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Improved survival in patients with FDG-PET/CT-based radiotherapy treatment planning for squamous cell anal cancer

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The aim of this retrospective analysis was to evaluate the impact of FDG-PET/CT-based target volume definition on locoregional control and survival, compared to conventional CT-based target volume definition and dose prescription. One hundred and twenty-two patients with squamous cell anal cancer were treated with curative radiotherapy (RT) alone (27%) or with RT with concurrent chemotherapy (73%) and analyzed. Forty-six percent had the early disease (stage I+II) and 54% were stage III. FDG-PET/CT-based staging was performed in 21% of the patients. The mean follow-up time was 60 months. Other risk factors affecting survival were investigated. According to initial staging in both groups (FDG-PET/CT and conventional CT) were 10% of stage IV disease, and they were excluded from radical radiotherapy and treated with palliative intent. Ninety-two percent of the patients achieved complete remission. Significant favorable factors in univariate analysis associated with disease-free survival (DFS) were PET/CT staging, T1/2 and N0 stage, and clinical stage I and II. Locoregional control (LRC) correlated with the T1/2 stage and initial performance status (PS) 0. There were no significant factors affecting overall survival (neither in univariate nor multivariate analysis). In multivariate analysis, the factor associated with better DFS was PET/CT staging and for LRC, PS 0 and concomitant chemoradiation. Acute toxicity was increased in the concurrent chemo-radiotherapy group. Two-, five- and ten-year overall survival rates were 83%, 69%, and 60%; disease-free survival rates were 76%, 73%, 73%; local control rates were 91%, 90%, and 90% and colostomy-free survival was 89%, 86%, and 81%, respectively. PET/CT staging allowed targeted dose escalation to the primary tumor and nodal metastases while decreasing dose to uninvolved regions, resulting in significantly improved DFS without compromising locoregional control.

Key words: anal carcinoma, PET/CT, survival, radiotherapy, chemotherapy, prognostic factors

Squamous cell carcinoma is the most common type of anal cancer, with rising incidence but a stable mortality rate over the past 20 years [1]. Improved treatment outcomes are achieved due to diagnostic and therapeutic advances based on a multidisciplinary approach. Surgical resection alone (with 5 mm safety margin) is appropriate in Tis lesions and small perianal cancers (T1 N0 M0 G1 tumors). The majority of cases are diagnosed in advanced stages requiring curative radiotherapy (RT). The Radiation Therapy Oncology Group (RTOG) 98-11 [2], ACT II [3], ACCORD 3 [4], and other trials [5, 6] led to an adoption of concurrent chemo-radiation as the standard treatment [7–9]. Salvage surgery has been reserved for non-responders or local recurrence. Chemotherapy alone is applied in metastatic or recurrent inoperable disease.

Achieving local control is a major predictor of treatment outcome. Different RT protocols are associated with varying levels of acute and late toxicity affecting the quality of life. The introduction of intensity modulated RT (IMRT) significantly reduced these toxicities [10, 11] and minimized treatment breaks. A strong emphasis has been placed on accurate gross tumor volume (GTV) definition. GTV is defined based on clinical findings (DRE) and tumor imaging by endoscopic and radiological methods including CT and MRI. Elective lymph node CTV delineation is based on well-defined guidelines [12]. Margin definition depends on motion control and set up variations among site protocols.

Recently, the role of 18-fluorodeoxyglucose positron emission tomography (PET) with computed tomography (CT) in clinical staging has been evaluated [13, 14].

PET/CT led to a change in the clinical stage in 17–24% patients compared to CT alone [15–17]. This necessitated radiation plan modification in up to one-fourth of patients [18, 19]. Follow-up after anal cancer treatment remains based on individual disease extent [20]. Complete response on PET/CT three months after chemoradiotherapy has been associated with prolonged survival [21, 22].

The aim of this retrospective study was to evaluate the clinical impact of PET/CT based radiotherapy planning in patients with squamous cell anal cancer and to assess its influence on disease-free survival, locoregional control, and overall survival.

Patients and methods

Patients. The cohort included 122 patients treated with curative intent for squamous cell anal carcinoma between 1998 and 2018 were retrospectively evaluated. 73% of patients were treated in combination with chemotherapy. The median age at the time of diagnosis was 61 years (range 30–88 years). The majority of patients were females (80%). Clinical stage I was present in 16%, stage II in 30%, and stage III in 54% of patients. 50% of all patients were smokers. All patients in the present cohort were p16-positive. No routine HIV testing was performed. The mean follow-up time was 60 months. Patient characteristics are shown in Table 1. The median waiting time from biopsy to RT start was 57 days. The median RT duration (external therapy including brachytherapy) was 53 days. The cut-off date for follow-up analysis was July 15th, 2019.

All patients underwent physical examination with digital rectal exploration (DRE) and endoscopic exam (anoscopy, rectoscopy, or colonoscopy). Conventional imaging consisted of abdominal and pelvic CT scan, chest X-ray, and transrectal or inguinal ultrasound or pelvic MRI. Twenty-six patients (21%) treated from 2014 onwards were staged with 18FDG – PET/CT and we have used PET/CT for radiotherapy planning in radically-treated patients. Disease extent was retrospectively restaged according to the 8th edition of TNM classification (International Union against Cancer Classification staging system UICC 2017).

During the whole period, there were 134 patients diagnosed with anal cancer and after initial imaging staging, 10% was excluded from curative treatment in both groups. In the group of all PET/CT staging, 3 patients (10%) were excluded and treated with palliative intent due to a diagnosis of distant metastases. In the conventional staging group, 11 patients (10%) were excluded due to the metastatic disease (9 patients) or poor performance status or advanced age (2 patients). PET/CT tailored treatment was used for the GTV

Table 1. Patients and treatment characteristics (Chi-square test).

Variable	Group	All	Conventional staging	PET staging	p-value
Mean age (range), years		61 (30-88)	61 (30-88)	63 (30-81)	0.486
WHO performance status, n (%)	0	47 (62)	30 (58)	17 (71)	0.723
	1	26 (34)	19 (37)	7 (29)	
	≥2	3 (4)	3 (5)	0 (0)	
Gender, n (%)	Female	98 (80)	74 (77)	24 (92)	0.083
	Male	24 (20)	22 (23)	2 (8)	
Histology grading, n (%)	G1–2	56 (60)	45 (62)	11 (52)	0.446
	G3–4	38 (40)	28 (38)	10 (48)	
Histology type, n (%)	Squamous	93 (80)	74 (77)	19 (73)	0.670
	Basaloid	29 (20)	22 (23)	7 (37)	
Clinical stage, n (%)	I	20 (16)	11 (12)	8 (31)	0.053
	II	36 (30)	31 (32)	6 (23)	
	III	66 (54)	54 (56)	12 (46)	
T stage, n (%)	T1–T2	73 (60)	55 (57)	18 (69)	0.271
	T3–T4	49 (40)	41 (43)	8 (31)	
N stage, n (%)	N0	63 (52)	48 (50)	15 (58)	0.486
	N1	59 (48)	48 (50)	11 (42)	
Pre-treatment SCCA oncomarker elevation, n (%)	Yes	20 (53)	5 (33)	15 (65)	0.054
	No	18 (47)	10 (67)	8 (35)	
Chemotherapy, n (%)	Yes	89 (73)	72 (75)	17 (65)	0.328
	No	33 (27)	24 (25)	9 (35)	
Smoking history, n (%)	Non–smoker	40 (48)	28 (49)	12 (76)	**0.027**
	Stop smokers	9 (11)	7 (10)	2 (12)	
	Smokers	35 (41)	33 (41)	2 (12)	
RT technique	3D–CRT	84 (69)	82 (85)	2 (8)	**<0.001**
	IMRT	38 (31)	14 (15)	24 (92)	
Time since diagnosis to treatment (range), days		62 (17–156)	64 (17–129)	59 (30–156)	0.487
Overall RT treatment time (range), days		57 (13–164)	58 (13–164)	55 (36–70)	0.516
Mean maximum dose (Gy) to primary tumor		59.5	60	58	0.106

definition of the primary tumor and lymph node involvement in planning CT.

Treatment. A summary of the treatment protocol is shown in Table 2. Planning CT was performed in a supine position. Delineation of the primary tumor and lymph nodes GTV was facilitated by fusion of planning CT with diagnostic imaging where possible. Only PET/CT negative lymph nodes received elective radiotherapy total dose 30.6–36 Gy according to RTOG 98-11 trial [2] (including CT-enlarged but FDG-negative inguinal lymph nodes [23] and including all T1-4 N0 stages). The PET/CT positive lymph nodes were treated to radical dose 50–60 Gy according to size, location, and proximity and tolerance of organs at risk. A 10 mm margin was added to derive clinical target volume (CTV) of the primary tumor. Patients were independently examined by two radiation oncologists to accurately verify the extent of the primary tumor. In a case of uncertainty of tumor extent, a margin of up to 20 mm was used. For affected lymph nodes, a 5 mm margin was used for CTV. Planning target volume (PTV) was derived adding a 7 mm margin to the CTV. Until 2013, patients were treated with 3D conformal techniques. From 2014 onwards, an IMRT technique with simultaneous boost (IMRT-SIB) was used, adhering to target volume delineation guidelines [24]. Patients with treatment position deviation of more than 5 mm in the first 3 fractions were daily repositioned using image guided RT (IGRT) with kV portals.

All patients received curative external beam radiotherapy which was combined with concurrent chemotherapy in 73% of patients (only patients younger than 70 years, WHO performance status 0–1 and no severe comorbidities). External beam RT was delivered with 6–18 MV photons to a total dose of 30.6–45.0 Gy in 1.8–2.0 Gy fractions. Primary tumor and lymphadenopathy received a boost to a total dose of 55–60 Gy. The boost was delivered with external beam radiotherapy (in 50%), interstitial brachytherapy (in 41%), or combination of both (in 9%). Brachytherapy was delivered at the end of external beam therapy in patients with tumors affecting less than half of the anal circumference (2 x 5 Gy interstitial brachytherapy once a week). The following constraints were used for plan optimization: 98% of PTV received ≥95% of the prescribed dose; bowel bag was contoured as a peritoneal cavity with dose constraints of V45 Gy <195 cc and V50 Gy <50 cc. Bladder with constraints of V50 <50% and femoral heads V50 was <5% [14]. Doses to external genitalia were kept at D_{mean} <35 Gy in women and D_{mean} <20 Gy in men. Concurrent chemotherapy consisted of mitomycin C 10 mg/m^2 intravenously on day 1, and 5-fluorouracil 1000 mg/m^2 in-day continuous intravenous infusion during weeks 1 and 5 of radiotherapy.

Post-treatment follow-up. Patients were followed up weekly until the resolution of acute post-radiation symptoms. Tumor response was evaluated at 8 and 12 weeks following RT completion. PET/CT scan was performed in stage III disease to assess complete remission (CR) 3 months after curative RT. Patients who achieved CR had a physical exam every 3 months first two years, every 6 months during year 3–5 and once a year thereafter. Anoscopy was performed once a year or at signs of progression. No imaging methods were used in the follow-up of asymptomatic patients. Patients remaining in CR beyond 5 years were referred to primary care practitioners for further follow-up.

Acute and late toxicities were scored using the RTOG toxicity scale. Acute toxicity was defined as appearing during or up to 3 months after the RT completion. Late toxicity was defined as toxicity occurring later than 3 months from the RT completion.

Statistical analysis. The endpoints were local control, disease-free survival, colostomy free survival, and overall survival (OS). The influence of tumor, patient or treatment-related factors on survival was investigated.

Loco-regional control (LRC) was defined as the time from the RT start to last clinical follow-up (in patients with remission) or to the date of local progression of the primary tumor or of the regional lymph nodes. Disease-free survival (DFS) was defined as the time from the RT start to the last clinical follow-up, local or distant failure, or death. Overall survival (OS) was defined as the time from the RT start to the last clinical follow-up or death of any cause.

The data were analyzed with statistical software SPSS version 19.0, p-values of less than 0.05 were considered to indicate statistical significance.

Univariate analyses of survival were carried out by the Kaplan-Meier method and the evaluation of differences between the groups was performed with the log-rank test. Univariate Cox proportional hazards regression analyses were performed to calculate HRs and CIs to evaluate the

Table 2. Treatment protocol according to staging procedure and combined treatment modalities.

TNM stage	Staging method	Application of concomitant chemotherapy	RT dose to lymph nodes	RT dose to primary tumor
T1/2/3/4 N0 M0	PET staging	Yes	30.6-36 Gy-45 Gy (according to RTOG 98-11) [24], pelvic lymph nodes contouring [12]	Total dose 50-60 Gy EBRT or BRT (in tumors affecting less than half of the anal circumference) IMRT SIB preferred
		No	45 Gy all pelvic lymph nodes	
	Conventional staging (CT/MRI)	No/Yes	45 Gy all pelvic lymph nodes	
T1/2/3/4 N1 M0	PET staging/ Conventional staging	No/Yes	45 Gy to all pelvic lymph nodes + boost to positive LN 10-14.4 Gy	Total dose primary tumor 55-60 Gy IMRT SIB preferred

influence of patient, tumor, and treatment characteristics on risk of mortality or recurrence.

A multivariate analysis of survival using prognostic factors with a p-value of less than 0.2 in univariate analyses according to risk factors was performed with the Cox proportional-hazards regression model using a forward stepwise method to define the independent contribution of each prognostic factor. Fisher's exact test was used to evaluate differences in toxicity and risk factors between groups.

Results

Treatment outcomes. After curative treatment 92% of patients achieved CR. The median OS was 136 months. The respective OS rates at 2, 5, and 10 years were 83%, 69%, and 60%. The respective DFS rates were 76%, 73%, and 73%. The respective LRC rates were 91%, 90%, and 90%. Distant metastases developed only within the first 2 years from therapy in 10% of patients. Colostomy free interval was 89%, 86%, and 81% at 2, 5, and 10 years, respectively. In all, 16 patients (14%) ended up needing a colostomy: it was required as a pre-treatment procedure in locally advanced disease in 4 patients, to maintain stool passage in persistent or recurrent disease in 7 patients and to manage late radiotherapy sequelae in 6 patients.

Factors associated with survival. In univariate analysis, significant favorable factors affecting DFS were the use of PET for staging and radiotherapy planning (Figure 1, 2, 3, 4), clinical stage I/II, stage T1/2, and the absence of clinically or radiologically involved lymph nodes (N0).

LRC was associated with T stage and initial WHO performance status in univariate analysis.

There were no significant factors affecting overall survival in univariate analysis and IMRT use had no impact on OS, DFS, or LRC (Table 3).

In multivariate analysis, DFS significantly correlated with PET staging (p=0.017, Table 4). Smoking history and conformal radiotherapy technique were more often present

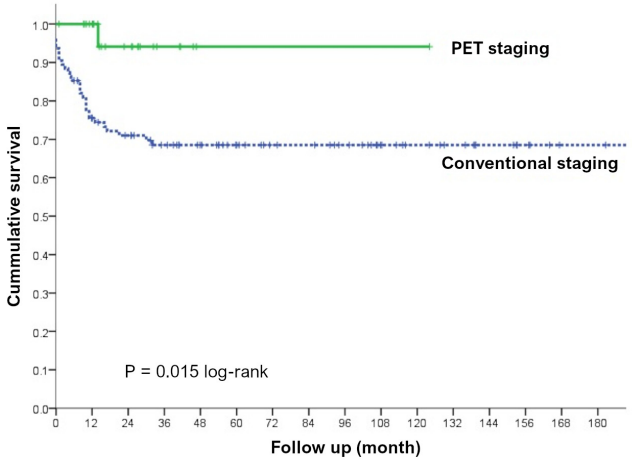

Figure 1. Kaplan-Meier analysis proved statistically significant improvement in disease-free survival with PET staging for all stages.

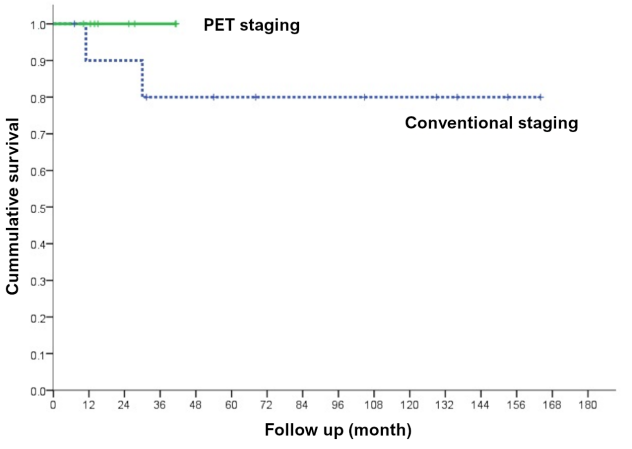

Figure 2. Kaplan-Meier analysis demonstrated improved disease-free survival with PET staging for stage I.

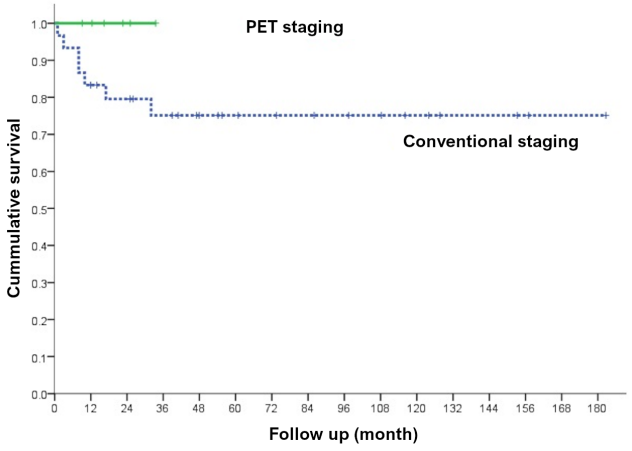

Figure 3. Kaplan-Meier analysis showed significantly improved disease-free survival with PET staging for stage II.

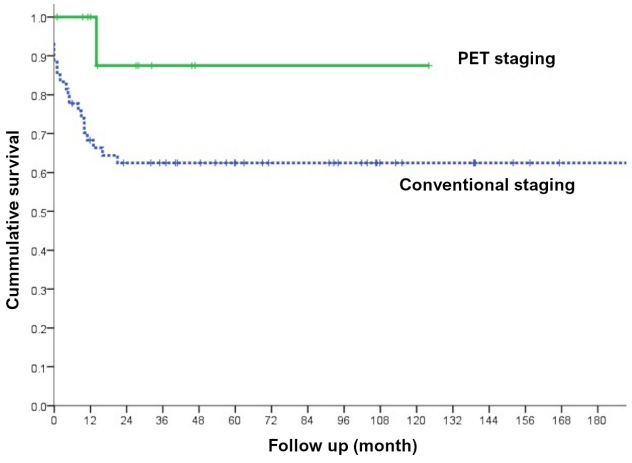

Figure 4. Kaplan-Meier analysis proved significantly improved disease-free survival with PET staging for stage III.

Table 3. Univariate Cox proportional hazards regressions analyses for overall survival (OS), loco-regional control (LRC), disease-free survival (DFS).

Prognostic factors	OS	LRC	DFS
	HR (95% CI), p value	HR (95% CI), p value	HR (95% CI), p value
Gender (F vs M)	1.458 (0.728–2.914), p=0.286	0.570 (0.321–1.012), p=0.055	0.752 (0.502–1.128), p=0.169
Age ≤ 60 vs > 60	1.701 (0.911–3.175), p=0.096	0.614 (0.195–1.936), p=0.405	0.652 (0.317–1.343), p=0.246
Clinical stage (I/II vs III)	1.026 (0.564–1.867), p=0.933	2,815 (0.762–10.406), p=0.121	**2.269 (1.039–4.955), p=0.040**
Clinical stage			
I vs II	1.478 (0.535–4.083), p=0.451	55184.553 (0.000–1.2E166, p=0.954	1.894 (0.393–9.118), p=0.426
I vs III	1.361 (0.57–3.589), p=0.533	99067 (0.000–2.30E166), p=0.952	3.441 (0.807–14.861), p=0.095)
T1/2 vs T3/4	1.220 (0.559–2.257), p=0.527	**4.842 (1.310–17.895), p=0.018**	**3.021 (1.437–6.354), p=0.004**
N0 vs N1 (UICC 8th edition)	1.181 (0.649–2.149), p=0.586	2,275 (0.685–7.558), p=0.180	**2.363 (1.106–5.050), p=0.026**
Histology grading G1/2 vs G3/4	1.210 (0.579–2.527), p=0.612	1.109 (0.248–4.957), p=0.892	1.513 (0.655–3.493), p=0.332
Histology type (squamous vs basaloid)	0.790 (0.388–1.609), p=0.517	1.053 (0.285–3.891), p=0.939	0.942 (0.419–2.117), p=0.884
WHO performance status			
0 vs 1	1.697 (0.649–4.440), p=0.281	**5.875 (1.185–29.128), p=0.030**	2.555 (0.951–6.864), p=0.063
0 vs 2	5.902 (0.666–52.291), p=0.111	0.000 (0.000–NS), p=0.990	3.476 (0.416–29.048), p=0.250
Pre-treatment SCC oncomarker elevation	1.289 (0.211–7.882), p=0.784	3.582 (0.373–34.577), p=0.268	2.975 (0.577–15.342), p=0.193
Chemo+RT vs RT	0.608 (0.319–1.162), p=0.132	0.355 (0.114–1.102), p=0.073	0.913 (0.406–2.055), p=0.826
Smoking history (no vs yes)	1.017 (0.488–2.121), p=0.964	2.501 (0.484–12.921), p=0.274	0.949 (0.385–2.342), p=0.910
RT technique (3D-CRT vs IMRT)	0.473 (0.164–1.361), p=0.165	0.481 (0.105–2.202), p=0.345	0.462 (0.176–1.209), p=0.116
PET/CT staging vs conventional staging	0.179 (0.024–1.318), p=0.091	0.034 (0.000–14.117), p=0.272	0.126 (0.170–0.927), p=0.042

Table 4. Multivariate analyses for overall survival (OS), loco-regional control (LRC), disease-free survival (DFS).

Prognostic factors	OS	LRC	DFS
	HR (95% CI), p value	HR (95% CI), p value	HR (95% CI), p value
Gender (F vs. M)	n.d.	p=0.655	n.d.
Age ≤ 60 vs > 60	p=0.374	n.d.	n.d.
Clinical stage (I/II vs III)	n.d.	p=0.828	p=0.079
T1/2 vs T3/4	n.d.	p=0.232	p=0.068
N0 vs N1 (UICC 8th edition)	n.d.	p=0.792	p=0.076
Histology grading G1/2 vs G3/4	n.d.	n.d.	n.d.
Histology type (squamous vs basaloid)	n.d.	n.d.	n.d.
WHO performance status			
0 vs 1	p=0.352	**8.101 (1.585–41476), p=0.012** 0,000 (not specified)	p=0.063
0 vs 2	p=0.114	p=0.991	p=0.427
Pre-treatment SCC oncomarker elevation	n.d.	n.d.	p=0.572
Chemo+RT vs RT	p=0.129	**5.164 (1.241–21.483), p=0.024**	n.d.
Smoking history (no vs yes)	n.d.	n.d.	n.d.
RT technique (3D-CRT vs IMRT)	p=0.556	n.d.	p=0.402
PET/CT staging vs conventional staging	p=0.131	n.d.	**13.186 (1.578–110.164), p=0.017**

in the conventional staging group, but it influenced neither OS, DFS nor LRC.

LRC in multivariate analysis was affected with initial WHO performance status and chemoradiotherapy, while the multivariate analysis revealed no independent prognostic factors for OS (Table 4).

Safety. As expected, acute postradiation reactions occurred more frequently in patients treated with concomitant chemotherapy. Grade 3/4 leukopenia occurred in 10% and grade 3/4 gastrointestinal toxicity in 8% of patients in the chemoradiation group. One patient (1.1%) died of febrile neutropenia. Grade 3/4 skin toxicity appeared in 55% of patients with no difference between the chemoradiation and radiation-only subgroups. No other grade 3–5 toxicity appeared in the radiotherapy-only subgroup. There was no grade ≥3 acute genitourinary toxicity.

Late gastrointestinal toxicity grade 3/4 occurred in 7.6% and late genitourinary toxicity grade 3/4 in 10.4% of patients.

Discussion

FDG-PET/CT has been proven to have a significant impact on staging [16, 25]. PET/CT had superior sensitivity for regional node staging compared to conventional imaging

(89% vs 62%) and led to changed treatment management in 16% of cases [17]. Similarly, the sensitivity of FDG-PET/CT resulted in modified RT treatment plans in 12.5 to 59.3% of patients [17, 19, 26]. Lower stages were influenced less than locally advanced disease (23% of T2 and 40% of T3/4) [17]. The specificity of PET/CT, as assessed by fine needle aspiration (FNA) biopsy, was 83%. The positive predictive value was 43% [27] suggesting overestimation of lymph node positivity in some cases. However, negative FNA might not conclusively rule out subclinical disease and comparative studies between FNA and pelvic lymphadenectomy are lacking. The above results have been recently corroborated by a study showing the superiority of sentinel lymph node biopsy over PET/CT in predicting survival [28]. An emerging application of CT/PET in anal cancer is the use of nonconventional PET parameters that show better prognostic potential than standardized uptake values [29].

The impact of PET integration into the radiotherapy planning on survival has not been evaluated yet. Complete response on PET/CT appeared to be a good prognostic factor for OS and PFS [26]. The recommended interval from RT to response evaluation was at least 3 months [30].

In our study, all patients received increased radiation dose to metabolically active lymph nodes. At the same time, information from PET/CT allowed reduction of dose to regional not affected lymph nodes areas in N0 disease (including CT-enlarged but FDG-negative inguinal lymph nodes [23] and including all T1–4 stages). We achieved better treatment outcome measures (5-year DFS, LC, and colostomy free interval: 73%, 90%, and 86%) than reported in RTOG 9811 (5-year DFS, LC, and CFI: 68%, 80%, and 72%) and RTOG 0529 trials (5-year DFS, LC, and CFI: 68%, 84%, and 74%), which could be explained with inclusion of stage I tumor (not included in RTOG 0529) and through exact radiotherapy treatment planning and lymph nodes dose distribution according to tumor extent. The p16 positivity of all tumors in our series could provide another explanation as such phenotype has been linked to better prognosis [31]. We found that staging PET/CT improves significantly DFS but not LRC, strongly suggesting that the improvement is due to decreased risk of distant metastases after precise pelvic radiotherapy with the increased dose to affected PET/CT positive lymph nodes.

Limitations of the present study include a non-randomized, retrospective design and the use of historical controls. The time-based identification of cohorts could have been associated with several confounders impacting outcomes, including improved management of toxicities, advances in radiotherapy techniques, and incremental experience gained by the treating team.

In conclusion, PET/CT is an important staging tool in squamous cell anal cancer and significantly improves DFS by improving the accuracy of nodal disease extent, which allowed tailored adjustment of RT dose to regional lymph nodes without detriment to LRC. These results suggest a role for PET/CT not only in routine staging but especially in RT planning in patients with localized and locally advanced squamous cell anal cancer.

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