Clinical and Translational Radiation Oncology 24 (2020) 83–87

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Treatment outcome after radiochemotherapy in anal cancer patients staged with ^{18}F-FDG-PET-CT

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ARTICLE INFO

Article history:
Received 6 April 2020
Revised 15 June 2020
Accepted 15 June 2020
Available online 18 June 2020

Keywords:
Anal cancer
Radiotherapy
PET
Radiochemotherapy

ABSTRACT

Background: Anal cancer (AC) is a malignancy with increasing incidence and commonly treated with radiochemotherapy. Positron-emission tomography-computed tomography (PET/CT) has been shown to improve treatment outcome in various oncological diseases, however, for AC long-term outcome data is sparse. The aim of the present study is therefore to report outcomes in our cohort of PET/CT staged AC patients treated with radiochemotherapy.

Methods: Patients with AC who were treated with radiochemotherapy in curative intent were included in this retrospective study if a PET/CT scan was performed pre-therapeutically. Information from PET/CT was considered for nodal and primary target volume definition. Radiotherapy dose to the primary tumor was 50–66 Gy and concomitant chemotherapy included 5-fluorouracil and mitomycin-C. The uptake of ^{18}F-fluorodeoxyglucose (FDG) was quantified using 50%-isocontour volumes of interests (VOIs) and measuring the standardized uptake value (SUV) and the metabolic tumor volume (MTV).^{18}F-FDG uptake was correlated with baseline clinical parameters and long-term oncological outcome. Survival estimates were determined according to Kaplan-Meier.

Results: A total of 60 patients were included in this study. Estimates for three-year overall survival (OS) and disease free survival (DFS) were 94.5% and 80%. Five patients developed local (n = 2) or locoregional and local (n = 3) failure. Baseline PET/CT related parameters correlated with primary tumor stage, nodal stage and tumor grading. DFS was independent of T-stage, N-stage and baseline ^{18}F-FDG-uptake.

Conclusion: In this cohort of PET/CT staged AC patients, excellent outcomes for DFS were seen. PET-based markers of tumor burden correlate with local stage of AC, however, are not of prognostic relevance for disease-free survival.

1. Introduction

Anal cancer is a rare malignancy with increasing incidence in the western world [1–2]. Standard of care in non-metastatic disease consists of combined modality treatment with radiotherapy and chemotherapy, aiming at organ preservation and long-term cure [3–5]. The introduction of positron emission tomography (PET-CT) in diagnosis and treatment guidance has resulted in optimized disease staging and treatment outcomes in several diseases such as lung cancer, head and neck cancer and lymphoma [6–9]. Also for anal cancer, the role of PET-CT especially for disease staging and its impact on target volume definition has been studied before [10–11]. Several studies investigated the association of pretherapeutic PET-CT parameters with the oncological outcome of patients with anal cancer, with partly conflicting results [12–14].

The purpose of this study was to report our long term-oncological outcome data in a PET-CT staged cohort of anal cancer patients treated with radiochemotherapy and to investigate the correlation between baseline PET/CT-parameters and survival data.

2. Material and methods

The study was approved by the institutional review board of the Medical Faculty in Tübingen (Study ID: 314/2018B02).

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https://doi.org/10.1016/j.ctro.2020.06.008
2405-6308/

2.1. Patient cohort

A retrospective analysis of patients with histologically confirmed anal cancer with a pretherapeutic PET-CT was conducted. Patients were treated at our institution from 2006 to 2016 with concomitant radiochemotherapy. Treatment consisted of normofractionated radiotherapy up to a total dose of 50–66 Gy in conventional or intensity modulated radiotherapy technique (IMRT). A dose of 45 Gy was applied to elective nodal areas. Target volume definition was based on all available clinical and imaging information. Specifically, $^{[18]}$F-FDG-uptake was included in the definition of the primary tumor and lymph nodes for boosting. Based on consensus recommendations, elective nodal areas included the mesorectal and presacral space, ischiorectal fossae, internal and external iliac and inguinal nodal areas. If perianal skin was involved, a 2 cm margin of perianal subcutaneous tissue and skin was included in the treatment volume [15]. Concomitant chemotherapy with 5-fluorouracil (5-FU) and mitomycin-c (MMC) as in the EORTC trial was applied [5]. If patients had contraindications for 5-FU, single agent MMC was applied. Patient and tumor characteristics as well as follow-up data were extracted from the patients' electronic chart. Tumor staging was performed according to the 7th edition of the TNM-classification.

3. $^{[18]}$F-FDG-PET/CT imaging

All PET/CT examinations were performed on a state-of-the art clinical scanner (Biograph mCT®, Siemens Healthineers). All patients fasted overnight before examination. Approximately 300 MBq 18F-FDG were injected intravenously 60 min prior to image acquisition. Standardized CT examination protocols included weight-adapted 90–120 ml intravenous CT contrast agent (Ultravist 370®, Schering AG). Portal-venous phase acquisitions were obtained with 70 s delay time using a tube voltage of 120 kV and a reference dose of 200mAs. Iterative CT reconstruction was performed using SAFIRE® (Siemens, Forchheim).

PET was acquired from the skull to the mid thigh level over six bed positions and reconstructed using a 3D ordered subset expectation maximization algorithm (two iterations, 21 subsets, Gaussian filter 2.0 mm, matrix size 400 × 400, and slice thickness 2.0 mm). PET acquisition time was 2–3 min per bed position.

3.1. Quantification of vital local tumor burden

PET quantification was performed measuring the mean, maximum and peak standardized uptake values (SUVmean/max/peak) as well as the metabolic tumor volume (MTV) based on 50%-isocontour volumes of interests (VOIs). SUVmax is defined as the highest single-pixel value within a defined volume of interest (VOI), whereas SUVpeak is defined as an average SUV within a small, fixed-sized VOI (1 ml) centered on maximum-uptake part of the lesion [16]. The use of the metabolic tumor volume has been proposed for assessing the degree of 18F-FDG accumulation in diverse cancer types, as it reflects the whole volume of the tumor rather than the SUVmax which represents only the most active part of the tumor [17]. These PET parameters were then correlated to local disease stage (TNM), grading, and DFS.

Unless otherwise stated, continuous parameters are reported as mean with standard deviation. Kaplan-Meier survival estimates are calculated from the last fraction of radiotherapy. Death of any cause, local, locoregional and distant treatment failures were considered events for DFS. Median follow-up was calculated using the inverse Kaplan-Meier method [18]. The log-rank test was used to compare groups in terms of survival, Mann-Whitney U-Tests to compare continuous variables.

A p-value < 0.05 was considered significant for all tests. All statistical analyses were performed in SPSS 25 (IBM, Armonk, New York, USA).

4. Results

4.1. Patient and treatment characteristics

A total of 60 patients (71.7% female, 28.3% male) with a median age of 64 years (range 35–95) met inclusion criteria. One patient was HIV-positive. 54 patients received combined chemotherapy with 5-FU and MMC, five patients received single agent MMC and one patient received single agent 5-FU concomitant to radiotherapy. Median radiotherapy dose was 60 Gy (IQR 60 Gy – 64 Gy), 45 patients were treated with IMRT, 15 patients with 3D conformal radiotherapy. Patient and treatment related parameters are summarized in Table 1. Mean ± SD MTV, SUV_{mean}, SUV_{max} and SUV_{peak} were 11.6 ± 13.4, 4.3 ± 2.3, 4.4 ± 2.4 and 11.3 ± 6.1. As shown in Table 2, higher tracer uptake was seen in patients with higher stage primary tumors, node positive disease and poorly differentiated tumors.

4.2. Outcomes

Median follow-up was five years. For the entire cohort, three-year and five-year DFS, overall survival and locoregional control were 80%/72.1%, 94.5%/81.6% and 91%/91% respectively. During follow up, two patients experienced isolated local failure at the primary tumor site and three patients presented with both local and regional failure. Distant failure was seen in a single patient. Patients with T3 or T4 tumors showed no inferior DFS compared with patients with primaries staged T1 or T2 (82.3% vs. 77.6% at three years, p = 0.58). The same accounts for nodal stage (N0 vs N+) with a three-year DFS of 78.1% vs. 82.1% (p = 0.85), see Fig. 1a and 1b. None of the studied PET-related quantitative parameters showed a prognostic relevance for DFS as depicted in Fig. 1c and 1d.

Table 1
Patient and tumor characteristics; IMRT – Intensity modulated radiotherapy. 5-FU – 5-Fluorouracil, MMC – Mitomycin-C, HIV – Human immunodeficiency virus.

Age (years, mean (range))		64	(35–95)
		n	
Gender	Male	17	28%
	Female	43	72%
T-stage	T1	4	7%
	T2	26	43%
	T3	21	35%
	T4	9	15%
N-stage	N0	31	52%
	N1	8	13%
	N2	11	18%
	N3	10	17%
Tumor grade	G1	1	2%
	G2	40	67%
	G3	15	25%
	Missing	4	7%
Histology	Squamous cell carcinoma	55	92%
	Basaloid carcinoma	1	2%
	Cloacogenic carcinoma	3	5%
	Sarcomatoid carcinoma	1	2%
Radiotherapy technique	IMRT	45	75%
	3D conventional	15	25%
Concomitant chemotherapy	5-FU + MMC	54	90%
	MMC mono	5	8%
	5-FU mono	1	2%
HIV status	positive	1	2%
	negative	59	98%

Table 2
18F-FDG uptake and baseline tumor characteristics. SUV – standardized uptake value.

	T1 and T2	T3 and T4	p	cN0	cN+	p	G1 or G2	G3	p
MTV	5.4(4.9)	17.8(16.1)	<0.001	9.3(9.7)	14.0(16.3)	0.193	10.6(14.3)	15.7(11.7)	0.035
SUV_{mean}	3.7(2.0)	4.8(2.5)	0.089	3.5(1.6)	5.1(2.6)	0.008	4.6(2.6)	3.4(1.0)	0.041
SUV_{max}	3.8(1.9)	5.0(2.7)	0.044	3.7(1.7)	5.2(2.8)	0.008	4.7(2.7)	3.6(1.2)	0.08
SUV_{peak}	9.3(4.4)	13.4(6.9)	0.001	9.1(3.7)	13.7(7.2)	0.001	11.8(6.9)	10.4(3.5)	0.476

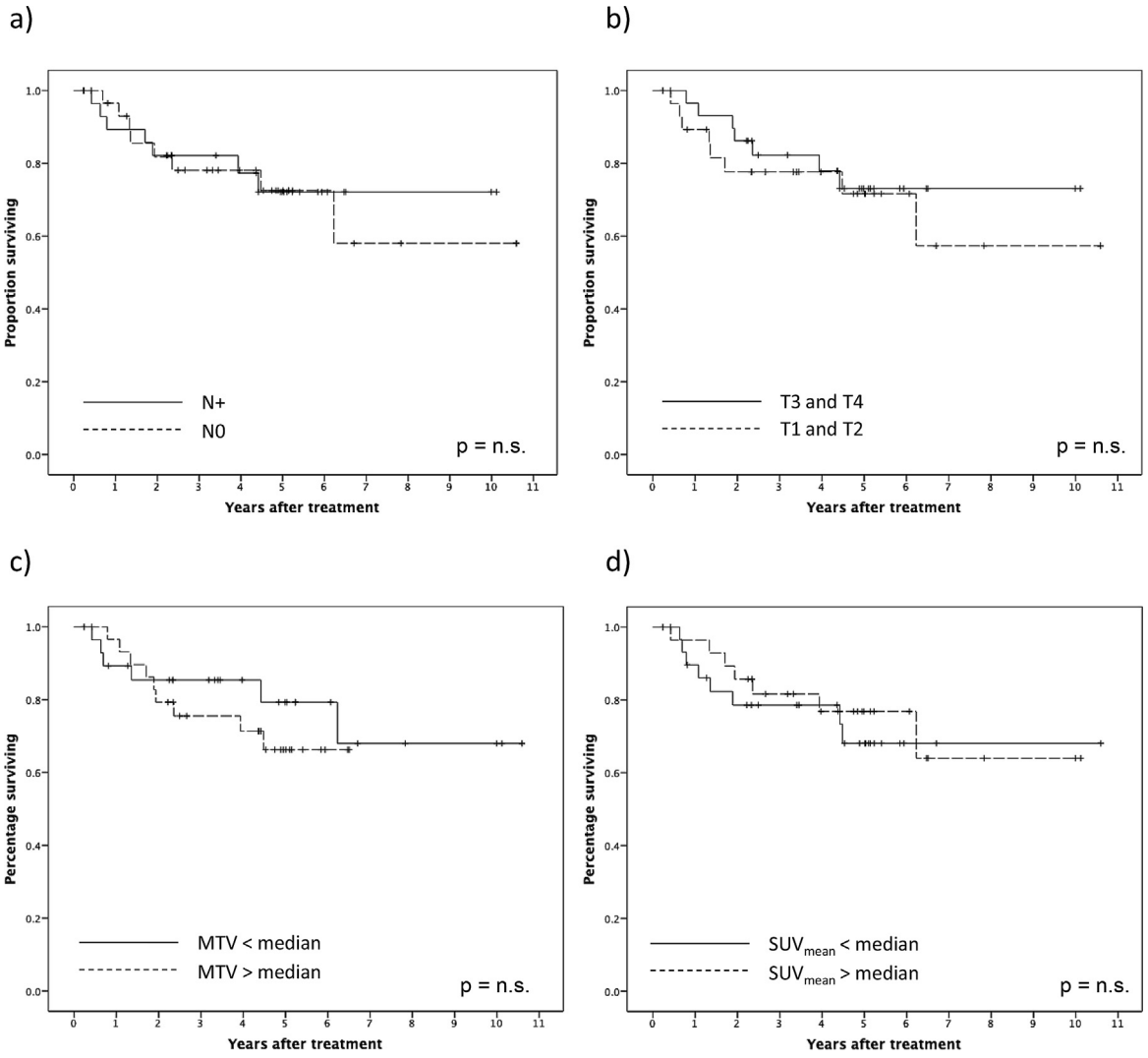

Fig. 1. Disease-free survival in dependence of nodal stage (a), T-stage (b), metabolic tumor volume (MTV) (c), SUV_{mean} (d). SUV- standardized uptake value, MTV – Metabolic tumor volume.

5. Discussion

In the current study we present oncological outcome data from a cohort of PET/CT staged anal cancer patients after radiochemotherapy. Despite comparable tumor stages, the observed three-year locoregional control rate and DFS of 91% and 80% are higher than in most of the previously reported studies [19]. For instance, in the ACT II trial, three-year progression free survival in the MMC/5-FU arm without maintenance chemotherapy was 73%, local control without colostomy 75%. In the EORTC trial locoregional control with radiochemotherapy was approximately 70% after three years and progression-free survival approximately 65% after three years [5,20].

For a variety of reasons, the inclusion of PET-CT in pretherapeutic staging of disease extent and in radiotherapy treatment planning might have been a key contributor to this very favorable result. First, PET-CT has been shown to result in nodal upstaging in approximately 20% of patients [21]. We routinely include the information from PET imaging in our nodal target volume definition and consider boosting of PET positive lymph nodes. In contrast to previous studies without PET guided target volume definition, DFS in our cohort was independent of nodal stage [22]. Intriguingly, De Winton and colleagues, who also used PET for staging and target volume definition, could not observe an impact of PET defined nodal stage on outcome [14]. Second and as shown by Nguyen and colleagues, most primaries can be delineated only

poorly based solely on CT but almost all anal tumors are [18]F-FDG avid, facilitating more accurate target volume definition [23]. Finally, as in other malignant diseases, PET can detect occult metastatic disease at initial staging and thus avoid unnecessary and toxic local treatments [24–26]. The avoidance of undertreatment by dose escalation of PET positive lymph nodes and more precise coverage of the primary tumor and the avoidance of toxic local overtreatment in previously undetected metastatic disease might have contributed to the very favorable survival data in this patient cohort.

In the present study, FDG uptake was higher in patients with more advanced primary tumors, poorly differentiated tumors and node positive disease. This is in line with the results of a prospectively conducted study of Deantonio et al. including 55 patients. They observed a statistically significant correlation between SUV_{max} and T- stage of patients and no association with treatment response or survival of patients [12]. Similarly, baseline PET uptake parameters such as SUV_{max} and SUV_{mean} and MTV had no impact on long-term outcomes in our cohort. In another retrospective study of 77 patients, a significant association between a high pretherapeutic SUV_{max} and a lower DFS and also a positive nodal status was seen, the latter itself is known an important negative prognostic factor in anal cancer [27]. Another retrospective study including 75 patients found a correlation of the MTV of the primary tumor and OS with a cut off value of 7 cm [3]. There was no significant correlation of SUV_{max} with OS or PFS of the patients [28]. Another study that included data of 19 patients derived from a prospective multi-center trial found a correlation between the MTV on pretreatment PET/CT and any tumor recurrence in anal cancer patients treated with radiochemotherapy. The defined MTV (volume encompassing 41% of SUV max) further showed very high discrimination (ROC AUC 0.89). In this study, pretreatment PET parameters did not predict for local recurrence [29]. Two other small retrospective studies found a correlation between MTV of the primary tumor and recurrence free survival and progression free survival, respectively. Cut off values for MTV were noticeably higher than in the above-mentioned study with 45 ml and 26 ml, respectively. Neither of these studies found an association of SUV_{max} and overall survival [30–31]. It should be noted though, that in both studies the subgroup of patients with high MTV consist of a very limited number of patients which might mask existing effects due to limited power. Another study evaluating the predictive value of pretherapeutic SUV_{max} in 110 patients with anal cancer found no significant association with local control or survival [13]. The results of existing studies remain conflicting and our findings are in line with several studies who failed to validate a positive correlation between baseline PET parameters and outcome of anal cancer patients.

Until now the optimal radiotherapy dose for anal cancer is matter of debate and doses between approximately 53 Gy and 60 Gy are considered standard for locally advanced disease. In the ongoing PLATO trials, the optimal radiotherapy dose both in terms of de-escalation in early stage tumors as well as escalation in locally advanced tumors is being investigated (ISRCTN88455282). Based on the available studies in literature, baseline PET tracer uptake is not suitable for defining the required target dose. While most published studies used FDG-PET for baseline assessment of disease, there is a strong rationale to assume that changes of functional imaging parameters during radiotherapy might be a stronger predictor of outcome than baseline parameters. This has already been proven in studies for other gastrointestinal primaries such as the rectum or the esophagus [32–33]. For instance, in a multicenter study of patients with esophageal carcinoma treated with neoadjuvant chemotherapy and subsequent radiochemotherapy, PET/CT after the first chemotherapy cycle was conducted. An early favourable metabolic response was associated with superior oncological outcomes. In patients without early favourable response, an intensification of neoadjuvant therapy was able to compensate for the unfavourable biological characteristics in these tumors [34]. Also, radiomics based on multiparametric MRI before and during radiochemotherapy in anal cancer patients appears to be a promising approach [35]. Consequently, such data might be a strong tool for personalizing treatment in terms of radiation dose. Indeed, also for anal cancer, tracer uptake after radiochemotherapy has been shown to be of prognostic value [23,36–37].

There are limitations that have to be considered when interpreting the results of our study. First and as stated before, long-term outcomes were very favorable in our cohort with very few recurrences. This low number of events however might have limited the statistical power to detect prognostic parameters. As with all studies that used PET for nodal staging, it has to be acknowledged that large comparative studies that benchmarked PET with surgical staging have not been conducted so far. Thus, there is a risk that PET guided target volume definition might result in both over- and undertreatment. However, undertreatment appears unlikely when considering outcome data from trials that included PET in the treatment process [14]. Finally, due to the retrospective nature of the study, unrecognized confounding factors or biasing cannot be ruled out.

6. Conclusion

FDG-PET staging and PET based treatment guidance might result in superior treatment results, however, baseline ^{18}F-FDG uptake did not predict outcome to treatment. Changes in PET tracer uptake during treatment might be a more powerful approach to personalize treatment and warrants further investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Cihan Gani is supported by the Clinician Scientist Program of the Medical Faculty, Eberhard Karls Universität Tübingen [Funding number: 363–0-0].

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