates of 73% and 71% for larger primaries were reported.[3,9,18]

In patients treated by RCT, local control rates for primary tumors up to 2 cm in diameter were in the range of 95-100%, for 2-5 cm 80-95% and for larger than 5 cm 65-80%.[2,5,27,30] Five-year survival rates, corrected for death from intercurrent disease, were about 95-100% when the primary was < 2 cm and in the range of 60-70% for larger tumors reflecting the good surgical salvage rates for local relapse after treatment with RCT.

It has been suggested by others[11] that a combination of preoperative RT and surgery or a more aggressive RCT including cisplatin based chemotherapy[12] could improve local tumor control and survival for patients with T4 tumors. In our series a total RT dose of less than 45 Gy with concomitant chemotherapy does not seem to be adequate for larger tumors (> 5 cm). Control rates and NED-survival were only 45% and 23% at 5 years. Following higher doses, however, results could be significantly improved (p=0.01). Surprisingly in our series refinements in the treatment technique had a significant impact on NED-survival and local control in univariate analysis. This could not be demonstrated by others.

In surgical series histopathologically confirmed involvement of perirectal, superior hemorrhoidal, pelvic or inguinal node groups was associated with 5-year survival rates of about 50%, being 25% worse than those of patients without nodal involvement[31] The presence of regional lymphnode metastases did not correlate with control of the primary tumor in patients managed with RT- or RCT protocols in the early series.[9,28] However, we found a striking difference in local tumor control for patients without regional metastases being 76% vs. 37% for patients with positive regional nodes (p=0.003). It appears that the application of routine CT-scanning of the pelvis for staging purposes may have detected enlarged nodes more accurately. Recently Myerson *et al.*[7] reported a worse disease-free survival of 52% for T1-3 N1-3 patients as compared to that of patients in T1-3 N0 stages which was as high as 88% at 10 years (p=0.03).

No data exists on patients treated by RT/RCT concerning the prognostic value of tumor DNA-content. In one large surgical series of flowcytometric DNA analysis of paraffin embedded tissue, ploidy was found to be strongly predictive for outcome, patients with diploid tumors having a 5-year survival of 75% compared to 55% for patients with aneuploid tumors.[31] Among serum markers of interest, only serum squamous cell carcinoma antigen (SCCAg) provided significant influence in one multivariate analysis predicting tumor specific death rates and recurrent carcinoma.[29]

In conclusion the results from the current study and others strongly suggest that with respect to certain prognostic factors further improvement in the therapy of anal canal cancer is possible, particularly modifications of the chemotherapeutic regimen and the radiation dose. Refinements in radia-

tion technique and fractionation schedules need to be prospectively evaluated to minimize late sequelae and to preserve anal sphincter function even in advanced cases.

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