Radiotherapy and Oncology 136 (2019) 21–28

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Prognostic utility of pre- and post-treatment FDG-PET parameters in anal squamous cell carcinoma

Adele Duimering [a], Terence Riauka [b], Yugmel Nijjar [a], Sunita Ghosh [c], Robert MacEwan [d], Heather Warkentin [b], Dan Schiller [e], Keith Tankel [a], Nawaid Usmani [a], Diane Severin [a], Tirath Nijjar [a], Alysa Fairchild [a], Karen Mulder [c], Corinne Doll [f], Clarence Wong [g], Kurian Joseph [a,*]

[a] Division of Radiation Oncology, Department of Oncology, Cross Cancer Institute; [b] Department of Medical Physics, Cross Cancer Institute; [c] Divison of Medical Oncology, Department of Oncology, Cross Cancer Institute; [d] Department of Oncologic Imaging, Cross Cancer Institute; [e] Department of Surgical Oncology, University of Alberta, Edmonton; [f] Division of Radiation Oncology, Department of Oncology, Tom Baker Cancer Centre, Calgary; and [g] Division of Gastroenterology, University of Alberta, Edmonton, Canada

ARTICLE INFO

Article history:
Received 16 December 2018
Received in revised form 9 March 2019
Accepted 13 March 2019
Available online 4 April 2019

Keywords:
Anal cancer
FDG-PET
Metabolic tumour volume
Intensity-modulated radiation therapy
Prognosis

ABSTRACT

Background and purpose: We prospectively assessed the contributions of PET to initial staging, early detection of treatment failures, and prognostication in patients with anal squamous cell carcinoma (ASCC).

Materials and methods: Consecutive patients with ASCC referred for radical chemoradiotherapy (CRT) consented to undergo FDG-PET imaging pre-treatment and at 3 and 6 months post-treatment. Clinicopathologic data were collected and CT and PET imaging reviewed for contribution to staging and recurrence detection. Maximum standardized uptake value (SUVmax), peak standardized uptake value (SUVpeak), metabolic tumour volume (MTV), and total lesion glycolysis (TLG) were assessed for association with progression-free survival (PFS), cause-specific survival (CSS), and overall survival (OS) using the Kaplan–Meier and Cox regression models.

Results: Between 2009 and 2016, 73 patients with clinical stages I-IIIB ASCC completed curative-intent CRT. Median follow-up was 48 months. 14 patients died and 18 patients experienced disease progression. 4-year PFS, CSS, and OS were 73%, 87%, and 84%, respectively. A pre-treatment MTV >35 cm^3 predicted for worse PFS ($p = 0.011$) and CSS ($p = 0.024$) on univariate and multivariate analyses, employing an MTV definition of voxels $\geq$25% of SUVmax. Higher 6-month post-treatment SUVmax and SUVpeak predicted for worse PFS and OS ($p \leq 0.011$). Pre-treatment SUVmax, SUVpeak, and TLG, and 3-month post-treatment SUVmax and SUVpeak did not significantly correlate with survival outcomes.

Conclusions: Our findings support that pre-treatment MTV provides meaningful prognostic information, with suggestion that an MTV delineation threshold of voxels $\geq$25% of SUVmax is appropriate in the anal region. Post treatment, the combination of clinical examination and PET effectively detected all treatment failures. Higher 6-month post-treatment SUVmax and SUVpeak predicted worse PFS and OS; however, the optimal timing of post-treatment PET imaging remains unclear.

Although anal squamous cell carcinoma (ASCC) remains an uncommon malignancy, representing 0.5% of new cancer cases and 0.2% of cancer deaths in the United States, its incidence is rising worldwide [1,2]. The majority of patients (80%) present with locoregionally confined disease, with treatment achieving five-year survival rates of 64–82% [1,3].

Magnetic resonance imaging (MRI) is the imaging modality of choice for locoregional assessment of ASCC, providing high-resolution multi-planar information for tumour characterization [4,5]. Increasingly, positron emission tomography with the glucose analogue 2-deoxy-2-[^{18}F] fluoro-D-glucose (FDG-PET) has been used in the initial workup of patients with ASCC. 91–98% of primary tumours are visible on PET, versus only 58–59% on CT [6,7]. The USA National Comprehensive Cancer Network and European ESMO-ESSO-ESTRO clinical practice guidelines recommend consideration of pre-treatment PET imaging to aid in pelvic lymph node evaluation [4,8]. PET detects 20% of inguinal lymph nodes that are normal on CT and 23% that are normal on physical examination, thus upstaging 17% of patients [6,7]. PET has also shown superiority to transanal and inguinal ultrasound for lymph node assessment [9]. It follows that PET is an asset in guiding radiotherapeutic management [10].

* Corresponding author at: Department of Radiation Oncology, Cross Cancer Institute, 11560 University Ave, Edmonton, AB T6G 1Z2, Canada.

https://doi.org/10.1016/j.radonc.2019.03.014
0167-8140/

Table 1
Findings of several published studies on the prognostic significance of FDG-PET characteristics in ASCC.

Study, Study Type	Country, Years	No. of patients (No. of events)	Parameter(s) Assessed	Outcome
Kidd et al. [11] 2010, Retrospective	USA, 2003–2007	77 (15 recurrences – local vs. distant not specified; 11 deaths)	**Pre-treatment SUVmax**	SUVmax > 5.6 predicts: - increased lymph node metastases ($p < 0.0001$) - worse 2-year DFS ($p = 0.05$) - increased risk of persistent or recurrent disease on post-therapy FDG-PET performed <4 mo post treatment completion ($p = 0.0402$)
Bazan et al. [12] 2013, Retrospective	USA, 2003–2011	39 (9 with disease progression – 3 local, 5 distant, 1 local & distant; 6 deaths)	**Pre-treatment** **SUVmax** **SUVpeak** **SUVmean** **TGA** **MTV** (total of primary and nodes, with threshold ≥50% of SUVmax)	SUVmax, SUVpeak, and SUVmean were not prognostic for survival outcomes. Higher TGA was associated with worse PFS ($p = 0.006$) and a trend towards worse OS ($p = 0.053$). Patients with MTV > 26 cc had worse 2-year PFS ($p = 0.003$) with a trend towards worse OS ($p = 0.367$). Higher MTV predicts: - worse 2-year OS ($p = 0.04$) - worse 2-year PFS ($p = 0.004$) - worse 2-year EFS ($p = 0.002$)
Deantonio et al. [19] 2015, Prospective	Italy	55	**Pre-treatment** **SUVmax**	SUVmax was not prognostic for survival outcomes.
Gauthé et al. [13] 2017, Retrospective	France, 2005–2013	75 (11 recurrences – 8 locoregional and surgically salvaged, 3 distant or locoregional but unresectable; 13 deaths)	**Pre-treatment** **SUVmax** **MTV** (primary only, with threshold of ≥50% of SUVmax)	SUVmax was not prognostic for survival outcomes. Patients with MTV > 7 cm^3 had worse OS ($p = 0.01$). Higher MTV predicts: - worse 4-year PFS ($p = 0.009$) - worse 4-year OS ($p = 0.04$)
Cardenas et al. [14] 2017, Retrospective	USA, 2003–2013	110 (12 local recurrences (no comment on distant recurrences); 25 deaths)	**Pre- and post-treatment** **SUVmax**	Pre-treatment SUVmax > 7.1 predicts decreased 2-year LR ($p = 0.0296$ on univariate analysis; NSS on multivariate analysis) (**unusual**). 3-month post-treatment SUVmax ≥ 6.1 predicts increased 2-year LR ($p = 0.0013$) and worse 2-year OS ($p = 0.0373$). Pre-to-post-treatment change in SUVmax of ≤−62.3% predicts worse 2-year OS ($p = 0.0298$).
Duimering et al. [present study] 2019, Prospective	Canada, 2009–2016	73 (18 recurrences – 10 local, 7 distant, 1 local & distant; 14 deaths)	**Pre- and post-treatment** **SUVmax** **SUVpeak** **Pre-treatment** **TLG** **MTV** (primary only, with thresholds of ≥25%, ≥40%, ≥50% of SUVmax)	Pre-treatment SUVmax, SUVpeak, and TLG were not prognostic for survival outcomes. Patients with pre-treatment MTV > 35 cm^3 had worse PFS ($p = 0.011$) and CSS ($p = 0.024$), employing an MTV definition of voxels ≥25% of SUVmax. Higher 6-month post-treatment SUVmax and SUVpeak predicted for worse PFS and OS ($p \leq 0.011$). 3-month post-treatment SUVmax and SUVpeak were not prognostic for survival outcomes.

DFS disease-free survival; EFS event-free survival; LR local recurrence; OS overall survival; PFS progression-free survival; TGA total glycolytic activity; TLG total lesion glycolysis.

Beyond informing staging and aiding radiotherapy planning, PET has been shown to provide useful prognostic information (Table 1). A review of 77 patients found higher pre-treatment maximum standardized uptake value (SUVmax) to predict worse 2-year disease-free survival (DFS) [11]. However, two subsequent studies were unable to confirm this finding and suggested that higher pre-treatment metabolic tumour volume (MTV) portends worse progression-free survival (PFS) and overall survival (OS) [12,13]. Total lesion glycolysis (TLG) has also been demonstrated by one small study to correlate with PFS [12]. A recent study assessed post-treatment PET imaging, finding that an SUVmax of ≥6.1 at 3 months post-treatment predicts poor 2-year local control (LC) and OS [14]. This corroborates the conclusions of three qualitative studies, demonstrating that metabolic response to chemoradiotherapy (CRT) is associated with better survival [15–17].

Given these varied results, it remains unclear how prognostic utility compares between SUVmax, TLG, and MTV. No published study has prospectively analysed all of these PET parameters, compared different MTV segmentation methods, and assessed both pre- and post-treatment PET imaging. We sought to achieve these objectives, to comprehensively contribute to the existing literature that may inform future customization of treatment on the basis of PET-derived prognostic factors.

Materials and methods

Patients

With Health Research Ethics Board of Alberta approval, clinicopathologic data were prospectively collected on 73 patients who received definitive CRT at our institution for histologically proven ASCC between 2009 and 2016. Of the 73 patients, 53 were enroled in a local prospective phase II study [18]. Patients who had undergone transanal tumour excision or had distant metastases at presentation were excluded. All patients underwent pre-treatment workup, which included a physical examination, diagnostic CT of the chest, abdomen, and pelvis, FDG-PET/CT (performed a median of 20.5 days prior to the first day of CRT), and core biopsy of inguinal lymph nodes clinically measuring over 1–1.5 cm.

Treatment

Radiation therapy entailed pelvic intensity-modulated radiotherapy in 30 fractions over 6 weeks. A dose of 45 Gy, in 1.5-Gy fractions, was prescribed to at-risk regions, including the mesorectum, ischiorectal fossa, and elective nodal regions (perirectal, inguinal, external and internal iliac to the common iliac vessel bifurcation superiorly, and pre-sacral). A simultaneous integrated boost of 54 Gy, in 1.8-Gy fractions, was prescribed to the primary tumour and involved nodes. The PET images were used at the treating radiation oncologist's discretion to guide target volume delineation. Concurrent chemotherapy consisted of bolus mitomycin C 10 mg/m^2 on days 1 and 29 and infusional 5-fluorouracil 1000 mg/m^2/day on days 1 to 4 and 29 to 32.

Follow-up

Patients were evaluated by history and physical examination at 6 weeks, 3 months, 6 months, 9 months, and 12 months following CRT completion, then at 6-month intervals to a minimum of 5 years. 3-month-post-treatment PET imaging was performed on 68 of the 73 patients, at a median of 85 days (range 39–157 days) following treatment completion. 6-month-post-treatment PET imaging was performed on 50 patients, at a median of 177 days (range 134–242 days) following treatment completion. Clinically suspected recurrences were confirmed by biopsy in 16 of the 18 cases.

PET imaging protocol

^{18}F-FDG-PET/CT scans were acquired on a Biograph mCT 40 scanner (Siemens Medical Solutions) with extended field of view (TrueV option), point spread function modelling (TrueX option), and time of flight acquisition (UltraHD option). After fasting for a minimum of 6 hours, patients were injected 60 minutes (±10 min) prior to their scan with 5.2 MBq/kg of ^{18}F-FDG and imaged for 2–2.5 minutes per bed position depending on patient girth. Patients underwent a low-dose CT scan using Siemens CareDose 4D and 120 kVp, which was used for attenuation and scatter correction in the PET reconstruction algorithm. Attenuation-corrected PET images were reconstructed using the TrueX (HD-PET) algorithm with 3 iterations and 24 subsets, a 2 mm Gaussian filter, and the scatter correction option selected, using 200- by 200-voxel images, 2 mm by 2 mm, with a slice thickness of 2 mm. Low-dose CT images were reconstructed using the I40t kernel and 512- by 512-voxel images, 0.5 mm by 0.5 mm, with a slice thickness of 1.5 mm.

PET analysis

PET images were analysed using HERMES Medical Solutions co-registration and fusion software. On pre-treatment PET scans, SUVmax, peak standardized uptake value (SUVpeak), MTV, and TLG were measured. These parameters are defined in Fig. 1. On post-treatment scans, SUVmax and SUVpeak were measured. All measurements were made within the primary tumour volume; lymph nodes were not analysed. MTV (cm^3) was defined as the volume of contiguous hypermetabolic tissue with a minimum SUV of 50% of the SUVmax within a region of interest that encompassed the anal canal and low rectum. The software-generated MTV was manually

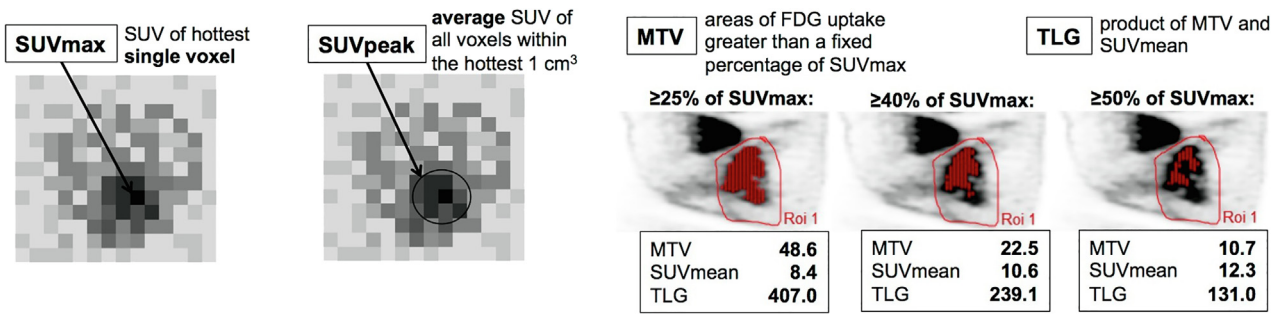

Fig. 1. Definitions of PET parameters: maximum standardized uptake value (SUVmax), peak standardized uptake value (SUVpeak), metabolic tumour volume (MTV) (cm^3) segmented by three different methods (to include voxels ≥ 25%, 40%, or 50% of SUVmax), and total lesion glycolysis (TLG) (cm^3).

"tidied up" to exclude extension of this volume outside of the gastrointestinal tract (e.g. into the bladder). Mean standardized uptake value (SUVmean) was taken to be the mean SUV of all voxels within this primary tumour MTV; the value was generated by the HERMES software. TLG was calculated as the product of the SUVmean and MTV of the primary tumour. As the literature is lacking uniformly accepted definitions of MTV and TLG, these parameters were additionally measured employing thresholds of 25% and 40% of SUVmax. The notations MTV_n and TLG_n will herein be used to denote MTV and TLG employing thresholds of *n* of SUVmax, with *n* representing 25%, 40%, or 50%. SUVpeak was calculated by the software as the average SUV of all voxels within the hottest 1 cubic centimetre constrained by the volume of interest and containing SUVmax.

Statistical analysis

Data were analysed using SPSS Statistics (version 23; IBM Corp.). Descriptive statistics were obtained for the study variables. Mean and standard deviation were reported for continuous variables, and frequency and proportions were reported for categorical variables. OS, PFS, and cause-specific survival (CSS) were analysed using the Kaplan–Meier (KM) estimates. When the medians were not obtained, survival probabilities were reported. Log rank statistics were used to compare more than one KM curve. Hazard ratios (HR) and corresponding 95% confidence intervals were obtained using Cox's proportional hazard model. Univariate and multivariate Cox regression analyses were performed to examine correlation of pre-treatment SUVmax, SUVpeak, MTV, and TLG and 3- and 6-month post-treatment SUVmax and SUVpeak to PFS, OS, and CSS. Receiver-operating-characteristic (ROC) analysis was used to determine cut-points of continuous variables that maximized sensitivity and specificity. PFS was calculated from the date of final radiotherapy fraction to first detection of locoregional or distant disease progression by examination or imaging. OS was calculated from the date of the final radiotherapy fraction to the date of death from any cause. CSS was calculated from the date of the final radiotherapy fraction to the date of death from ASCC. A p-value of <0.05 was considered significant for all statistical analysis.

Results

Patient, tumour, and treatment characteristics

The characteristics of the 73 patients in this study are summarized in Table 2. Most of the patients were female, of median age 59 years (range 37–88). The most frequent stage grouping based on diagnostic CT of the chest, abdomen, and pelvis and physical examination was stage II. PET imaging resulted in increased N stage in 20 patients, increased T stage in 3 patients, and increased overall stage in 16 patients, for a most frequent stage grouping of IIIB. 32 patients had suspected involvement of inguinal lymph node(s) on physical examination or imaging. 20 of these 32 patients underwent inguinal lymph node core biopsy, of which 12 were positive, 7 were negative, and 1 was nondiagnostic.

71 of the 73 patients received CRT. 2 patients had chemotherapy omitted due to poor performance status and received curative-intent radiotherapy alone. The radiation prescription to the primary tumour was 54 Gy in 1.8-Gy fractions for 68 patients and 50.4 Gy in 1.8-Gy fractions for 3 patients. The 2 frail patients for whom chemotherapy was omitted were prescribed 50 Gy and 52.5 Gy, respectively, in 2.5-Gy fractions, with a premeditated treatment break. 72 of the 73 patients completed radiotherapy as prescribed, in 6 cases requiring an unplanned break. 1 patient had radiotherapy aborted following 46.8 Gy due to grade-3 enteritis.

Table 2
Patient characteristics ($N = 73$). TNM staging is per the American Joint Committee on Cancer 7th ed.

Characteristic	No. (%) of patients	
Sex		
Male	22 (30.1)	
Female	51 (69.9)	
Age, years		
Median ± SD (range)	59 ± 10.2 (37–88)	
Stage, AJCC 2010	Derived from CT chest/abdomen/pelvis and physical examination	Derived from PET/CT and physical examination
T stage		
T1	2 (2.7)	2 (2.7)
T2	20 (27.4)	18 (24.7)
T3	46 (63.0)	48 (65.8)
T4	5 (6.8)	5 (6.8)
N stage		
N0	48 (65.8)	33 (45.2)
N1	3 (4.1)	6 (8.2)
N2	14 (19.2)	17 (23.3)
N3	8 (11.0)	17 (23.3)
M stage		
M0	73 (100)	73 (100)
Stage group		
I	2 (2.7)	1 (1.4)
II	42 (57.5)	30 (41.1)
IIIA	7 (9.6)	7 (9.6)
IIIB	22 (30.1)	35 (47.9)
Defunctioning stoma (pre-treatment)	10 (13.7)	
Treatment		
Radiotherapy alone	2 (2.7)	
Chemoradiotherapy	71 (97.3)	
Chemotherapy		
5-FU + 2 cycles of MMC	71 (97.3)	
Required dose modification	19 (26.8)	
Radiotherapy		
Technique		
IMRT	72 (98.6)	
3-D CRT	1 (1.4)	
Dose prescription		
54 Gy/30#	68 (93.2)	
Required unplanned break	6 (8.8)	
Required treatment abortion	1 (1.5)	
Other dose prescription	5 (6.8)	

PET characteristics

Using thresholds of 50%, 40%, and 25% of SUVmax, the median primary tumour MTV were 8 cm^3 (SD 16, range 0.5–83 cm^3), 14 cm^3 (SD 20, range 0.9–105 cm^3), and 29 cm^3 (SD 30, range 2–134 cm^3). Again with thresholds of 50%, 40%, and 25% of SUVmax, the median primary tumour TLG were 101 cm^3 (SD 197, range 7–1270 cm^3), 130 cm^3 (SD 234, range 9–1503 cm^3), and 203 cm^3 (SD 273, range 14–1720 cm^3). The median pre-treatment SUVmax and SUVpeak were 16 (SD 8, range 3–43) and 14 (SD 7, range 3–35), respectively. On 3-month-post-treatment PET, the median SUVmax and SUVpeak were 3.9 (SD 2.4, range 2.0–15.8) and 3.5 (SD 1.9, range 1.9–12.5). On 6-month-post-treatment PET, the median SUVmax and SUVpeak were 3.8 (SD 3.0, range 1.7–18.6) and 3.6 (SD 2.7, range 1.6–18.6).

Oncologic outcomes

At median follow-up of 48 months (range 8–97 months), 14 patients had died: 10 from ASCC, 2 from other malignancies (mesothelioma, uterine cancer) without evidence of ASCC recurrence, and 2 from other causes without documented cancer recurrence at last follow-up. 18 patients experienced disease progression: 10 locally, 7 distantly, and 1 both locally and distantly. 4-year PFS, CSS, and OS were 73%, 87%, and 84%, respectively. Median PFS and OS were 39.1 months (range 1.1–67.5 months) and

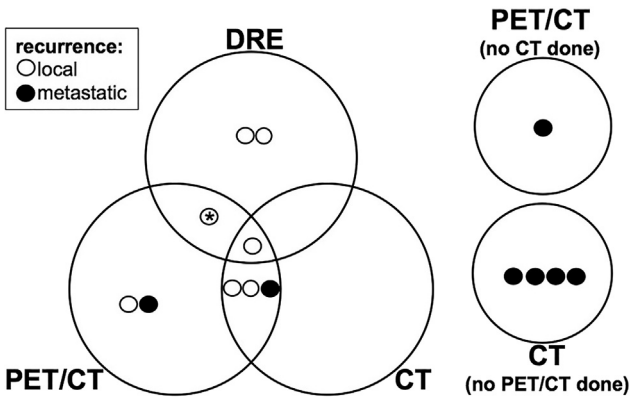

Fig. 2. Modes by which treatment failures (N=18) were detected. N=1 colonoscopy-detected local recurrence is not represented. *The DRE-PET intersection may actually contain 4 local recurrences, as 3 detected by DRE and not visible or indeterminate on CT did not have a PET performed. DRE digital rectal examination.

43.3 months (range 4.6–97.1 months). The median intervals from treatment completion to local and metastatic progression, respectively, were 7.1 months (range 3.4–25.5 months) and 5.4 months (range 1.1–44.1 months). Progression occurred across disease stages (II, $n = 7$; IIIA, $n = 1$; IIIB, $n = 10$) and 11 of the 18 patients had nodal involvement. Neither patient who was treated with radiotherapy alone experienced disease progression or died.

Value of PET in detecting treatment failures

Of the 68 patients who underwent 3-month-post-treatment PET imaging, 61 patients were reported by the cancer centre radiologists to have a complete metabolic response. 1 patient had progressive inguinal adenopathy (and was successfully salvaged by inguinal lymph node dissection), 2 patients had distant metastatic disease (one of whom had an isolated retroperitoneal lymph node recurrence and was successfully salvaged with radiotherapy), and 4 patients had indeterminate residual anal canal FDG uptake, which was ascribed to these 4 scans having been done rather prematurely following treatment completion (median 45 days, range 39–48 days).

Of the 50 patients who underwent 6-month-post-treatment PET imaging, 43 patients were reported to have a complete metabolic response. 5 patients had local disease recurrence detected, despite all 5 having had a complete metabolic response on 3-month-post-treatment PET. Of these 5 local recurrence cases, 3 had clinical evidence of recurrence on digital rectal examination and 2 did not. 1 patient had metastatic progression (the same patient who was noted to have metastases on the 3-month-post-treatment scan). The interpretation of one PET scan was confounded by Crohn's related fistula.

Fig. 2 outlines the modes by which disease progression was first detected. All treatment failures were detectable by the combination of digital rectal examination and PET imaging; however, when used in isolation, clinical examination, PET, or CT failed to detect some recurrences. The 3- and 6-month-post-treatment PET in isolation detected 3 and 5 unique recurrences, respectively.

Value of PET in prognostication

Univariate Cox regression analysis regarding pre-treatment SUVmax, SUVpeak, MTV, and TLG when considered as continuous variables failed to demonstrate any statistically significant correlation with PFS or OS (Supplemental Table 1). ROC analysis was then used to categorize the continuous variables based on sensitivity and specificity. Among the continuous variables, only MTV showed statistical significance, with cut-points of 35 cm^3, 7.75 cm^3, and 8 cm^3 for MTV_{25}, MTV_{40}, and MTV_{50}, respectively. Univariate Cox regression analysis with these cut-points demonstrated significantly worse PFS and CSS when $MTV_{25} > 35$ cm^3 (HR 3.325, $p = 0.016$ for PFS; HR 5.003, $p = 0.042$ for CSS). These correlations remained significant on multivariate analysis (Table 3). There was no significant correlation between MTV_{40} and MTV_{50} and PFS or CSS, or any MTV and OS (Table 3). The Kaplan–Meier PFS curves are presented in Fig. 3, with once again a significant p-value for MTV_{25} ($p = 0.011$) and only trends to a PFS association for MTV_{40} ($p = 0.058$) and MTV_{50} ($p = 0.123$). Survival probabilities for the MTV_{25} Kaplan–Meier analysis (Fig. 3) are presented in Supplemental Table 2, demonstrating significantly worse PFS ($p = 0.011$) and CSS ($p = 0.024$) if pre-treatment $MTV_{25} > 35$ cm^3, compared to ≤ 35 cm^3, though there is no significant difference in OS.

Post treatment, higher SUVmax and SUVpeak at 6 months significantly correlated with worse PFS and OS (Supplemental Table 3;

Table 3
Univariate and multivariate Cox regression analyses for pre-treatment MTV associations with PFS, OS, and CSS. ROC curve analysis was used to determine MTV cut-points with optimal sensitivity and specificity. Bold indicates a statistically significant association.

MTV (cm^3)	Progression-Free Survival			Overall Survival			Cause-Specific Survival		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Cox univariate analysis									
$MTV_{25} > 35$ vs. ≤ 35	**3.325**	**[1.247, 8.867]**	**0.016**	2.268	[0.758, 6.791]	0.143	**5.003**	**[1.059, 23.649]**	**0.042**
$MTV_{40} > 7.75$ vs. ≤ 7.75	3.772	[0.862, 16.500]	0.078	2.266	[0.495, 10.365]	0.292	3.431	[0.429, 27.446]	0.245
$MTV_{50} > 8$ vs. ≤ 8	2.125	[0.797, 5.664]	0.132	0.924	[0.323, 2.642]	0.883	2.039	[0.527, 7.895]	0.302
Cox multivariate analysis									
$MTV_{25} > 35$ vs. ≤ 35	**3.323**	**[1.234, 8.947]**	**0.017**	2.514	[0.827, 7.638]	0.104	**5.380**	**[1.125, 25.742]**	**0.035**
T status (T3/4 vs. T1/2)	1.006	[0.327, 3.091]	0.992	0.457	[0.151, 1.383]	0.166	0.528	[0.135, 2.064]	0.359
$MTV_{25} > 35$ vs. ≤ 35	**3.291**	**[1.233, 8.785]**	**0.017**	2.291	[0.761, 6.900]	0.140	**4.941**	**[1.041, 23.451]**	**0.044**
N status (pos vs. neg)	1.270	[0.492, 3.281]	0.621	0.914	[0.315, 2.651]	0.869	1.165	[0.327, 4.147]	0.814
$MTV_{25} > 35$ vs. ≤ 35	**3.348**	**[1.253, 8.949]**	**0.016**	2.267	[0.754, 6.813]	0.145	**5.276**	**[1.111, 25.050]**	**0.036**
Non-standard chemo*	1.116	[0.397, 3.142]	0.835	0.989	[0.307, 3.201]	0.989	1.895	[0.531, 6.758]	0.325
$MTV_{25} > 35$ vs. ≤ 35	**3.479**	**[1.295, 9.349]**	**0.013**	2.286	[0.760, 6.872]	0.141	**5.239**	**[1.102, 24.909]**	**0.037**
Non-standard RT*	0.635	[0.144, 2.795]	0.548	0.888	[0.197, 4.010]	0.877	0.566	[0.071, 4.505]	0.591
$MTV_{25} > 35$ vs. ≤ 35	**3.242**	**[1.190, 8.833]**	**0.021**	2.289	[0.758, 6.917]	0.142	**5.116**	**[1.068, 24.501]**	**0.041**
SUVmax	0.992	[0.930, 1.059]	0.814	1.005	[0.929, 1.087]	0.898	1.011	[0.919, 1.112]	0.825
$MTV_{25} > 35$ vs. ≤ 35	**3.300**	**[1.126, 8.954]**	**0.019**	2.291	[0.760, 6.899]	0.141	**5.109**	**[1.070, 24.391]**	**0.041**
SUVpeak	0.997	[0.925, 1.075]	0.937	1.008	[0.922, 1.101]	0.867	1.013	[0.910, 1.128]	0.813

* "Non-standard chemo" implies that dose modification(s) were made. "Non-standard RT" implies that an unplanned break was taken during radiotherapy or that a dose/fractionation other than 54 Gy/30 was delivered.

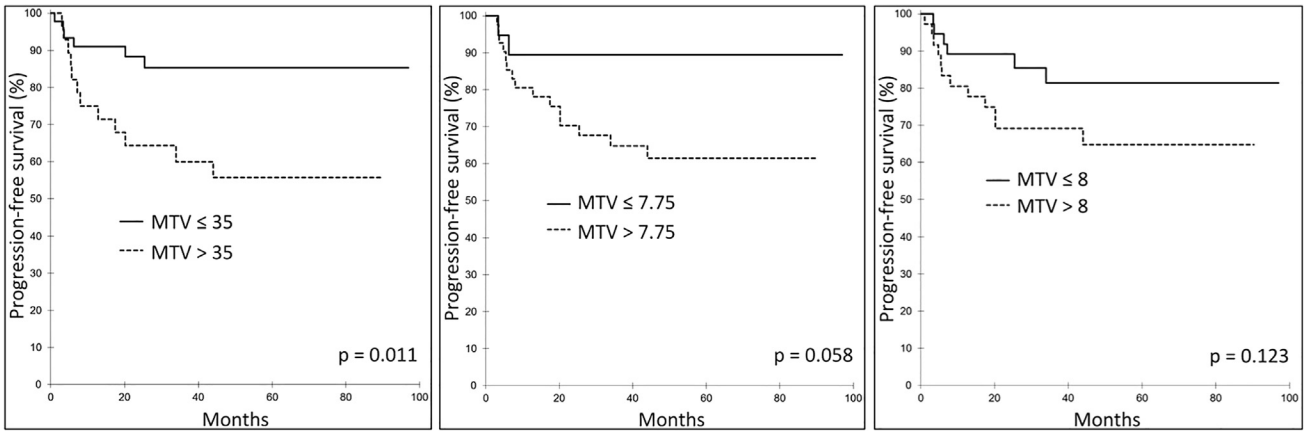

Fig. 3. Kaplan-Meier analysis demonstrating that higher pre-treatment MTV predicts for worse PFS for all MTV definitions: including voxels **A.** ≥25% of SUVmax (MTV_{25}), **B.** ≥40% of SUVmax (MTV_{40}), and **C.** ≥50% of SUVmax (MTV_{50}). However, statistical significance was only reached for MTV_{25} (**A.** p = 0.011, **B.** p = 0.058, and **C.** p = 0.123). MTV cut-points of 35 cm^3 (**A.**), 7.75 cm^3 (**B.**), and 8 cm^3 (**C.**) were selected by ROC curve analysis to optimize specificity and sensitivity.

all HR 1.2, $p \leq 0.011$). 3-month-post-treatment SUVmax and SUVpeak did not predict PFS or OS (HR 1.0–1.2, $p > 0.2$).

Discussion

Studies evaluating the prognostic significance of PET metabolic parameters have been primarily retrospective and yielded inconsistent results (Table 1). Only one prospective analysis has been published, evaluating 55 patients [19]. The authors found pre-treatment SUVmax to not predict metabolic tumour response to treatment, DFS, or OS. Three retrospective analyses corroborated these findings [12–14]. The Kidd et al. study is an outlier, associating SUVmax > 5.6 with worse 2-year DFS ($p = 0.05$) [11]. More recently Cardenas et al. published the contradictory finding that SUVmax > 7.1 predicts decreased 2-year local recurrence on univariate analysis ($p = 0.0296$), with significance lost on multivariate analysis [14]. In light of these variable findings, we were not surprised to find no correlation between pre-treatment SUVmax or SUVpeak and survival outcomes.

Two published analyses have assessed the prognostic utility of MTV [12,13]. Employing a segmentation threshold of ≥50% of SUVmax, each found higher pre-treatment MTV to predict significantly worse PFS and OS. Our data demonstrated primary tumour $MTV_{25} > 35$ cm^3 to predict significantly worse PFS and CSS than $MTV_{25} \leq 35$ cm^3, though to have no association with OS.

To the best of our knowledge, correlation between different MTV segmentation thresholds has not been studied in ASCC. Logically, provided consistency is maintained within a study, MTV definition, despite affecting absolute MTV value, should not alter its prognostication ability [12]. That we demonstrated significant PFS association for MTV delineated using a threshold of 25% of SUVmax, though no association using thresholds of 40% or 50% of SUVmax, brings into question the reliability of using MTV for prognostication in this tumour site. Albeit, it remains possible that with only 14 deaths and 18 treatment failures, our study was simply underpowered to detect prognostic differences by MTV, or the closely correlated TLG.

Our analysis may be the first to support 25% of SUVmax as a reasonable MTV segmentation threshold for ASCC. By visual evaluation, whether a 25%, 40%, or 50% of SUVmax threshold best represented the tumour volume seemed simply to depend on tumour anatomy. In some cases, a threshold of 25% of SUVmax appeared to overestimate the visible tumour extent, while in other tumours, the frequently employed threshold of 50% of SUVmax failed to encompass all visible tumour. Though PET inter-reader variability has been assessed by Paidpally et al. to be excellent for lung, head and neck, and breast tumours, we found MTV determination in the anal canal region to be particularly subjective in tumours with low SUV relative to surrounding tissue, discontinuous tumours, and tumours in close proximity to the bladder [20].

PET utility in the post-treatment setting continues to be debated, with post-radiotherapy inflammation and anal sphincter contraction confounding scan interpretation [17,21,22]. We found that PET did contribute uniquely to detection of treatment failures, in that there was a small subset of recurrences detectable by PET that were not detectable by CT or clinical examination. Furthermore, although metabolic parameters at 3 months post treatment were not prognostic, higher SUVmax and SUVpeak on 6-month-post-treatment PET imaging predicted significantly worse PFS and OS. This finding may reflect the protracted nature of tumour response [23].

It is common for early post-treatment PET to demonstrate abnormal FDG uptake; for example, 59 patients in the Kidd et al. analysis underwent PET imaging an average of 3.4 months (and median of 2 months) following treatment completion, with 24% of these scans demonstrating abnormal FDG uptake consistent with persistent or recurrent disease [11]. While it is recognized that persistent hypermetabolism at 3 months post treatment confers poorer outcomes, it remains undetermined whether early intervention performed on the basis of early post-treatment PET findings improves salvage outcomes [14–16].

The optimal post-treatment timing of PET imaging has not been elucidated, with 3 or 6 months typically seen in our province. A post-hoc analysis of the UK ACT II trial suggested that 26 weeks from the start of CRT (i.e. 4.5 months following treatment completion) is the ideal time to assess clinical response, to avoid unnecessary early salvage of patients who might, upon re-evaluation 3 to 4 months later, have gone on to achieve a complete response [23]. In our study population, although more recurrences were observed on the 6-month-post-treatment PET ($n = 6$), 2 of the 3 recurrences detected on the 3-month-post-treatment PET were successfully treated, including one metastatic recurrence. Although we cannot draw conclusions on the optimal timing of post-treatment PET imaging, 6 months post treatment appears to offer reasonable sensitivity for treatment failures while limiting false-positive findings [24].

Consistent with findings of other analyses, PET (versus CT) increased overall stage in 22% of our study population, primarily by nodal upstaging [25,26]. Acknowledging the low specificity (83%) and positive predictive value (43%) of PET imaging for evaluating malignant inguinal lymph node involvement, we pursued

core biopsies when necessary [27,28]. Only 60% of suspicious inguinal lymph nodes returned histologically positive. While protocols such as RTOG 0529 [29] implicate adjustment of treatment volumes for nodal involvement, it remains unknown whether the theoretical disease control benefit of increasing radiation dose to non-biopsied FDG-avid inguinal nodes outweighs the potentially increased toxicity. Conversely, PET does have a high negative predictive value (100% per Mistrangelo et al.) and refraining from boosting CT-enlarged but PET-negative inguinal lymph nodes has been shown to not increase failure rates [27,30].

Perhaps the most obvious utility of PET is to guide target volume delineation [31]. In a series of 27 cases, PET resulted in alterations to GTV and CTV contours in 56% and 37% of cases [32]. Interestingly, the PET-derived target volumes were significantly larger than the CT-derived ones, and although published literature is lacking, it might be inferred that CT-derived contours risk underestimating the burden of disease. MRI, particularly diffusion-weighted imaging, is a useful adjunct for delineating disease, and the advent of PET/MRI scanners may be particularly beneficial to ASCC management [33]. Better definition of disease extent may lead to more tailored, lower toxicity radiation plans, providing grounds to treat elective regions to a lower dose while reserving 45 Gy for FDG-avid disease, and additional boost for bulky disease [34]. Higher MTV may guide selection of patients for dose escalation; an area that warrants further prospective study.

A main limitation to this and other ASCC outcome analyses is that the small numbers of outcome events hinder the emergence of statistically significant correlations. Furthermore, institutional differences in PET imaging and analysis protocols limit the generalizability of MTV risk-stratification cut-points. With our study representing a first prospective attempt to confirm the prognostic utility of MTV, the next step is a larger prospective analysis. With a well-powered study, meticulously attending to consistency in PET protocol, it is likely that there will be sufficient evidence to support customization of radiotherapy technique to improve outcomes and decrease toxicity.

In conclusion, this study indicates that MTV is the most prognostically useful metabolic tumour parameter, with higher pre-treatment MTV predicting worse PFS and CSS. Conversely, pre-treatment SUVmax, SUVpeak, and TLG were not prognostic of survival outcomes. In the post-treatment setting, higher SUVmax and SUVpeak at 6 months following CRT predicted for significantly worse PFS and OS; however metabolic parameters at 3 months post-treatment were not prognostic. Larger prospective analysis is warranted to inform the promising prospect of risk-adapted therapy on the basis of metabolic tumour characteristics, as well as elucidate the optimal timing of post-treatment PET imaging.

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding

This study was funded by an Alberta Cancer Board seed funding grant and an Alberta Innovates Health Solutions Grant: 2011-RES0008619. The funding agencies had no role in study design, data analysis, or manuscript preparation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.03.014.

References

[1] Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018.
[2] Islami F, Ferlay J, Lortet-Tieulent J, Bray F, Jemal A. International trends in anal canal incidence rates. Int J Epidemiol 2017;46:924–38.
[3] Gunderson L, Winter K, Ajani J, 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.
[4] Glynne-Jones R, Nilsson P, Aschele C, et al. Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Eur J Surg Oncol 2014;40:1165–76.
[5] Goh V, Gollub F, Liaw J, et al. Magnetic resonance imaging assessment of squamous cell carcinoma of the anal canal before and after chemoradiation: can MRI predict for eventual clinical outcome? Int J Radiat Oncol Biol Phys 2010;78:715–21.
[6] Nguyen BT, Joon DL, Khoo V, et al. Assessing the impact of FDG-PET in the management of anal cancer. Radiother Oncol 2008;87:376–82.
[7] Cotter SE, Grigsby PW, Siegel BA, et al. FDG-PET/CT in the evaluation of anal carcinoma. Int J Radiat Oncol Biol Phys 2006;65:720–5.
[8] Benson AB III, Venook A, Mahmoud M, et al. Anal carcinoma. In: NCCN Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network. 2018. https://www.nccn.org/professionals/physician_gls/pdf/anal_blocks.pdf. Accessed 25 June 2018.
[9] Sveistrup J, Loft A, Berthelsen A, et al. Positron emission tomography/computed tomography in the staging and treatment of anal cancer. Int J Radiation Oncol Biol Phys 2012;83:134–41.
[10] Grigsby PW. FDG-PET/CT: new horizons in anal cancer. Gastroenterol Clin Biol 2009;33:456–8.
[11] Kidd E, Dehdashti F, Siegel B, et al. Anal cancer maximum F-18 fluorodeoxyglucose uptake on positron emission tomography is correlated with prognosis. Radiother Oncol 2010;95:288–91.
[12] Bazan J, Koong A, Kapp D, 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.
[13] Gauthé M, Richard-Molard M, Fayard J, et al. Prognostic impact of tumour burden assessed by metabolic tumour volume on FDG-PET/CT in anal canal cancer. Eur J Nucl Med Mol Imaging 2017;44:63–70.
[14] Cardenas M, Spencer C, Markovina S, et al. Quantitative FDG-PET/CT predicts local recurrence and survival for squamous cell carcinoma of the anus. Adv Radiat Oncol 2017;2:281–7.
[15] Schwarz J, Siegel B, Dehdashti F, et al. Tumor response and survival predicted by post-therapy FDG-PET/CT in anal cancer. Int J Radiation Oncol Biol Phys 2008;71:180–6.
[16] Day F, Link E, Ngan S, et al. FDG-PET metabolic response predicts outcomes in anal cancer managed with chemoradiotherapy. Br J Cancer 2011;105:498–504.
[17] Houard Cl, Pinaquy JB, Mesguich C, et al. Role of 18F-FDG-PET/CT in posttreatment evaluation of anal carcinoma. J Nucl Med 2017;58:1414–20.
[18] Joseph K, Nijjar Y, Warkentin H, et al. Prospective phase II study of tomotherapy based chemoradiation treatment for locally advanced anal cancer. Radiother Oncol 2015;117:234–9.
[19] Deantonio L, Milia M, Cena T, et al. Anal canal FDG-PET standardized uptake value: correlation with tumor characteristics, treatment response and survival. Radiol Med 2016;121:54–9.
[20] Paidpally V, Mercier G, Shah B, et al. Interreader agreement and variability of FDG-PET volumetric parameters in human solid tumours. Am J Roentgenol 2014;202:406–12.
[21] Mahmud A, Poon R, Jonker D. PET imaging in anal canal cancer: a systematic review and meta-analysis. Br J Radiol 2017;90. Epub 2017 Oct 3.
[22] Saboo S, Zukotynski K, Shinagare A, et al. Anal carcinoma: FDG-PET/CT in staging, response evaluation, and follow-up. Abdom Imaging 2013;38:728–35.
[23] Glynne-Jones R, Sebag-Montefiore D, Meadows H, et al. Best time to assess complete clinical response after chemoradiotherapy in squamous cell carcinoma of the anus (ACT II): a post-hoc analysis of randomised controlled phase 3 trial. Lancet Oncol 2017;18:347–56.
[24] Verecellino L, Montravers F, de Parades V, et al. Impact of FDG-PET/CT in the staging and follow-up of anal carcinoma. Int J Colorectal Dis 2011;26:201–10.
[25] Wells IT, Fox BM. PET/CT in anal cancer – is it worth doing? Clin Radiol 2012;67:535–40.
[26] Bhuva N, Glynne-Jones R, Sonoda L, et al. To PET or not to PET? That is the question. Staging in anal cancer. Ann Oncol 2012;23:2078–82.
[27] Mistrangelo M, Pelosi E, Bello M, et al. Comparison of positron emission tomography scanning and sentinel node biopsy in the detection of inguinal node metastases in patients with anal cancer. Int J Radiat Oncol Biol Phys 2010;77:73–8.
[28] Caldarella C, Annunziata S, Treglia G, et al. Diagnostic performance of positron emission tomography/computer tomography using fluorine-18 fluorodeoxyglucose in detecting locoregional nodal involvement in patients with anal canal cancer: a systemic review and meta-analysis. Sci World J 2014. eCollection; 196068.

[29] Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 2013;86:27–33.
[30] Mai S, Welzel G, Hermann B, et al. Can the radiation dose to CT-enlarged but FDG-PET-negative inguinal lymph nodes in anal cancer be reduced? Strahlenther Onkol 2009;185:254–9.
[31] Albertsson P, Alverbratt C, Liljegren A, et al. Positron emission tomography and computer tomographic (PET/CT) imaging for radiation therapy planning in anal cancer: A systemic review and meta-analysis. Crit Rev Oncol Hematol 2018;126:7–12.
[32] Krengli M, Milia M, Turri L, et al. FDG-PET/CT imaging for staging and target volume delineation in conformal radiotherapy of anal carcinoma. Radiat Oncol 2010;5:10.
[33] Prezzi D, Mandegaran R, Gourtsoyianni S, et al. The impact of MRI sequence on tumour staging and gross tumour volume delineation in squamous cell carcinoma of the anal canal. Eur Radiol 2018;28:1512–9.
[34] Trautmann T, Zuger J. Positron emission tomography for pretreatment staging and posttreatment evaluation in cancer of the anal canal. Mol Imaging Biol 2005;7:309–13.