



Long-term results achieved by guideline-based stage-dependent management of anal cancer in a non-HIV population

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Abstract

Purpose Therapy of anal cancer follows national and international guidelines that are mainly derived from randomized trials. This study aimed to analyze long-term results of stage-dependent treatment of anal cancer in a non-selected patient cohort.

Patients and method All consecutive patients treated for anal cancer between 2000 and 2015 were retrieved from a prospective database. Risk-dependent screening for human immunodeficiency virus showed no infection. Main outcome measure was overall survival with respect to tumor site and treatment. Secondary endpoints were cause-specific survival, stoma free survival, and the rate of salvage operations.

Results In total, 106 patients were treated for anal cancer. Of those, 69 (65.1%) suffered from anal canal cancer and 37 (34.9%) from anal margin cancer. Three patients with synchronous distant metastases were excluded from analysis. The majority of patients ($n = 79$, 76.7%) were treated by chemoradiotherapy in curative intention. Twenty-two patients underwent local surgery. Five-year overall survival was 73.1% and cause-specific survival at 5 years was 87.4%. Overall, 14 patients (13.6%) needed salvage surgery. Their 5-year cause-specific survival was 57.7%. A permanent ostomy was avoided in 77.7%.

Conclusions Treatment of anal cancer results in low rates of salvage surgery and permanent ostomies, when therapy was determined by a multidisciplinary team following national and international guidelines.

Keywords Anal cancer · Overall survival · Cause specific survival · Chemoradiotherapy · Salvage surgery

Introduction

Anal cancer is a rare tumor in comparison with other entities and accounts for 2–4% of malignancies of the gastrointestinal tract [1–3]. The incidence is estimated to be approximately 1/100,000 persons per year with about 800 to 1000 new cases reported annually in Germany. The number of newly diagnosed carcinomas has increased over the past decades caused by the rising incidence of human immunodeficiency virus (HIV) and the change of sexual behavior [1, 3–6].

In up to 80%, the tumors are histologically squamous cell carcinomas (SCC) which are sensitive to chemoradiotherapy. Other malignant entities are adenocarcinoma (3–9%), melanoma (2–4%), and basal cell carcinoma (< 1%) [2, 6]. Chemoradiotherapy was introduced by Nigro in 1973 and established as standard treatment in 1984 for squamous cell carcinoma [3, 7–9]. Therefore, all current guidelines recommend chemoradiotherapy for advanced tumors. The management of T1 and small T2 tumors, however, differs somewhat between national recommendations. The National

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Comprehensive Cancer Network (NCCN) guidelines currently recommend local excision only for T1 tumors of the anal margin [10] whereas the German guidelines dating back to 2002 allow local excision for T1 anal canal tumors, too [11]. The German-Austrian guidelines for anal cancer in people living with HIV include resection of small tumors of the anal margin without restriction to the T1 category [12]. With respect to TNM classification, however, the distinction between anal canal cancers and anal margin cancers has been abandoned with the 8th edition published in 2017 because of a lack of evidence that tumors at the two sites behave differently [13].

Tumor persistence or recurrence after chemoradiation requires surgery which is necessary in up to 15% of all patients [6, 14, 15]. The so-called salvage operation is usually performed as abdominoperineal excision (APE) resulting in a permanent colostomy.

Contemporary treatment guidelines are mainly derived from randomized studies [16–19] or small series, whereas data on how these recommendations apply to non-selected patient cohorts is lacking. Our study investigates long-term results of stage-dependent multidisciplinary treatment for anal canal and anal margin tumors with respect to overall survival (OS), cause-specific survival (CSS), stoma-free survival, and the rate of salvage operations in a consecutive patient cohort.

Patients and methods

All patients referred to our hospital for treatment of anal cancer have been documented in a prospective database since January 2000. The database was supplemented by a comprehensive chart review for this study which is retrospective in nature. We included all patients registered until December 2015 to allow for an adequate time of follow-up.

The diagnosis of anal cancer was established by clinical examination, biopsy, and histological confirmation. Locoregional staging further included endoanal ultrasound and magnetic resonance imaging (MRI). Lymph node enlargement or irregularity of shape was taken as positive signs for inguinal lymph node involvement. Histologic confirmation of these lymph nodes was not performed in these patients because locoregional advanced disease was presumed and chemoradiotherapy scheduled. Search for distant metastases was either done by chest-X-ray and liver ultrasound or by computed tomography of the chest and abdomen. Tumors were classified into cancers of the anal canal and cancers of the anal margin as defined by the Union Internationale Contre le Cancer (UICC). They were staged according to the valid 6th and 7th editions of the UICC TNM classification and reclassified into the 7th edition for a uniform assessment.

For staging, we took the best available information, which was either the pathological classification or, in case of no operation, the clinical classification retrieved from MRI scans. HIV screening was only performed if lifestyle or sexual orientation suggested that patients were at risk.

Management of the disease was discussed in a multidisciplinary team, where the patients were presented by the colorectal surgeon who provided clinical details. Cross-sectional imaging was presented by the radiologist. The pathologist supplemented details from histology. A joint decision was made by the surgeon, the radiation oncologist, and the medical oncologist. The latter two assessed the patients scheduled for chemoradiotherapy thereafter and decided about the extent and mode of therapy. In case of incomplete resection, tumor persistence, or tumor recurrence, the patient was again presented at the MDT for further discussion.

Decision-making followed the German guidelines published in 2002 [11] except in cases of previous irradiation for another cancer or if the performance status of patients was too poor to receive curative chemoradiotherapy. Recommendations from guidelines published over the years were taken into account as appropriate [10, 12, 20–22]. Treatment decisions made between the years 2000 and 2002 already reflected the strategy of the guidelines; therefore, all patients available in the database were included. The 2002 German guidelines also recommended local excision for T1N0 anal canal tumors, if the main mass of the sphincters could be preserved. Therefore, local excision of early anal canal tumors was also considered to be a treatment option. In case of insufficient resection with residual tumor (R1-resection) chemoradiotherapy was additionally performed in curative intention.

Radiotherapy was planned for the tumor region and the groins with a dose between 45 and 50 Gy. A boost of 5–15 Gy was applied to the tumor region and another boost of 5–6 Gy to suspected positive lymph nodes in the groins. It was delivered as external beam radiation using a multifield 3D-conformal technique (minimum six fields) in the earlier phase of the study. From 2003, patients received intensity-modulated radiotherapy (IMRT) which was superseded by volumetric intensity modulated arc therapy (VMAT) in 2010.

Mainstay of chemotherapy was mitomycin with a dose of 12 mg/m² on days 1 and 29 as well as 5-fluorouracil with 1000 mg/m² for 4 days in weeks 1 and 5. The chemotherapy regimen was eventually left to the medical oncologist's discretion; therefore, some patients considered to be at high risk for recurrence received concomitant cisplatin, some other patients deemed unfit received only fluorouracil-based chemotherapy. If the patient was unfit to receive chemotherapy at all, radiotherapy only was delivered as treatment alternative.

For the purpose of this study, patients with distant metastases were only documented according to their demographic and tumor characteristics, but were excluded from further

analysis. All patients had regular follow-up in our coloproctology clinic and in the department of radiation therapy every 3 months in the first year and annually thereafter. All patients were examined by physical and rectal digital examination as well as by proctoscopy. Ultrasound and imaging were additionally performed as appropriate. In the case of a suspected persistent tumor or local recurrence, patients underwent further examination with MRI, examination under anesthesia, and biopsies of suspicious areas. After chemoradiation, the timing of biopsies was dependent on the extent of clinical response. If response was complete, biopsies were avoided in order to not further damage the often vulnerable post-radiation tissues [23]. If response was incomplete, biopsy was deferred for at least 6 months to allow for further tumor shrinkage. Only if no response was detectable, biopsies were taken 6 to 8 weeks after termination of CRT. If tumor cells could still be identified at least at the 6 months interval after chemoradiation, the patient was scheduled for salvage surgery. However, for the formal differentiation of persistent or recurrent tumor, we chose 1 year between the end of curative chemoradiotherapy and the detection of a malignancy. Follow-up for this study terminated on 31st March 2019. Patients without a current status at the closing date or with a follow-up of fewer than 5 years were considered lost to follow-up.

Ethical counseling was sought with the responsible institutional review committee (Saxon Physicians Chamber, EK-BR-78/17-1); however, according to national law, no formal approval was required.

For statistical analysis, we used SPSS version 21.0 (IBM Corp., Armonk, NY). Main outcome measure was OS. Secondary endpoints were CSS, rate of salvage operations, and stoma free survival. For the comparison of patient and tumor factors, we used the χ^2 test, the Fisher's exact test, and the *t* test as appropriate. Survival analysis was performed according to Kaplan-Meier, and groups were compared with the log rank test. Starting point for survival analysis was the date of tumor diagnosis. For OS, all death irrespective of cause was considered event. In calculation of CSS, only death with documented tumor was taken into account. For stoma-free survival, death or the presence of a stoma at last follow-up was considered event. Patients who survived longer than 5 years were censored at the 5-year threshold. Patients with incomplete observation were censored at the date of last available information. *p* values of < 0.05 were considered statistically significant.

Results

In the time period between 2000 and 2015, we treated 106 consecutive patients with anal cancer. Only one intracutaneous adenocarcinoma of the anal margin (Morbus Paget) was detected amongst these patients, all other tumors were

SCC. Of these patients, 69 (65.1%) presented with cancer of the anal canal and 37 (34.9%) with cancer of the anal margin. The median age of patients with anal canal cancer was 63 years (36–92); whereas, the median age of patients with anal margin cancer was significantly lower with 57 years (34–92; *p* = 0.020). Median follow-up of surviving patients was 87 months in the entire group (16–172) and differed not significantly between the two groups (anal canal 89 months (29–172) and anal margin 79 months (16–142); *p* = 0.553). Two patients were lost to follow-up.

We saw more advanced tumors in the group of anal canal cancers (T3–4: *n* = 24, 34.8%) than in anal margin cancers (T3–4: *n* = 6, 16.2%). The rate of lymph node positive tumors was significantly higher in the group of anal canal cancer (*n* = 33, 47.8%) as compared with the group of anal margin cancer (*n* = 6, 16.2%). Only three of our patients (all with anal canal cancer) presented with distant metastases at time of diagnosis.

Additionally, SCC-antigen levels were retrieved in 81 patients (76.4%) which were elevated (> 1.5 ng/ml) [24] in 37.0%. Characteristics of the patient population are given in Table 1.

Risk-dependent screening for HIV did not reveal any infection with the immunodeficiency virus.

After exclusion of the three patients with distant metastases, 66 patients remained in the group of anal canal cancer. Of these, five patients (7.6%) were treated by local excision. All but one of these five patients had a histopathologically free resection margin. The patient with positive margin status additionally received radiotherapy. Of the other patients, 57 (86.4%) received chemoradiotherapy and two patients (3.0%) only radiotherapy in curative intention. The latter two patients were deemed to be unfit for chemotherapy. Another patient with an advanced tumor (1.5%) refused chemotherapy and irradiation was considered to be palliative because of a T3N3 tumor. This patient died 2 months later without completion of the scheduled radiation dose. One patient with extensive disease and a low performance status (1.5%) died in hospital after palliative stoma fashioning. There was no recurrence amongst the five patients with local excision. In the group with curative (chemo)radiotherapy, we detected nine patients with persistent tumors (15.3%) of which one patient was not operated on because of poor performance status. The other eight patients (13.6%) underwent salvage surgery. Furthermore, we saw five locoregional recurrences (8.5%), amongst them one of the patients with radiotherapy only. Three of these patients received salvage APE (5.1%); one (1.7%) could be treated by local excision alone. In this particular case, the patient refused the necessary APE. During close follow-up, the patient remained tumor free. The remaining patient (1.7%) underwent inguinal lymph node excision. One patient presented with peritoneal metastases after curative CRT. Forty-three patients

Table 1 Patient population

	Anal canal cancer (<i>n</i> = 69)	Anal margin cancer (<i>n</i> = 37)	Total (<i>n</i> = 106)	<i>p</i> value
Follow-up in months (median, range)	89 (29–172)	79 (16–142)	87 (16–172)	0.553
Age in years (median, range)	63 (36–92)	57 (34–92)	60 (34–92)	0.020
Sex				
Male	29 (42.0)	21 (56.8)	50 (47.2)	0.148
Female	40 (58.0)	16 (43.2)	56 (52.8)	
T-category				
1	9 (13.0)	14 (37.8)	23 (21.7)	0.011
2	36 (52.2)	17 (45.9)	53 (50.0)	
3	9 (13.0)	4 (10.8)	13 (12.3)	
4	15 (21.7)	2 (5.4)	17 (16.0)	
N-category				
0	36 (52.2)	31 (83.8)	67 (63.2)	0.007
1	15 (21.7)	2 (5.4)	17 (16.0)	
2	11 (15.9)	4 (10.8)	15 (14.2)	
3	7 (10.1)	0	7 (6.6)	
N-category				
0	36 (52.2)	31 (83.8)	67 (63.2)	0.001
Positive	33 (47.8)	6 (16.2)	39 (36.8)	
Distant metastases				
No	66 (95.7)	37 (100)	103 (97.2)	0.550
Yes	3 (4.3)		3 (2.8)	
Grading ^a				
Well	7 (10.3)	10 (28.6)	17 (16.5)	0.010
moderate	48 (70.6)	24 (68.6)	72 (69.9)	
Poor	13 (19.1)	1 (2.9)	14 (13.6)	
Pretherapeutic SCC level (< 1.5 ng/ml) ^b				
Normal	33 (67.3)	18 (56.3)	51 (63.0)	0.312
Elevated	16 (32.7)	14 (43.8)	30 (37.0)	

Values in parentheses are percentage if not otherwise specified

SCC, squamous cell carcinoma antigen level

^aMissing for three patients

^bMissing for 25 patients

(74.6%) had a clinical complete response after chemoradiotherapy and were considered to be cured.

In the group of anal margin cancer (*n* = 37) local excision was possible in 16 patients (43.2%). There were two incomplete resections (R1) which additionally necessitated chemoradiotherapy. A third patient with incompletely resected cancer did not receive further therapy because of advanced age but remains tumor free after 52 months. Furthermore, one patient with a narrow resection margin received adjuvant radiotherapy. Nineteen patients (51.4%) received chemoradiotherapy and another patient (2.7%) radiotherapy in curative intention. One patient (2.7%) needed APE as primary treatment because of previous irradiation for prostate cancer. Amongst the 12 patients following local R0 excision only, we detected one recurrence that

was treated with chemoradiotherapy as salvage treatment. Two patients (16.7%) presented with inguinal lymph node metastases who also received CRT as salvage modality. The other nine patients (75.0%) remained tumor free. One of the patients after additional CRT following R1 resection developed a recurrence and was successfully treated by local excision. In the 20 patients treated curatively with (chemo)radiotherapy there was one persistent (5%) and two recurrent tumors (10%). All three were treated by salvage surgery. The other 17 patients (85.0%)—including the one patient receiving only radiotherapy—had a complete response without any sign of relapse during follow-up. Flow charts of applied treatment are shown in Figs. 1, 2, and 3. The regimens of chemoradiotherapy are demonstrated in Table 2.

Fig. 1 Patient population and initial treatment overview

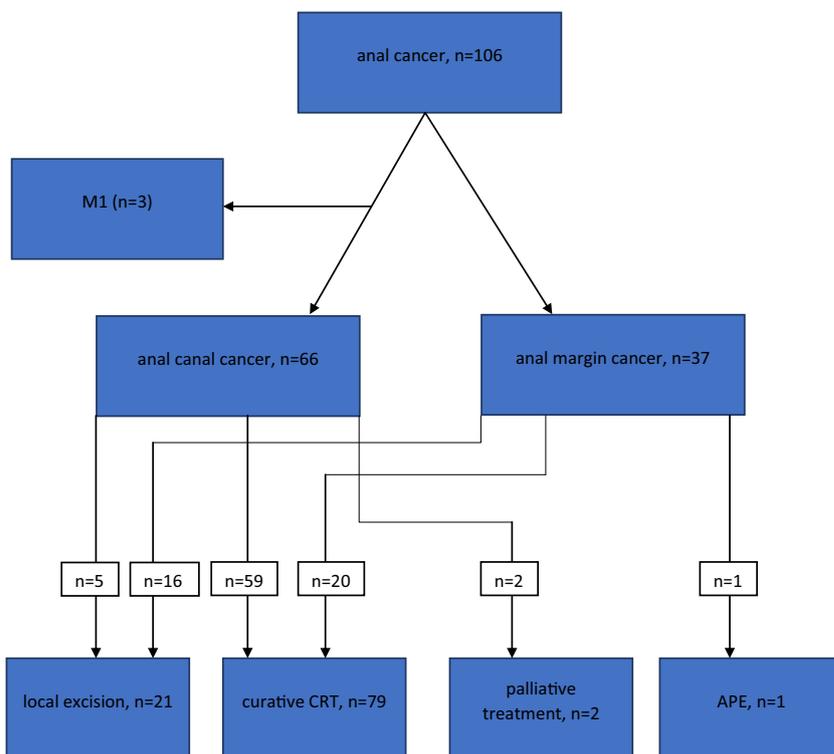


Fig. 2 Flowchart of treatment for anal canal cancer includes locoregional recurrence in inguinal lymph nodes

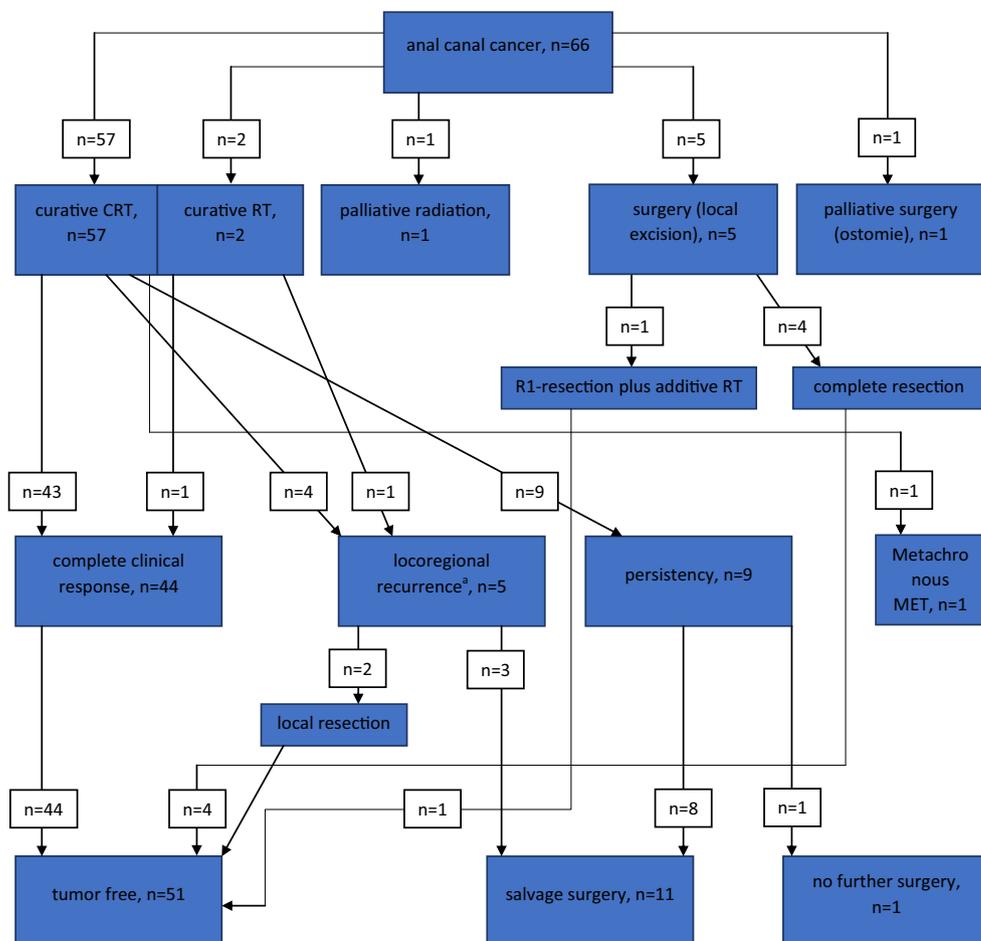
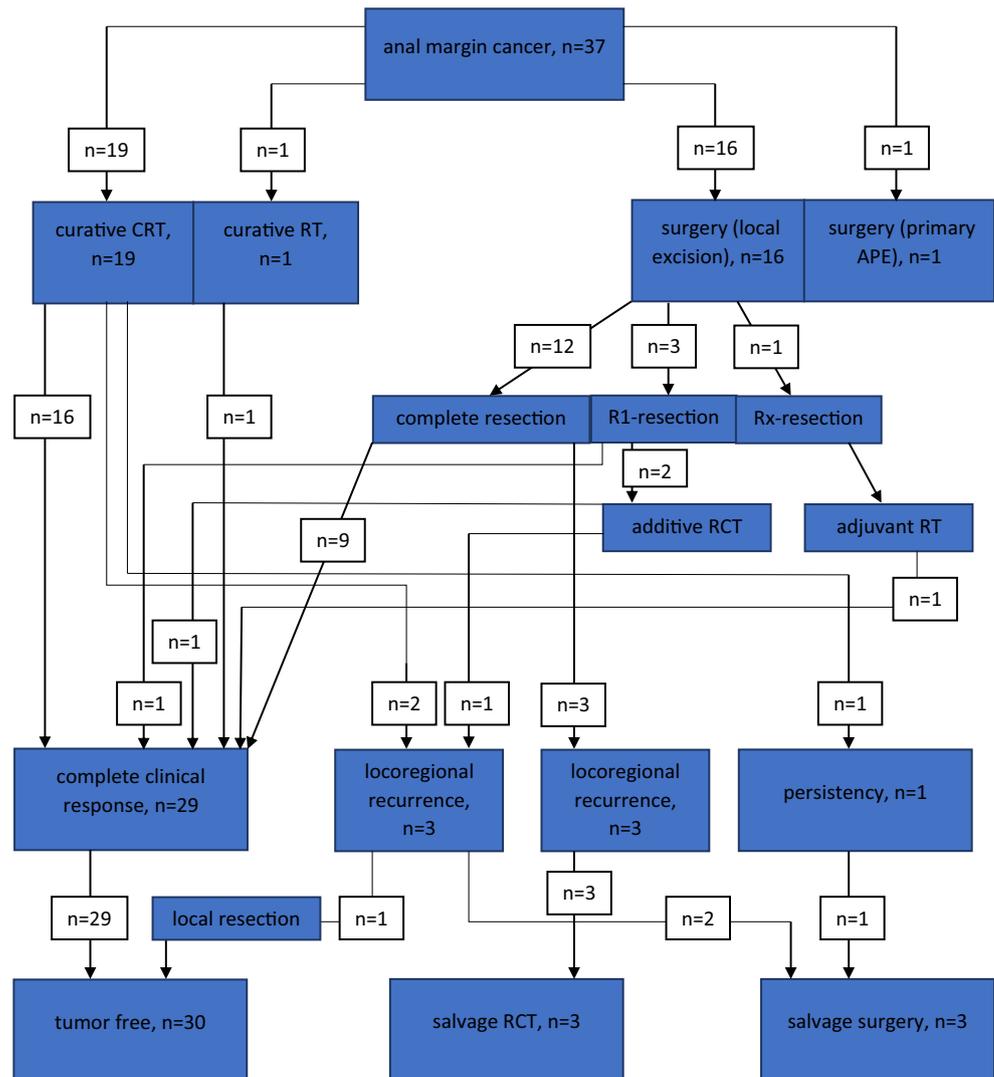


Fig. 3 Flowchart of treatment for anal margin cancer



In summary, we performed a total of 15 APE in both groups (14 salvage APE plus one APE as first-line treatment). A further two permanent colostomies were necessary because of persistent perineal pain and bowel obstruction. Additionally, nine patients required a diverting ileostomy before curative treatment. Only three ileostomies could be reversed (33%). This resulted in a permanent stoma rate of 22.3% ($n = 23$). In-hospital mortality for all patients undergoing an operative procedure was 4.2%. Salvage surgery was performed as APE in four patients and as extralevator abdominoperineal excision (ELAPE) in ten patients with ten flap reconstructions (five vertical rectus abdominis muscle (VRAM) flaps, five bilateral VY-fasciocutaneous flaps). In one patient, an extended ELAPE with cystectomy was necessary due to tumor infiltration, while in another patient, unilateral inguinal dissection was done because of involved lymph nodes (Table 3).

Five-year OS of all patients was 73.1%. There was no significant difference between the two groups but a tendency

towards longer survival for anal margin cancer (anal canal cancer 67.5% and anal margin cancer 83.2%; $p = 0.071$, Table 4; Fig. 4). A similar trend was found in the CSS rates at 5 years (anal canal cancer 83.2% and anal margin cancer 94.3%, both groups 87.4%; $p = 0.120$, Fig. 5). If early T-categories (T1–2) were compared with advanced T-categories (T3–4), there was a significant survival difference in OS (82.7 vs. 44.9% $p < 0.001$) and CSS (91.6 vs. 74.3% $p = 0.017$; Figs. 6 and 7; Table 4). Five-year OS of patients undergoing chemoradiation (or radiotherapy only) in curative intention was 73.6%. A trend towards longer survival was found if chemoradiotherapy was performed completely (77.7 vs. 58.2%, Table 4). Reasons for incomplete therapy were side effects of chemotherapy and radiation that could neither be managed by dose reduction nor by an interruption of irradiation. The 5-year survival rate of the 14 patients requiring salvage surgery was 35.7% overall and 31.2% from the date of the salvage operation including one immunocompromised patient suffering from a myelodysplastic syndrome who died

Table 2 Type of (chemo)radiotherapy

	Localization		Total (<i>n</i> = 87)
	Anal canal (<i>n</i> = 61)	Anal margin (<i>n</i> = 26)	
Treatment intention			
Curative	59 (96.7)	20 (76.9)	79 (90.8)
Complete	43	17	60
Incomplete	16	3	19
Additive ^a	1 (1.7)	2 (7.7)	3 (3.4)
Adjuvant	0	1 (3.8)	1 (1.2)
Palliative	1 (1.7)	0	1 (1.2)
Salvage	0	3 (11.5)	3 (3.4)
Regimen CTx ^b			
5-FU/mitomycin	52 (85.2)	17 (65.3)	69 (79.3)
5-FU/cisplatin	3 (4.9)	5 (19.2)	8 (9.2)
Xeloda	1 (1.7)	0	1 (1.2)
5-FU alone	1 (1.7)	1 (3.8)	2 (2.3)
None (RT alone)	4 (6.6)	2 (7.7)	6 (6.9)
Unknown	0	1 (3.8)	1 (1.2)

Values in parentheses are percentage if not otherwise specified; patients (*n* = 87) with (chemo)radiotherapy; synchronous distant metastases (M1) excluded

5-FU, 5-fluorouracil; RT, radiotherapy

^a All complete

^b Chemotherapy

postoperatively because of septicaemia. Their CSS after 5 years was 57.7 and 53.7%, respectively. Stoma-free survival after 5 years was 62.7% in the cohort of M0 patients (Fig. 8).

Discussion

Our study shows the results that can be achieved in a consecutive series of patients with anal cancer if treatment decisions closely follow the framework of standard guidelines. It proves that anal cancer has a good prognosis according to overall survival and cause-specific survival, with low rates of ostomies and salvage surgery. Our reported rate of 87.4% CSS after 5 years means that death with tumor hardly occurs in these patients if they are treated by a multidisciplinary team

and are closely followed-up. Hence, only few patients with anal cancer cannot be cured. It is important to note that our series comprises only patients without HIV infection. HIV is known to raise the risk of anal cancer significantly [1, 4, 6], and it is assumed that the increasing incidence of anal cancer worldwide can be attributed to this increased risk [5, 25, 26].

In our region of Germany, the incidence of HIV infections is very low. In a population of 4.08 million [27] only 2100 persons with HIV (0.05%) are reported [28]. Additionally, median age of our patients was 60 years which further decreases the likelihood of HIV infections. We therefore did not test patients for HIV systematically but only those who were suspected to be at risk. This is in accordance with the recommendations of other investigators who recommend general testing for HIV only for patients with an according

Table 3 Salvage abdominoperineal excision

Type of salvage surgery	Localization		Total (14)
	Anal canal (11)	Anal margin (3)	
APE	3	1	4 (28.6%)
ELAPE plus VRAM-Flap	4		4 (28.6%)
ELAPE plus VY-Flap	3	2	5 (35.7%)
Extended ELAPE plus VRAM-Flap	1		1 (7.1%)

APE, abdominoperineal excision; ELAPE, extralevator abdominoperineal excision; VRAM-Flap, vertical rectus abdominis myocutaneous flap

Table 4 Overall survival

	Number	Survival rate at 5 years	95% confidence interval	Events	<i>p</i> values
All	103	73.1	64.5 ... 81.7	27	
Localization					
Canal	66	67.5	55.9 ... 79.1	21	0.071
Margin	37	83.2	70.9 ... 95.5	6	
T-category					
1–2	76	82.7	74.1 ... 91.3	13	< 0.001
3–4	27	44.9	25.1 ... 64.7	14	
N-category					
0	66	78.2	68.0 ... 88.4	14	0.134
Positive	37	64.2	48.5 ... 79.9	13	
Grading ^a					
1–2	88	76.7	67.7 ... 85.7	20	0.003
3	12	40.0	11.4 ... 68.6	7	
SCC ^b					
Normal (≤ 1.5 ng/ml)	49	75.5	63.3 ... 87.7	12	0.702
Elevated (> 1.5 ng/ml)	29	70.2	52.8 ... 87.6	8	
Radiotherapy ^c					
All	82	73.6	63.8 ... 83.4	21	
Complete	65	77.7	67.3 ... 88.1	14	0.057
Incomplete	17	58.2	34.5 ... 81.9	7	

Patients with synchronous distant metastases (M1) excluded

^a Missing for three patients

^b Missing for 25 patients

^c Curative and additive intent only

lifestyle [3]. Given these facts, we herein present data of a homogenous cohort of non-HIV-infected patients with sporadic anal cancer.

In general, 5-year survival rates of anal carcinomas are reported to be in the range of around 80% for the entire group. Additionally, Kim et al. [29] recently showed a continuous improvement of CSS over time by means of conditional disease-specific survival. OS rate in our cohort compares favorably with the literature [17, 19, 30–34] although it is difficult to compare results because most studies and investigations examine and evaluate data of patients who either suffer from anal canal cancer only (exclusion of anal margin cancer) [19, 30, 31] or who exclusively received chemoradiation [17, 19, 31, 34]. The tendency towards a lower survival rate in anal canal cancer in our cohort can be explained with the higher age and higher tumor stages in this group. Very likely, anal margin cancer is diagnosed earlier in the course of the disease, presumably because of the better accessibility.

Five-year OS following chemoradiotherapy in curative intent was 73.6% in our patient cohort. This is in line with the results of other studies which range from 62.1 to 89% [15, 17, 19, 30, 33–35]. Hardt et al. [35] presented a 5-year OS after chemoradiotherapy of 79%; however, this study is limited because of a short follow-up. The randomized studies of

James et al. [17] and Ajani et al. [31] who compared different regimen for chemoradiation with or without maintenance [17] reported 5-year OS of 73 to 78%. In cases of complete clinical response after 26 weeks, Glynne-Jones et al. [16] even showed an OS of 87%. Since the results of our study are within the same range, we can give proof that treatment strategies of these randomized trials can be generalized for non-selected patient cohorts.

Salvage surgery is needed in 10 to 20% according to the literature [15, 19, 34–37]. Our results are at the lower end of this range with 13.6%. One reason might be the higher number of anal margin cancer in our study, while other studies exclusively were investigating anal canal cancer [19], had rather few numbers of anal margin cancer [35], or did not specify the ratio [15, 34].

OS after salvage surgery was quite low in our series compared with many other reports [15, 17, 34–39] that presented rates of 33 to 86%. Small patient numbers, postoperative mortality, and different approaches to calculation of survival rates render direct comparison difficult. The OS of 35.7% and CSS of 57.7% in patients with salvage operation in our cohort reflects advanced tumor stages and non-response to chemoradiotherapy.

Rate of permanent colostomy is another marker for quality of life. Not only patients with salvage surgery require a

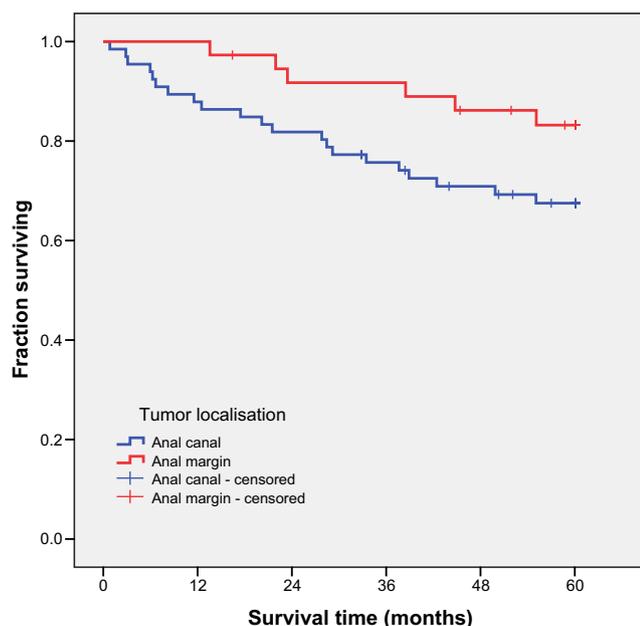


Fig. 4 Overall survival for the entire cohort ($n = 103$) at 5 years was 73.1% (anal canal cancer ($n = 66$) 67.5%, anal margin cancer ($n = 37$) 83.2%, $p = 0.071$)

colostomy but also patients who suffer from anal pain, fecal incontinence, and bowel obstruction. The ostomy rate in our series was 22.3% which is in the range of the figures given in the literature (17.1 to 30.4%) [14, 17, 19, 33, 37, 38]. Reversal of protective ostomies happens at the most in 50% [8] and is usually hindered either from high age or persistent complications of chemoradiotherapy like incontinence, stenosis, and co-morbidities.

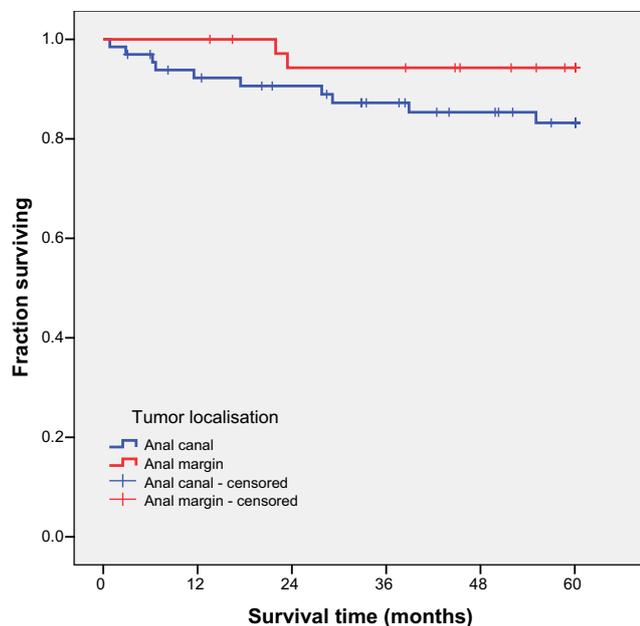


Fig. 5 Cause-specific survival for the entire cohort ($n = 103$) at 5 years was 87.4% (anal canal cancer ($n = 66$) 83.2%, anal margin cancer ($n = 37$) 94.3%, $p = 0.120$)

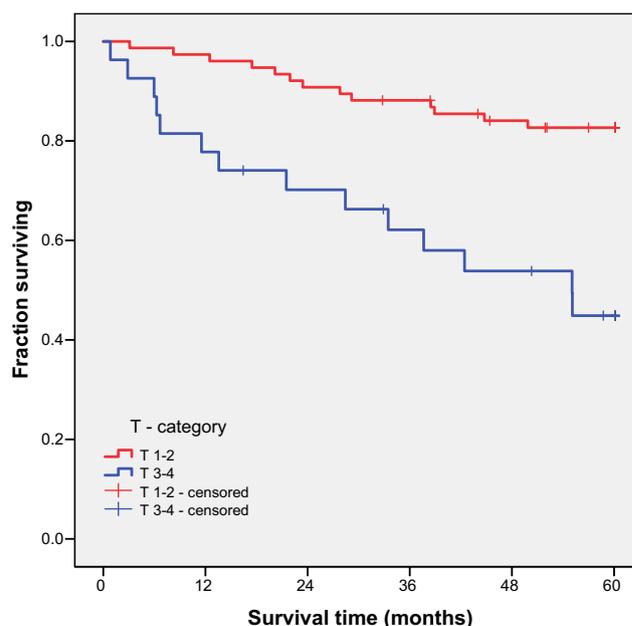


Fig. 6 Overall survival at 5 years for T1–2 carcinomas ($n = 76$) 82.7% and for T3–4 carcinomas ($n = 27$) 44.9% ($p < 0.001$)

The strengths of the presented data are the extensive follow-up period, the rather homogenous patient cohort, and the accordance to treatment with evolving guidelines. We report results in a contemporary non-selected cohort that can be achieved within a multidisciplinary setting that reflect the translation of randomized studies into daily clinical practice. The fact that survival rates equal the rates of randomized trials shows that the strategies investigated therein can be expanded to non-study patients as well.

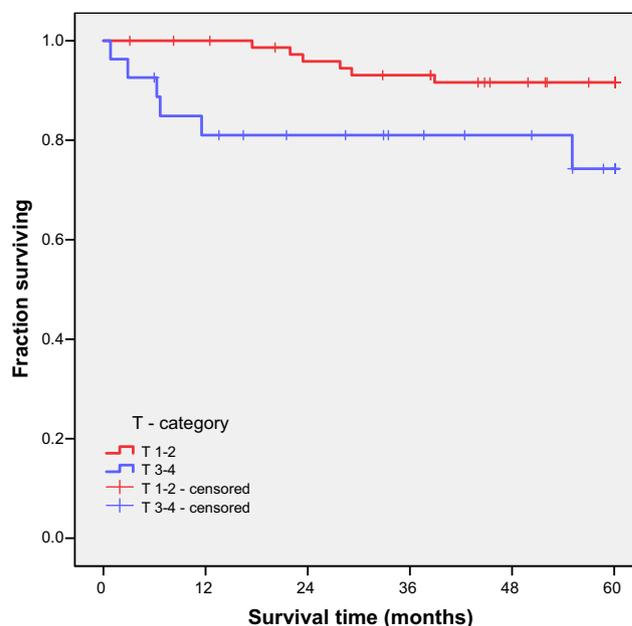


Fig. 7 Cause-specific survival at 5 years for T1–2 carcinomas ($n = 76$) 91.6% and for T3–4 carcinomas ($n = 27$) 74.3% ($p = 0.017$)

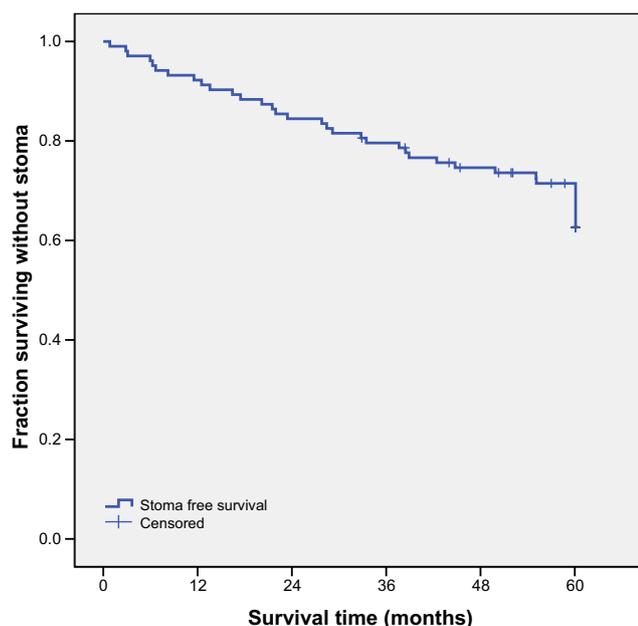


Fig. 8 Stoma-free survival for the entire cohort ($n = 103$) at 5 years was 62.7%

Whether local excision of early cancers not only in anal margin cancer but also in cancer of the anal canal should be considered a treatment option needs to be further investigated. A study by Chai et al. [40] showed similar survival figures in T1N0 cancers if local excision and CRT were compared.

One limitation of the study is the size of the cohort which is owed to the rarity of the disease. In our catchment area of approximately 250,000 inhabitants, however, we treated more than twice as many patients as expected. Another limitation is the missing status for human papilloma virus (HPV) which has not been routinely performed in our department. There is evidence for higher incidences of anal cancer amongst patients contaminated with HPV, especially with subtypes HPV16 and HPV18 [8, 9, 25, 41]. Only lately was vaccination for girls and also for boys advised in order to reduce the overall risks of HPV-related diseases. Mennini et al. [42] estimated a further reduction of anal cancer of 35% in men in 100 years if a nine-valent vaccination was performed. There are even recommendations for secondary vaccination against oncogenic HPV [43], but its use is still controversial in anal cancer.

Conclusion

Implementation of current guidelines results in a good prognosis for anal cancer patients with low rates of permanent ostomy and long-term survival. Important for good outcomes and early detection of persistent or recurrent disease is a close cooperation in a multidisciplinary team including surgeons, medical oncologists, radiation oncologists, radiologists, and

pathologists as well. Within this framework, the need for salvage surgery and permanent ostomies can be minimized.

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