Eur J Nucl Med Mol Imaging (2017) 44:63–70
DOI 10.1007/s00259-016-3475-5

ORIGINAL ARTICLE

Prognostic impact of tumour burden assessed by metabolic tumour volume on FDG PET/CT in anal canal cancer

Mathieu Gauthé[1,2] · Marion Richard-Molard[3] · Juliette Fayard[4] · Jean-Louis Alberini[1] · Wulfran Cacheux[4] · Astrid Lièvre[4,5,6]

Received: 5 April 2016 / Accepted: 25 July 2016 / Published online: 9 August 2016
© Springer-Verlag Berlin Heidelberg 2016

Abstract
Purpose The aim of this study was to confirm the prognostic value of metabolic tumour volume (MTV) at the primary site on initial work-up FDG PET/CT in patients with squamous cell carcinoma (SCC) of the anal canal.
Methods Patients with a recent diagnosis of SCC of the anal canal without metastases undergoing PET/CT for initial work-up and treated with (chemo)radiotherapy were retrospectively reviewed. Computer-aided MTV and SUVmax were determined. Survival rates were estimated using the Kaplan-Meier method. Cox regression analysis was used to evaluate prognostic variables of progression-free survival and overall survival (OS).
Results The study group comprised 75 patients who had an initial work-up PET/CT. Five patients (6.7 %) had stage I disease, 22 (29.3 %) stage II disease, 20 (26.7 %) stage IIIA disease, and 28 (37.3 %) stage IIIB disease. Median follow-up was 51 months (range 10 – 117 months). Global 4-year OS was 82.7 %, ranging from 100 % in patients with stage I disease to 75 % in patients with stage IIIB disease. MTV at the primary site was significantly and independently correlated with OS ($p < 0.05$), as patients with MTV less than 7 cm^3 had a better prognosis. SUVmax was not correlated with survival parameters. Metabolic involvement of the inguinal lymph nodes was also correlated with a poor outcome in the univariate analysis ($p < 0.05$).
Conclusion MTV at the primary site is a prognostic biomarker in anal canal cancer. Hypermetabolic inguinal lymph nodes also appear to be correlated with survival.

Keywords Anal cancer · FDG · PET/CT · Metabolic tumour volume · Initial work-up

Introduction

Squamous cell carcinoma (SCC) of the anal canal is a rare but increasingly common malignancy, accounting for 0.4 % of all malignancies and 0.2 % of all cancer deaths [1]. In the majority of patients anal SCC is diagnosed at a localized or locally advanced stage (only 5 % have metastatic disease at the time of diagnosis) [1, 2] and concurrent chemoradiotherapy (CRT) is the standard treatment in this setting [3]. The 5-year survival in patients with all clinical stages of this disease is 65.5 %, ranging from 79.7 % in those with localized disease to 32 % in those with metastatic disease [1, 2]. The three major prognostic factors for progression-free survival (PFS) and overall survival (OS) are site (anal canal vs. perianal skin), size (primary tumours <2 cm in diameter are associated with a better prognosis), and nodal status [4]. Pretreatment prognostic factors able to more accurately identify patients at high risk of recurrence who may benefit from optimized treatment are therefore lacking. There is increasing evidence of the usefulness of ^{18}F-FDG PET/CT in the management of anal SCC.

A recent study conducted in 39 patients showed that total metabolic tumour volume (MTV), defined as the

✉ Mathieu Gauthé
mathieugauthe@yahoo.fr

1 Médecine Nucléaire, Institut Curie, Saint-Cloud, France
2 Médecine Nucléaire, Hôpital Tenon, 4 rue de la Chine, 75020 Paris, France
3 Radiothérapie, Institut Curie, Saint-Cloud, France
4 Oncologie Médicale, Institut Curie, Saint-Cloud, France
5 Service des Maladies de l'Appareil Digestif, CHU Pontchaillou, Rennes, France
6 Université Rennes 1, Rennes, France

sum of the volumes above a standardized uptake value of 50 % of the SUVmax within the primary tumour and involved nodes, may be a reliable prognostic marker, as a higher pretreatment total MTV was associated with a poorer OS, PFS and event-free survival [5]. MTV that reflects the volume of tumour tissue with hypermetabolic activity on PET is an increasingly valuable biomarker in several solid malignancies [5–8]. The authors also concluded that more studies on this parameter are needed to validate these findings [5]. The National Comprehensive Cancer Network (NCCN) recommends considering PET/CT for staging T2–T4 N0 or any N+ anal canal cancer [9].

The aim of this study was to confirm the prognostic value of pretreatment MTV measured at the primary site on initial work-up FDG PET/CT in a large series of patients with localized or locally advanced anal SCC treated with radiotherapy (RT) or CRT.

Materials and methods

Patients

All patients referred to one of the two hospitals of our institution with anal SCC between September 2005 and July 2013 were retrospectively reviewed. Inclusion criteria were patients undergoing pretreatment staging PET/CT for a recent diagnosis of localized anal SCC, histologically documented and not previously treated. Exclusion criteria were other histological types of anal canal tumours and perianal skin tumours, previously treated anal tumours, patients undergoing PET/CT imaging only during or after RT/CRT and patients with distant metastases (stage IV).

This study was conducted in accordance with the principles of the amended Declaration of Helsinki and was approved by the institutional review board; the need for written informed consent was waived.

Initial work-up and patient staging

Initial work-up of patients, including transanal ultrasonography (TAUS), and/or pelvic MRI and/or contrast-enhanced CT (CE-CT) of the chest, abdomen and pelvis, was recorded. All patients were restaged according to the AJCC classification [2] using all available imaging studies. The diagnosis of inguinal node involvement was cytologically confirmed when lesions were ambiguous on clinical examination and/or imaging work-up.

Treatment

Patients were treated according to national guidelines published in the *Thésaurus national de cancérologie digestive* (French Digestive Oncology Thesaurus) [10]. Stage I and low-risk stage II (T2 ≤ 3cm N0) cancers were treated exclusively with external RT (total dose 45 Gy plus a boost dose of 20 Gy to the primary target volume by brachytherapy or external RT). High-risk stage II (T2 > 3cm N0 and T3 N0) and stage III (A and B) cancers were treated with concurrent CRT, comprising pelvic external RT (total dose 45 Gy plus a boost dose of 20 Gy to the primary target volume by brachytherapy or external RT) and 5-fluorouracil (5FU)/cisplatin or 5FU/mitomycin C chemotherapy (choice of regimen left to the discretion of the referring physician after treatment plan validation in a multidisciplinary meeting).

PET/CT protocol

PET/CT scans were performed before treatment. All patients fasted for at least 6 h before the examination and blood glucose levels were determined (normal range 4.4 – 6.7 mmol/l). Standard whole-body PET/CT (Discovery D690; GE Healthcare) was performed from the vertex to the mid-thigh 60 min after intravenous administration of FDG (3 – 4 MBq/kg) with imaging times of 3 to 5 min per bed position depending on the patient's weight. A low-dose CT scan without contrast enhancement was performed according to a standardized protocol for attenuation correction and anatomical localization prior to PET acquisition. Images were reconstructed using the OSEM (ordered-subsets expectation maximization) weighted method based on two iterations and 24 subsets.

PET/CT interpretation

Computer-aided MTV and SUVmax were calculated using dedicated software (ADW Workstation; GE Healthcare). PET/CT images were interpreted in the axial, coronal, and sagittal planes. SUVmax was determined according to the standard formula, calculating activity in the volume of interest (VOI) from the input data recorded as injected activity (becquerels per millilitre) or injected dose (becquerels per kilogram body weight), and corrected for time delay. All PET/CT images were reviewed twice by the same experienced nuclear medicine physician who was blinded to the clinical data.

The primary site was identified as abnormal focal uptake in the anal canal, with or without a corresponding anatomical lesion on CT. MTV was defined as the hypermetabolic tissue volume with a cut-off greater than 50 % of SUVmax at the primary site. SUVmax and MTV values were determined automatically after a semiautomatic determination of the VOI around the anal canal tumour by the nuclear medicine physician, excluding the bladder and hypermetabolic lymph nodes. The 50 % cut-off was chosen on the basis of numerous studies of

tumours in a variety of sites demonstrating that MTV defined using a 50 % cut-off is significantly correlated with patient outcome [5–8]. Lymph node extension on PET/CT was classified according to four anatomical areas (based on the TNM classification): perirectal, pelvic (internal and external iliac lymph nodes), inguinal and presacral. Criteria for positives nodes were abnormal FDG uptake defined as greater than mediastinal uptake, and/or an abnormal anatomical structure on CT defined as greater than 15 mm in shortest diameter, asymmetrically enlarged, or with evidence of central necrosis.

Patient follow-up

Patients were followed up at least weekly during treatment. After completing therapy, they were evaluated clinically every 3 to 4 months for 2 years, then every 6 months for 3 years, and annually thereafter. A CE-CT scan of the chest, abdomen and pelvis was performed annually [10]. Persistent disease was defined as histologically proven residual disease within 6 months after completion of treatment. After a complete response to RT or CRT, when clinical examination and/or imaging revealed signs of local or metastatic disease, biopsies of suspicious lesions were performed, whenever feasible, to confirm tumour recurrence.

Statistical analysis

Data were analysed using R software (2014; R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria). Survival rates were estimated using the Kaplan-Meier method. PFS was calculated as the time from the date of initiation of RT or CRT to the date of histologically documented recurrence or persistent disease within 6 months after completion of treatment. OS was calculated from the date of initiation of RT or CRT to the date of death from any cause or last follow-up. Survival curves were compared using the log-rank test. Time-dependent receiver operating characteristic (ROC) analysis was used to determine area under the curve and cut-off values to estimate the prognostic ability of MTV and SUVmax. Cox regression univariate analysis was used to evaluate prognostic variables for prediction of PFS and OS. Cox regression multivariate analysis was performed to determine the associations between risk factors identified in the univariate analysis ($p < 0.05$) adjusted for confounders and outcome. The prognostic variables analysed included age at diagnosis, gender, TN (tumour node) status and clinical stage, and lymph node extension for each anatomical area on PET/CT. A p value less than 0.05 was considered to be statistically significant.

Results

Patient and tumour characteristics

Between September 2005 and July 2013, 75 patients had an initial work-up FDG PET/CT for anal SCC. Patient characteristics are summarized in Table 1.

In addition to PET/CT for initial imaging work-up, 86.7 % of patients underwent TAUS and 77.3 % CE-CT of the chest, abdomen and pelvis, and more than half of the patients had pelvic MRI (Table 2). Overall, 13 patients had hypermetabolic inguinal lymph nodes on PET/CT. Tumour involvement was cytologically confirmed in six patients. In the other seven patients, the diagnosis was based on clinical examination with (five patients) or without (two patients) pelvic MRI. Each diagnosis of inguinal lymph node involvement was finally validated in a multidisciplinary meeting.

Most patients (77.3 %) received concurrent CRT, combining external RT (median radiation dose to the primary tumour 65 ± 6.6 Gy) and chemotherapy, mostly (in 48 patients) with a 5FU/cisplatin based combination (Table 2).

Follow-up, survival and prognostic factors

Follow-up Median follow-up was 51 months (range 10 – 117 months). Median PFS and OS according to T, N and stage groups are summarized in Table 3. OS rate at 4 years was 82.7 % (100 %, 91 %, 80 % and 75 % in patients with stage I, II, IIIA and IIIB disease, respectively). Seven patients (9 %) did not achieve a complete response to RT or CRT. Eleven patients (14.7 %) relapsed (eight had locoregional relapse amenable to salvage surgery and three had unresectable or distant metastatic relapse). Thirteen patients died, 12 from anal canal cancer and 1 from metastatic urothelial carcinoma. One patient was lost to follow-up after 35 months of follow-up.

Kaplan-Meier analysis of MTV and SUVmax The median injected activity, imaging time and blood glucose serum level before FDG injection were 4.4 ± 0.8 MBq/kg, 60 ± 11 min and 5.3 ± 0.9 mmol/l, respectively. No FDG extravasation at the injection site was recorded. From the ROC analysis, the MTV cut-off value was 7 cm^3 (AUC 0.73; $p = 0.009$) and the SUVmax cut-off value was 18 (AUC 0.59; $p = 0.31$) at the primary site. MTV at the primary site of less than 7 cm^3 was significantly associated with OS ($chi^2 = 11.276$; $p = 0.01$; Fig. 1), but was not significantly associated with PFS ($chi^2 = 3.313$; $p = 0.07$; Fig. 2). There were no significant differences in PFS or OS according to the defined cut-off value for SUVmax.

Univariate analysis MTV at the primary site was a significant predictor of OS ($p = 0.0011$), but not PFS. The presence of

Table 1 Patient and tumour characteristics

Characteristic	Value
No. of patients	75
Male	8 (10.7 %)
Female	67 (89.3 %)
Age (years)	
Median	63.8 ± 9.9
Range	40 – 88
HIV-positive	2 (2.6 %)
Tumour stage	
I	5 (6.7 %)
II	22 (29.3 %)
IIIA	20 (26.7 %)
IIIB	28 (37.3 %)
TNM stage	
T1	8 (10.7 %)
T2	36 (48 %)
T3	21 (28 %)
T4	10 (13.3 %)
N0	29 (38.7 %)
N1	21 (28 %)
N2	9 (12 %)
N3	16 (21.3 %)

hypermetabolic inguinal lymph nodes on PET/CT was correlated with a poorer PFS ($p = 0.009$) and OS ($p = 0.04$). An advanced T stage (T3/T4) was also correlated with PFS ($p = 0.048$) and OS ($p = 0.034$; Tables 4 and 5). HIV status was not analysed, as the study population included only two HIV-positive patients.

Table 2 Initial work-up and type of treatment

Factor	No. (%) of patients
Initial imaging work-up	
PET/CT	75 (100 %)
Pelvic MRI	44 (58.7 %)
Contrast-enhanced CT	58 (77.3 %)
Transanal ultrasonography	65 (86.7 %)
Lymph node extension on PET/CT	
Perirectal	23 (30.6 %)
Pelvic	10 (13.3 %)
Inguinal	13 (17.3 %)
Presacral	8 (10.6 %)
Radio(chemo)therapy	
Exclusive radiotherapy	17 (22.6 %)
Concurrent chemoradiotherapy	58 (77.3 %)
Cisplatin-based	48
Mitomycin-C-based	7
Capecitabine alone	3

Multivariate analysis Multivariate analysis was performed using the predictors identified as significant in the univariate analysis. After adjustment for MTV at the primary site, hypermetabolic lymph nodes on PET/CT and T stage for PFS and OS, MTV at the primary site was found to be an independent predictive factor for OS ($p = 0.028$; Tables 4 and 5). No other factors were statistically significant for either PFS or OS.

Discussion

MTV is an increasingly valuable biomarker for malignancies in multiple sites [6–8]. In this study, MTV was calculated using a cut-off of 50 % on the basis of numerous studies of tumours in a variety of sites showing that that this parameter is significantly correlated with patient outcome [5–8]. In this study, patients with an MTV at the primary site greater than 7 cm^3 had a significantly poorer OS. The prognostic value of MTV was stronger than those of TN and stage, and was confirmed in multivariate analysis. Therefore, our results, based on a larger series, support the findings reported of Bazan et al. [5] concerning the value of MTV assessed by FDG PET/CT in patients with anal SCC, although in our study MTV was only determined at the primary site, which we considered to be a simpler method for routine clinical practice.

We secondarily evaluated the prognostic impact of involved lymph nodes according to their anatomical area, as this information may lead to a change in RT fields. Our analysis showed that inguinal lymph node involvement on PET/CT was associated with poorer PFS and OS. Previously published criteria to define a positive PET/CT lymph node were used [11, 12]. As inguinal involvement in anal canal cancer is a known prognostic indicator of locoregional recurrence and a poor OS [13, 14], its predictive significance on PET/CT was expected. Although prophylactic inguinal node irradiation is known to improve locoregional control in patients with locally advanced (T3/T4) tumours, its benefit remains controversial in patients with early-stage anal tumours (T1/T2) without nodal involvement, and there is no consensus about its systematic implementation [13–15]. However, inguinal irradiation may lead to severe morbidity. Therefore, the potential reduction in the risk of isolated inguinal recurrence with inguinal irradiation must be balanced against a higher risk of radiation-related side effects, and it is therefore crucial to improve the selection of patients who may benefit from this treatment.

The value of FDG PET/CT for staging anal cancer, particularly for involved lymph node detection, has been shown [11]. Excluding perirectal lymph nodes for which some small nodes can be missed, we consider that most other pelvic lymph nodes were sampled. Thus, the presence of positive inguinal nodes on PET/CT may be an indication for specific inguinal irradiation. We assume that other lymph node sites were not prognostic because they

Table 3 Survival according to AJCC tumour (T) and nodal (N) classification and stage

Stage	No. of patients	Progression-free survival (months)		Overall survival (months)	
		Median	95 % CI	Median	95 % CI
Tumour stage					
I	5	55	36 – 85	60	40 – 89
II	22	45	35 – 60	59	46 – 68
IIIA	20	47.5	31 – 60	51	35 – 62.5
IIIB	28	35	28.5 – 53	42	36 – 59
T stage					
T1	8	57	41 – 85	64.5	45 – 89
T2	36	45	35 – 45	53	44 – 59
T3	21	33	11.5 – 54	43	32.5 – 68
T4	10	45	8 – 60	49.5	25 – 72
N stage					
N0	29	47	36 – 60	60	47 – 67
N1	21	50	36.5 – 56	55	40.5 – 68
N2	9	32	6 – 64	36	24.5 – 102
N3	16	33.5	24.5 – 56	40.5	36.5 – 65

are systematically included in the RT fields and therefore treated, regardless of disease stage. Finally, false-positive findings may occur in reactive nodes, especially in HIV-positive patients [11], but as there were only two HIV-positive patients in our study, this possibility could not have affected the results. If the prognostic significance of these metabolic parameters was validated, they could indicate the need for more aggressive treatment, such as adequate inguinal irradiation and chemotherapy dose escalation or intensification in patients with pathological inguinal lymph nodes and/or MTV at the anal primary site of >7 cm^3.

As previously reported, advanced T stage was correlated with a poorer PFS and OS in the univariate analysis. However, this prognostic impact was not confirmed in the multivariate analysis, which may have been due to a lack of power resulting from the small size of our population and the imbalance between the stage groups (T1 and T4

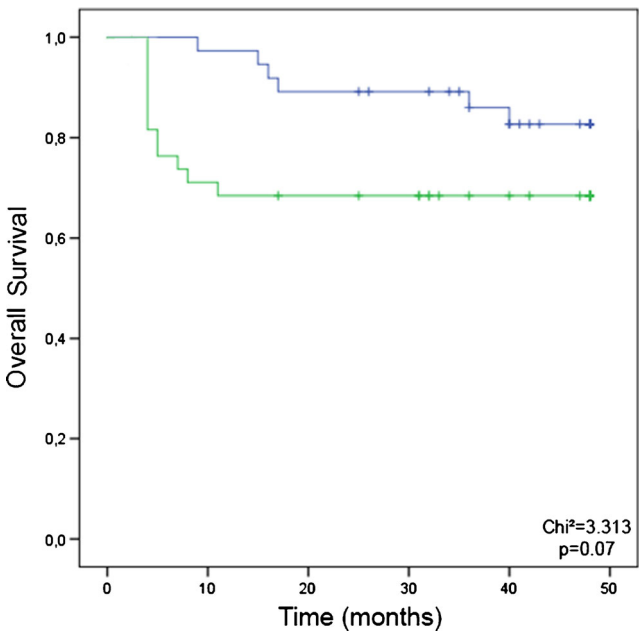

Fig. 1 Kaplan-Meier analysis of OS in relation to MTV at the primary site. The *green line* represents patients with MTV >7 cm^3; the *blue line* represents patients with MTV ≤7 cm^3. *Bars* represent censored individuals

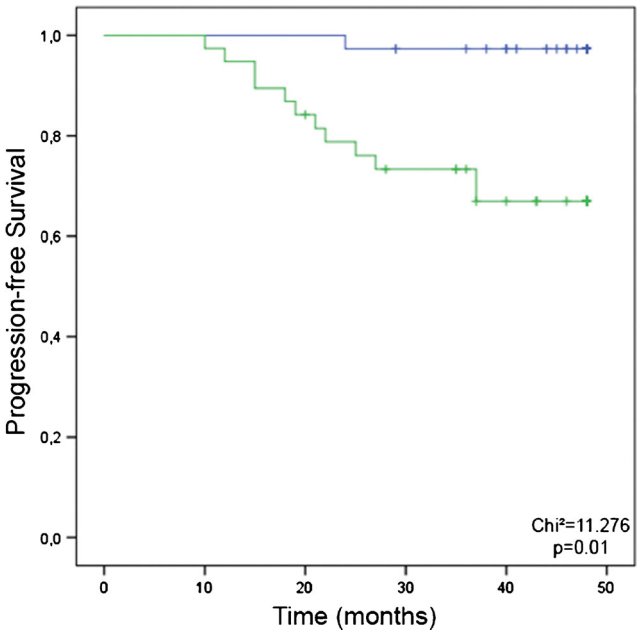

Fig. 2 Kaplan-Meier analysis of PFS in relation to MTV at the primary site. The *green line* represents patients with MTV >7 cm^3; the *blue line* represents patients with MTV ≤7 cm^3. *Bars* represent censored individuals

Table 4 Prognostic significance of the tested parameters in Cox univariate and multivariate analyses for progression-free survival

Variable	Progression-free survival (months), median (95 % CI)	Hazard ratio	*p* value
Univariate analysis			
Age at diagnosis (> vs. ≤65 years)	41 (32 – 50)/42.5 (36 – 56)	0.745	0.557
Sex (female vs. male)	43 (36 – 54)/35.5 (9 – 55)	0.575	0.382
MTV at primary site (> vs. ≤7 cm^3)	34.5 (25 – 52)/49 (40 – 60)	2.402	0.080
SUVmax at primary site (> vs. ≤18)	44.5 (32 – 77)/42 (34 – 52)	1.098	0.882
T stage (T3/T4 vs. T1/T2)	36 (24 – 54)/47.5 (40 – 55)	2.608	0.048
Nodal status (positive vs. negative)	41 (32 – 54)/47 (36 – 60)	1.083	0.870
Clinical stage (IIIA/IIIB vs. I/II)	41 (32 – 45)/49 (36 – 60)	1.263	0.641
Hypermetabolic nodes on PET/CT (positive vs. negative)			
Perirectal ($n = 23$)	42 (31 – 58.5)/42 (35 – 55)	0.717	0.558
Locoregional within pelvis ($n = 10$)	36 (5 – 68)/45 (36 – 54)	1.540	0.495
Inguinal ($n = 13$)	25 (5 – 36)/48.5 (40 – 55)	3.087	0.026
Presacral ($n = 8$)	46 (32 – 112)/42 (36 – 50)	0.041	0.323
Multivariate analysis			
MTV at primary site (> vs. ≤7 cm^3)		1.690	0.360
Inguinal lymph nodes on PET/CT (positive vs. negative)		2.118	0.192
T stage (T3/T4 vs. T1/T2)		1.512	0.500

were notably under-represented). Tumour size >5 cm has been reported to be a stronger prognostic factor in anal carcinoma [3, 16, 17]. Unfortunately, these findings were not available at the time of our study.

Physiological uptake in the gastrointestinal tract is frequently observed and may complicate the detection of digestive cancers. Malignancy may be differentiated from a benign lesion or physiological uptake using combined PET/CT imaging. We detected all primary sites even though T1 lesions may be missed on PET/CT. We emphasize that our series included only a small number of patients with T1 anal SCC for which physiological artefact could have interfered with the interpretation. This point may be a limitation of our study.

Table 5 Prognostic significance of the tested parameters in Cox univariate and multivariate analyses for overall survival

Variable	Overall survival (months), median (95 % CI)	Hazard ratio	*p* value
Univariate analysis			
Age at diagnosis (> vs. ≤65 years)	45 (36 – 55)/58 (44.5 – 65	1.853	0.268
Sex (female vs. male)	51 (44 – 59)/47 (24 – 68	0.576	0.474
MTV at primary site (> vs. ≤7 cm^3)	41.5 (35 – 56)/57 (47 – 68	14.14	0.011
SUVmax at primary site (> vs. ≤18)	59.5 (36 – 86)/51 (43 – 59	1.008	0.992
T stage (T3/T4 vs. T1/T2)	43 (37 – 66)/55 (45 – 62	3.585	0.034
Nodal status (positive vs. negative)	45 (37 – 57)/60 (46 – 67	2.273	0.213
Clinical stage (IIIA/IIIB vs. I/II)	45 (37 – 57)/60 (46 – 68	3.435	0.109
Hypermetabolic nodes on PET/CT (positive vs. negative)			
Perirectal ($n = 23$)	46 (41 – 68)/53 (42 – 61.5	0.457	0.308
Locoregional within pelvis ($n = 10$)	43 (38 – 72)/53 (44.5 – 59.5	0.583	0.606
Inguinal ($n = 13$)	36 (24.5 – 43)/55.5 (46 – 64	4.457	0.008
Presacral ($n = 8$)	49.5 (37 – 117)/51 (44 – 59	0.631	0.658
Multivariate analysis			
MTV at primary site (> vs. ≤7 cm^3)		10.875	0.028
Inguinal lymph nodes on PET/CT (positive vs. negative)		2.579	0.126
T stage (T3/T4 vs. T1/T2)		1.055	0.937

Several studies have shown that SUVmax is not a reliable predictor of outcome, and as expected, no correlation was observed between SUVmax and PFS or OS in our study. This can be explained by the presence of inflammation, which can interfere with SUVmax values and lead to its lack of prognostic significance. Moreover, heterogeneity in PET/CT acquisition parameters, such as injected activities, imaging time, blood glucose serum levels before FDG injection and presence of extravasation, might have contributed to the absence of a significant correlation between SUVmax and PFS or OS. We consider that this consideration would not have interfered with the findings of our study as the acquisition parameters were quite uniform.

CRT is the cornerstone of curative therapy for locally advanced anal carcinoma. The 5FU-mitomycin-C association is the historical standard combination that remains the preferred standard of care [16]. However, 5FU/cisplatin is a valid alternative, which is frequently used by our institution's radiation oncologists. The recent randomized phase III study ACTII demonstrated the equivalence of the two CRT regimens in terms of complete response and local control, with slightly lower myelotoxicity in the 5FU/cisplatin arm [18]. In our study, these two different chemotherapy regimens were used. The choice of chemotherapy was left to the discretion of the referring physician, but the 5FU/cisplatin combination was prescribed in most patients for several reasons: the fear of mitomycin-C-related toxicity by some physicians, the proven efficacy of 5FU/cisplatin shown in a phase II study [19], and the habits of the physicians who actively participated to the Unicancer Accord 03 trial [20]. However, the trend has recently been changing following the results of the ACTII trial that failed to demonstrate the superiority of 5FU/cisplatin over 5FU/mitomycin-C [18], that should remain standard treatment in combination with RT.

Furthermore, the impact of the CRT regimen on outcome was not assessed because of the disequilibrium between the 2 groups with only seven patients receiving mitomycin-C-based CRT in our study. Because of the small sample size no conclusion can be drawn on this question which has already been addressed more appropriately and much more reliably in the large phase III ACTII trial. Patients with metastatic stage IV disease were excluded from this study because, in contrast with earlier stages, they are not treated by exclusive RT or CRT.

A recent review emphasized the increasing use of FDG PET/CT in anal canal cancer [21]. The NCCN also recommends PET/CT for RT treatment planning [9] and FDG PET/CT can also be used to detect additional sites of disease so that unnecessary salvage surgery after initial CRT can be avoided [21]. Some studies have highlighted the impact of posttreatment (>8 weeks) PET/CT to confirm complete response to CRT by showing that a partial metabolic response in the primary anal tumour, assessed in terms of SUVmax, after completion of CRT is associated with a poorer PFS and OS compared with patients with a complete metabolic response [12, 21–23]. In two studies, a PET response was a stronger predictor of survival than pretreatment T or N classification [12, 24]. Moreover, PET/CT assessment 3 months after CRT has been reported to have a sensitivity of 100 %, a specificity of 97.4 %, a positive predictive value of 66 %, and a negative predictive value of 100 % for the detection of persistent disease [25]. No data are available concerning the value of early assessment of metabolic response during CRT by PET/CT.

The main limitations of this study are its retrospective design, and the long inclusion period due to the rarity of anal SCC. Moreover, even if our series was the largest ever reported on the prognostic impact of pretherapeutic MTV in anal carcinoma, the sample size was still small, which could explain why we found a significant difference in OS but no significant difference in PFS. Differences in PET/CT imaging protocols between institutions could also have introduced slight variability in MTV measurements. Finally, variation in the treatment received (RT or CRT, different chemotherapy regimens associated with RT) may also have led to bias in our study. Because of these limitations, the prognostic value of pretherapeutic MTV needs to be validated in a larger prospective study.

Conclusion

This study confirmed the value of MTV at the primary site as a prognostic biomarker for OS in anal canal cancer. Metabolic involvement of the inguinal lymph nodes on the initial workup PET/CT also appeared to be correlated with PFS and OS. These metabolic parameters must now be validated in a larger prospective study. As the treatment of most patients with anal canal cancer comprises RT, we consider that PET/CT should be performed for all stages of anal canal cancer in view of the growing evidence of the value of PET/CT in defining RT fields and in indicating the need for more aggressive treatment in patients with hypermetabolic lesions.

Compliance with ethical standards

Funding None.

Conflicts of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments.

Research involving human participants and/or animals For this type of study formal consent is not required.

Informed consent This study was approved by the institutional review board; the need for written informed consent was waived.

References

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. SEER Stat Fact Sheets: Anal Cancer. Bethesda, MD: National Cancer Institute. 2016. http://seer.cancer.gov/statfacts/html/anus.html. Accessed 4 Aug 2016
2. Edge S, Byrd D, Compton CC, Fritz A, Greene FL, Trotti A. AJCC cancer staging manual. 7th ed. New York: Springer; 2010. p. 165–73.
3. Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson 3rd AB, Thomas Jr CR, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. JAMA. 2008;299:1914–21.
4. Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson 3rd AB, Thomas Jr CR, et al. Prognostic factors derived from a prospective database dictate clinical biology of anal cancer: the intergroup trial (RTOG 98-11). Cancer. 2010;116:4007–13.
5. Bazan JG, Koong AC, Kapp DS, Quon A, Graves EE, Loo BW, et al. Metabolic tumor volume predicts disease progression and survival in patients with squamous cell carcinoma of the anal canal. J Nucl Med. 2013;54:27–32.
6. Lee P, Weerasuriya DK, Lavori PW, Quon A, Hara W, Maxim PG, et al. Metabolic tumor burden predicts for disease progression and death in lung cancer. Int J Radiat Oncol Biol Phys. 2007;69:328–33.
7. Dibble EH, Alvarez ACL, Truong M-T, Mercier G, Cook EF, Subramaniam RM. 18F-FDG metabolic tumor volume and total glycolytic activity of oral cavity and oropharyngeal squamous cell cancer: adding value to clinical staging. J Nucl Med. 2012;53:709–15.
8. Schellenberg D, Quon A, Minn AY, Graves EE, Kunz P, Ford JM, et al. 18Fluorodeoxyglucose PET is prognostic of progression-free and overall survival in locally advanced pancreas cancer treated with stereotactic radiotherapy. Int J Radiat Oncol Biol Phys. 2010;77:1420–5.
9. Benson AB 3rd, Venook AP, Bekaii-Saab T, Chan E, Chen YJ, Cooper HS et al. Anal carcinoma. In: NCCN Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network. 2016. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed 4 Aug 2016.
10. Deutsch E, Brunet R, Peiffert D, Salmon R, Siproudhis L, Touboul E. Cancer du canal anal. In: Thésaurus National de Cancérologie Digestive (TNCD). Société Nationale Française de Gastro-Entérologie. 2010. http://www.tncd.org/. Accessed 4 Aug 2016.
11. Cotter SE, Grigsby PW, Siegel BA, Dehdashti F, Malyapa RS, Fleshman JW, et al. FDG-PET/CT in the evaluation of anal carcinoma. Int J Radiat Oncol Biol Phys. 2006;65:720–5.
12. Day FL, Link E, Ngan S, Leong T, Moodie K, Lynch C, et al. FDG-PET metabolic response predicts outcomes in anal cancer managed with chemoradiotherapy. Br J Cancer. 2011;105:498–504.
13. Ortholan C, Resbeut M, Hannoun-Levi J-M, Teissier E, Gerard J-P, Ronchin P, et al. Anal canal cancer: management of inguinal nodes and benefit of prophylactic inguinal irradiation (CORS-03 Study). Int J Radiat Oncol Biol Phys. 2012;82:1988–95.
14. Tomaszewski JM, Link E, Leong T, Heriot A, Vazquez M, Chander S, et al. Twenty-five-year experience with radical chemoradiation for anal cancer. Int J Radiat Oncol Biol Phys. 2012;83:552–8.
15. Zilli T, Betz M, Bieri S, Ris F, Roche B, Roth AD, et al. Elective inguinal node irradiation in early-stage T2N0 anal cancer: prognostic impact on locoregional control. Int J Radiat Oncol. 2013;87:60–6.
16. Gunderson LL, Winter KA, Ajani JA, Pedersen JE, Moughan J, Benson AB, et al. Long-term update of US GI intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol. 2012;30:4344–51.
17. Flam M, John M, Pajak TF, Petrelli N, Myerson R, Doggett S, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. J Clin Oncol. 1996;14:2527–39.
18. James RD, Glynne-Jones R, Meadows HM, Cunningham D, Myint AS, Saunders MP, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 × 2 factorial trial. Lancet Oncol. 2013;14:516–24.
19. Peiffert D, Giovannini M, Ducreux M, Michel P, François E, Lemanski C, et al. High-dose radiation therapy and neoadjuvant plus concomitant chemotherapy with 5-fluorouracil and cisplatin in patients with locally advanced squamous-cell anal canal cancer: final results of a phase II study. Ann Oncol Off J Eur Soc Med Oncol ESMO. 2001;12:397–404.
20. Peiffert D, Tournier-Rangeard L, Gérard J-P, Lemanski C, François E, Giovannini M, et al. Induction chemotherapy and dose intensification of the radiation boost in locally advanced anal canal carcinoma: final analysis of the randomized UNICANCER ACCORD 03 trial. J Clin Oncol. 2012;30:1941–8.
21. Saboo SS, Zukotynski K, Shinagare AB, Krajewski KM, Ramaiya N. Anal carcinoma: FDG PET/CT in staging, response evaluation, and follow-up. Abdom Imaging. 2012;38:728–35.
22. Vercellino L, Montravers F, de Parades V, Huchet V, Kerrou K, Bauer P, et al. Impact of FDG PET/CT in the staging and the follow-up of anal carcinoma. Int J Colorectal Dis. 2010;26:201–10.
23. Schwarz JK, Siegel BA, Dehdashti F, Myerson RJ, Fleshman JW, Grigsby PW. Tumor response and survival predicted by post-therapy FDG-PET/CT in anal cancer. Int J Radiat Oncol Biol Phys. 2008;71:180–6.
24. Kidd EA, Dehdashti F, Siegel BA, Grigsby PW. Anal cancer maximum F-18 fluorodeoxyglucose uptake on positron emission tomography is correlated with prognosis. Radiother Oncol. 2010;95:288–91.
25. Mistrangelo M, Pelosi E, Bellò M, Ricardi U, Milanesi E, Cassoni P, et al. Role of positron emission tomography-computed tomography in the management of anal cancer. Int J Radiat Oncol. 2012;84:66–72.