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Positron emission tomography with computed tomography imaging (PET/CT) for the radiotherapy planning definition of the biological target volume: PART 2

Alba Fiorentino[a,*], Riccardo Laudicella[b], Elisa Ciurlia[c], Salvatore Annunziata[d], Valentina Lancellotta[e], Paola Mapelli[f], Carmelo Tuscano[g], Federico Caobelli[h], Laura Evangelista[i], Lorenza Marino[j], Natale Quartuccio[k], Michele Fiore[l], Paolo Borghetti[m], Agostino Chiaravalloti[n,o], Maria Ricci[p], Isacco Desideri[q], Pierpaolo Alongi[r], AIRO Giovani - Italian Association of Radiation Oncology-Young Members and AIMN -Italian Association of Nuclear Medicine- Young Members Working Group

[a] Radiotherapy Oncology Department, General Regional Hospital "F. Miulli", Acquaviva delle Fonti-Bari, Italy
[b] Department of Biomedical and Dental Sciences and of Morphofunctional Imaging, University of Messina, Italy
[c] Radiotherapy Oncology Department, Vito Fazzi Hospital, Lecce, Italy
[d] Fondazione Policlinico A. Gemelli IRCCS-Università Cattolica Sacro Cuore, Roma, Italy
[e] Fondazione Policlinico Universitario A. Gemelli IRCCS, UOC di Radioterapia, Dipartimento di Scienze Radiologiche, Radioterapiche ed Ematologiche, Roma, Italy
[f] Department of Nuclear Medicine, IRCCS San Raffaele Scientific Institute, Milan, Italy
[g] Radiotherapy Oncology Department, Azienda Ospedaliera Bianchi-Melacrino-Morelli, Reggio Calabria, Italy
[h] Clinic of Radiology and Nuclear Medicine, University Hospital Basel, University of Basel, Basel, Switzerland
[i] Nuclear Medicine Unit, Veneto Institute of Oncology IOV – IRCCS, Padua, Italy
[j] Radiotherapy Oncology Department, REM, Viagrande, Catania, Italy
[k] Nuclear Medicine Unit, ARNAS Civico Palermo, Palermo, Italy
[l] Radiation Oncology, Campus Bio-Medico University, Rome, Italy
[m] Radiation Oncology Department University and Spedali Civili, Brescia, Italy
[n] IRCCS Istituto Neurologico Mediterraneo (INM) Neuromed, Pozzilli, Italy
[o] Department of Biomedicine and Prevention, University of Rome Tor Vergata, Italy
[p] Department of Radiological, Oncological and Pathological Sciences, Sapienza University of Rome, Rome, Italy
[q] Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", Section of Radiation Oncology, University of Florence, Italy
[r] Department of Radiological Sciences, Nuclear Medicine Service, Fondazione Istituto G. Giglio, Cefalu, Italy

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ABSTRACT

Aim: Positron Emission Tomography with Computed Tomography (PET/CT) has been proven to be useful in the definition of Radiotherapy (RT) target volume. In this regard, the present expert review summarizes existing data for pancreas, prostate, gynecological and rectum/anal cancer.
Methods: A comprehensive search of published original article was made, based on SCOPUS and PubMed database, selecting the paper that evaluated the role of PET/CT in the definition of RT volume.
Results: FDG-PET has an important and promising role for pancreatic cancer. Choline PET/CT could be useful for identifying high-risk volumes for prostate cancer; while PSMA PET/CT is still under evaluation. FDG PET/CT in gynecological cancers has been shown to impact external-beam RT planning. The role of FDG-PET for Gross Tumor volume identification is crucial, representing a useful and powerful tool for anal and rectal cancer.
Conclusion: Taken together, molecular and functional imaging approaches offer a major step to individualize radiotherapeutic approach.

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* Corresponding author at: Radiotherapy Oncology Department, General Regional Hospital "F. Miulli", Strada Prov. 127 Km 4, 70021, Acquaviva delle Fonti-Bari, Italy.
E-mail address: a.fiorentino@miulli.it (A. Fiorentino).

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1. Introduction

Radiotherapy (RT), used for 60–70% of solid tumors, is a crucial treatment modality for patients affected by cancer. As regards the evolution of diagnosis and treatment, including positron emission tomography with computed tomography imaging (PET/CT) and intensity-modulated radiotherapy (IMRT) or volumetric arc radiotherapy (VMAT), improvements in terms of accuracy in tumor's detection are nowadays necessary (Alongi et al., 2019).

For RT planning, the implementation of PET/CT imaging has led to at least two relevant innovations. First, biological data obtained from PET/CT imaging produces a sensible change in volume definition and second, the metabolic information can be further utilized to characterize the anatomical gross tumor volume (GTV) by identifying functional sub-volumes leading to the definition of a biological target volume (BTV) (Alongi et al., 2019).

Furthermore, the role of PET-CT with Fluorine-18 labelled 2-deoxy-2-fluoro-D-glucose (18 F-FDG) or other tracers has been proposed and studied for the precise definition of RT Target Volume in several cancer patients. The aim of the present analysis is to review the present literature regarding implications of PET/CT for RT target volume definition in the following anatomical districts: pancreas, prostate cancer, gynecological cancer and rectum/anal cancer. Thus, a collection of available published data was made to emphasize strength and weaknesses.

1.1. Pancreatic cancer

1.1.1. Nuclear medicine point of view

Pancreatic cancer is a highly malignant disease with a severe mortality rate (Fiore et al., 2017). In operable patients, the role of ^{18}F-FDG PET/CT is contentious. While some authors found no benefit in the pancreatic adenocarcinoma staging, other researchers reported a clinical value similar to that yielded in other types of cancer in operable pancreas cancer patients (Matsumoto et al., 2013; Burge et al., 2015, Table 1).

On the other hand, ^{18}F-FDG seems to have a significant prognostic value in these patients. A recent study demonstrated a correlation between pre-operative ^{18}F-FDG PET/CT and CA19-9 and histopathologic tumor regression after radiochemotherapy (RT-CHT) in patients with initial borderline resectable and locally advanced pancreatic cancer (LAPC) (Mellon et al., 2017). Furthermore, tumor metabolism as assessed prior to RT-CHT by ^{18}F-FDG PET/CT has been proven to correlate with different survival outcomes (Dholakia et al., 2014; Li et al., 2015).

1.1.2. Radiation oncology point of view

There are still many unresolved issues related to the delineation of the GTV in LAPC. The use of ^{18}F-FDG PET/CT for target volume definition in tumors of the gastrointestinal tract has been recently investigated, but interest is rapidly growing (Lambrecht and Haustermans, 2010; MacManus et al., 2009). In general, pancreatic tumours are FDG-avid and ^{18}F-FDG PET/CT parameters have been shown to be of prognostic value for both progression-free survival (PFS) and overall survival (OS) after stereotactic body radiotherapy (SBRT) (Schellenberg et al., 2010).

Incorporating functional imaging into GTV delineation is attractive, as it may allow for an automation of the target delineation process and to identify areas that may benefit from RT dose boosting, by reducing the target volume and the exposure volumes of the organs at risk (OAR) and safely escalating the target radiation dose (Wilson et al., 2014). In a few studies, ^{18}F-FDG PET/CT has been used to define the GTV [Chang et al., 2009; Schellenberg et al., 2008]. Unfortunately, the clinical value of adding ^{18}F-FDG PET/CT to target volume delineation is still a matter of debate, due to the lack of pathological validation. Ford et al. suggested that ^{18}F-FDG PET/CT may play a relevant role in distinguishing the primary tumour from the duodenum (Ford et al., 2009).

Few studies seem to indicate a great potential for future developments, although the assessment of the additional value over standard protocols warrants further investigation.

Take home message: FDG-PET has an important role for differential diagnosis between pancreatitis and adenocarcinomas and for the detection of distant metastasis, while it is a promising tool for the definition of radiotherapy target volume.

1.2. Prostate cancer

1.2.1. Nuclear medicine point of view

The application of PET/CT with radio-labeled choline in RT treatment has been largely increased during the last years (Anon, 2019, Table 2). Both [^{11}C] and [^{18}F] choline PET/CT have been demonstrated to be a reliable imaging biomarker for early stage prostate cancers (PCa), in terms of enabling the identification of dominant intraprostatic regions, and for metastatic cancer (Schwarzenböck et al., 2013; Picchio et al., 2010).

New radioatracers targeting prostate-specific membrane antigen (PSMA) have been recently developed (Table 2). A high expression of PSMA in malignant prostate tissue compared to lower expression in benign prostate tissue has been reported in preclinical studies (Mhawech-Fauceglia et al., 2007; Silver et al., 1997). Zambglou et al. (Zamboglou et al., 2015) compared MRI and ^{68}Ga-PSMA PET/CT for their ability to delineate the dominant intraprostatic lesions and provided concordant results for its delineation in 47% of patients (Tables 3–5).

1.2.2. Radiation Oncology point of view

Molecular imaging represents the main possibility in defining BTV. Moreover, some authors suggested that the role of choline-PET/CT for clinical target volumes selection and delineation is crucial when BTVs protrude outside the prostate gland or are located in the prostate fossa (Kairemo et al., 2015; Würschmidt et al., 2011).

Compared to the conventional whole prostate dose escalation, an integrated boost to the macroscopic malignant lesion might potentially improve tumor control rates without increasing toxicity. Pinkawa et al. (Pinkawa et al., 2012) showed, in a prospective study of 46 PCa patients, the safety of a dose escalation to a macroscopic intraprostatic lesion performed with ^{18}F-choline PET-CT. A dose of 76 Gy (2 Gy/fractions) was delivered to the prostate, with or without simultaneous integrated boost up to 80 Gy.

Alongi et al evaluated the impact of Choline-PET/CT in decision-making strategy of 60 patients with localized PCa eligible to definitive RT The authors showed that Choline-PET/CT shifted treatment

Table 1
PET Tracers for pancreatic cancer.

Radiopharmaceutical agent	Sensitivity (95% CI)	Specificity (95% CI)	Indication	Ref
18 F-FDG	80-100% 93.6% 80%	80% 21.4% 60%	Diagnosis d.d. pancreatitis and adenocarcinomas detection of distant metastasis	(Matsumoto et al., 2013; Li et al., 2015)

Table 2
PET Tracers for prostate cancer.

Radiopharmaceutical agent	Sensitivity (95% CI)	Specificity (95% CI)	Indication	Ref
18 F-11C/Choline	66-79%	–	Detection of primary tumor	(Schwarzenböck et al., 2013; Picchio et al., 2010)
	41.2%	99.1%	Detection of lymph nodes	
	38-95%	–	Recurrent prostate cancer	
68Ga-PSMA	65.9%	94.5%	Distinguish between PCa and other cancers	(Mhawech-Fauceglia et al., 2007; De Bari et al., 2018)
	49–75%	87–95%	Detection of primary tumor	
	45–90%	85–90%	Recurrent prostate cancer	

indication in 21% of cases: six intermediate risk shifted to high risk and consequently were irradiated on prostate, seminal vesicles, and pelvic nodes; in seven high risk cases, the Choline-PET/CT showed bone and/or N uptake, and consequently, a simultaneous integrated boost on PET positive sites was prescribed (Alongi et al., 2015)

Kuang et al. (Yu et al., 2015) investigated the expected tumor control probability (TCP) and normal tissue complication probability (NTCP) for prostate VMAT with and without RT boost to an intraprostatic dominant lesion defined by ^{18}F-fluorocholine PET/CT in 30 localized PCapatients. The whole-prostate PTV received 79 Gy, while a simultaneous boost doses to dominant lesion of 100 Gy and 105 Gy was prescribed for 2-VMAT plans. No significant differences in bladder and femoral head NTCP between plans and a slightly lower rectal NTCP have been observed.

However, there is currently no consensus regarding the possibility to use a RT boost to image defined GTVsas standard of care (Bauman and Maider, 2013).

Choline PET/CT is a valuable tool also to detect lymph node (LN) metastases in patients with biochemical failure after primary treatment for PCa. In this setting, imaging parameters derived by (11)C-choline PET/CT such as metabolic tumor volume (MTV) seems able to impact on survival outcomes. In a study of Incerti et al. the most discriminative cutoff value for MTV values was an MTV threshold of 60% (MTV60) of greater than 0.64 cm.In particular, MTV60 and extrapelvic disease were the best predictors of tumor RT response for biochemical and clinical relapse free survival in PCa patients with LN recurrence after primary treatment (Incerti et al., 2015).However, Choline PET/CT present low sensitivity for PSA value less than 1 ng/ml (Castellucci and Picchio, 2013). To improve the diagnostic accuracy of PET/CT in the RT planning of PCa, PSMA tracer was evaluated. In fact, Gallium68 PSMA-11 (HBED-CC)-PET/CT has been shown as a useful tool in the restaging of post radical prostatectomy, RT or androgen deprivation therapy patients presenting biochemical relapse of PCa. De Bari et al showed that PSMA imaging could change the decision-making process in up of 70% of patients (De Bari et al., 2018). A very recent paper by Schmidt-Hermann et al (Schmidt-Hegemann et al., 2018) has reinforced the utility of PSMA PET/CT before radiotherapy in 172 patients, particularly in post-operative setting. Ga68-PSMA PET/CT demonstrated the ability to change the radiotherapy approach in 50% and 77%, respectively in patients with a PSA recurrence (n = 31/62) and a PSA persistence (n = 68/88) after radical prostatectomy.

Take home message: choline PET/CT could be useful for identifying high-risk RT volumes, including LN, for prostate cancer; while PSMA PET/CT is still under evaluation for the RT target definition.

1.3. Gynecological cancer

1.3.1. Nuclear medicine point of view

FDG PET/CT has been shown to influence the diagnostic work-up and the selection of RT target volumes in gynecological cancer. In particular, PET/CT could be useful in patients with cervical cancer candidate to RT and preliminary data suggest a potential use also in patients with endometrial cancer, uterine sarcoma and ovarian cancer (Caroli and Fanti, 2010).

In a recent analysis by Lazzari et al about cervical cancer (Lazzari et al., 2014), FDG PET/CT leads to a better staging and definition of disease and has the potential of showing LN metastasis within the pelvis and in the para-aortic area Table 3). The latter data are confirmed by a recent systematic review (Salem et al., 2011).

In endometrial cancer, LN status is also an important issue and FDG-PET/CT may replace LN surgical procedure particularly in obese patients (Haie-Meder et al., 2010).

FDG-PET/CT have been widely studied in gynecological cancer, with different aims (diagnostic, prognostic and RT target definition) (Caroli and Fanti, 2010). Segmentation algorithms could have an impact on the MTV and this could bring uncertainties in PET/CT guidance of tumor RT. In a recent paper by Xu et al, iterative adaptive algorithm segmentation seems to be more suitable than the fixed percentage threshold method to estimate the tumor volume of cervical primary squamous cell carcinoma (Xu et al., 2017). FDG-PET/CT volumes may reflect microscopic infiltration of gynecological cancer and may differs from morphological volumes obtained by MR. Interestingly, FDG PET-CT SUV-based primary tumor volume estimation at 30% to 35% of SUVmax values correlates significantly with the MR volumes for primary cervical tumor with squamous histology (Upasani et al., 2012).

Furthermore, more robust data are needed about the potential use in gynecological cancer of new tools such as radiopharmaceuticals (e.g. hypoxia), hybrid scanners (e.g. PET/MR) and semi-quantitative parameters (e.g. texture analysis). In particular, hypoxia tracers could help to better define the tumor radiosensitivity, whilst PET/MR could improve functional and morphological imaging in the abdomino-pelvic district (Lyng and Malinen, 2017; Zhang et al., 2019).

1.3.2. Radiation Oncology point of view

In radiotherapy planning for gynecological cancer 18 FDG PET-CT plays a major role (Kidd et al., 2013; Schwarz et al., 2008a; Kidd et al., 2010a; Yildirim et al., 2008). Considering that prognosis also depends on para-aortic nodal status, pathological FDG uptake may indicate if radiation fields need to be extended to the para-aortic area, and/ or that total doses need to be increased to involved nodes within the pelvis and/or the para-aortic area (Lagasse et al., 1980; Van Nagell et al.,

Table 3
PET Tracers for gynecological cancer.

Tracer	Sensitivity (95% CI)	Specificity (95% CI)	Indication	Reference
18 F-FDG	75,00%	50,00%	detection of para-aortic nodal status and change management strategy in locally advanced cervical cancer (LACC)	(Kidd et al., 2010a)

Table 4
PET Tracers for gynecological cancer.

Tracer	Sensitivity (95% CI)	Specificity (95% CI)	Indication	Reference
18 F-FDG	93,00%	81,00%	Diagnostic performance and impact on management of PET/CT	(Nguyen et al., 2008a)
	100,00%	97,40%	PET-CT compared with CT scan, sentinel node biopsy results of inguinal lymph nodes, and anal biopsy results in staging and in follow-up of anal cancer.	(Vercellino et al., 2011)
	89,00%	–	FDG-PET on the nodal staging, radiotherapy planning and prognostication of patients with primary anal cancer.	(Mistrangelo et al., 2012a)

1971; Kupets and Covens, 2001; Esthappan et al., 2004; Kidd et al., 2010b; Belhocine et al., 2002; Stehman et al., 1991; Peters et al., 2000; Varia et al., 1998). Patients with positivepara-aortic nodes increased their survival rate when extended-field irradiation and concurrent radio-chemotherapy was administered (Lagasse et al., 1980; Van Nagell et al., 1971; Kupets and Covens, 2001; Esthappan et al., 2004; Kidd et al., 2010b).

Mazzola et al reported the preliminary results of RT-CHT with simultaneous integrated boost to macroscopic disease delineated by a FDG-PET, for 30 elderly patients affected by locally advanced squamous cervical carcinoma, unable to undergo brachytherapy. The authors concluded that with a median follow up of 32 months, 66 Gy to the macroscopic disease is safe and effective with the 3-year local control of 91% for stage II and 67% for stage III (Ricchetti et al., 2017). Nevertheless, brachytherapy remains the treatment of choice for the definitive treatment of cervical cancer.

Using PET/CT-guided IMRT, Esthappan et al. proposed dose escalation to 59.4 Gy to positive para-aortic LN and 50.4 Gy to the para-aortic region (Lagasse et al., 1980). They also proposed guidelines for selecting PET/CT-guided IMRT treatment parameters in cervical carcinoma with positive para-aortic lymph nodes. Further studies will better define the total dose to the para-aortic nodes as it might not be necessary in cases of distant metastases.

When recurrent cervical carcinoma is treated with salvage radiotherapy, PET/CT helps in limiting irradiated volumes, thus reducing the risk of complications (Stryker and Mortel, 2000).

In brachytherapy procedure, tumour volume is crucial and PET/CT is a very useful tool. In 11 patients with cervical cancer a comparison study with two-dimensional (2D) treatment planning orthogonal RT based brachytherapy concluded that 3D treatment planning based on FDG-PET (Haasbek et al., 2008) was feasible and accurate. In another evaluation (Malyapa et al., 2002), FDG-PET-based treatment planning improved dose tumour coverage without significantly increasing bladder and rectum doses, moreover, the authors highlighted that tumour volume reduced by a mean of 50% within 20 days of beginning irradiation (Lin et al., 2007).

In conclusion, the role of PET/CT has been shown for radiotherapy planning in cases of para-aortic lymph node metastases, enlarged pelvic LN, uterine canal involvement, high tumour-grade and advanced stage disease. In the next future, PET-CT in RT is set to evolve into advanced techniques of dose painting, utilizing complex IMRT plans guided by FDG-avid metabolic activity. PET-CT-based brachytherapy optimization is feasible and could provide 3D metabolic and dosimetry information about tumours and organs at risk. Larger prospective studies and cost-efficacy reviews are advocated.

Take home message: FDG PET-CT is the most sensitive imaging modality for detecting LN metastases andhas been shown to impact external-beam radiotherapy planning by modifying the treatment field.

1.4. Anal cancer

1.4.1. Nuclear medicine point of view

Although its increasing incidence (due to known risk factors like human papilloma virus (HPV) and human immunodeficiency virus (HIV)), anal cancer is an uncommon disease accounting for ˜0.4% of all malignancies. The standard management of localized/locally advanced anal cancer is radical RT-CHT with sphincter-preservation, otherwise abdominal-perineal resection is reserved for salvage (Abbas et al., 2010). Diagnosis and pre-treatment staging are influenced by the size of gross tumor, nodal involvement (which are the two most important prognostic factors) and the presence/absence of metastatic disease (Amin et al., 2017; Gunderson et al., 2013). 18F-FDG-PET/CT may provide diagnostic useful information for anal cancer, due to its high FDG avidity (up to 98%) (Saboo et al., 2013): and for the latter motivation it represents as an “optional but often recommended” modality in the workup of patients with anal cancer for staging, assessing treatment response and for detecting disease recurrence. [Glynne-Jones et al., 2014; Anon, 2018]

Several studies reported a higher sensitivity of FDG-PET/CT for the detection of primary tumor, regional LN metastases, and distant disease compared to conventional imaging: in general, the reported sensitivity for primary tumors on FDG PET/CT ranges from 89%–100%, as compared to 58%–75% for CT (Cotter et al., 2006; Nguyen et al., 2008a; Vercellino et al., 2011; Mistrangelo et al., 2012aTable 4 Table 4).

18 F-FDG-PET/CT has been shown to be a useful tool for therapy's response assessment (generally performed after 12 weeks from chemotherapy) and for the purposes of RT planning in patients with anal cancer. PET/CT is reported to significantly modify RT planning in a variable range between 13–23% of patients (Nguyen et al., 2008a; Winton et al., 2009; Bannas et al., 2011a). In this sense, as a result of PET/CT comparation to CT alone, a recent study by Krengli et al. suggested changes in the size and shape of gross tumor volume and clinical tumor volume (Krengli et al., 2010a).

The more intensely FDG-avid primary disease is associated with an increased risk of nodal metastasis at diagnosis, increased risk of persistent or recurrent disease post-therapy, and lower disease-free survival. This suggests that FDG uptake's intensity could be a prognostic biomarker (Kidd et al., 2010c). In a recent study, found a statistically significative correlation between pre-treatment SUVmax value, T stage and histological type of primitive anal cancer and high correlation between MTV and worse OS, PFS or event free survival (EFS) (Deantonio et al., 2016; Bazan et al., 2013). Furthermore, Gauthe et al. demonstrated that MTV at the primary site was significantly and independently correlated with OS ($p < 0.05$), as patients with MTV less

Table 5
PET Tracers for rectal cancer.

Tracer	Sensitivity (95% CI)	Specificity (95% CI)	Indication	Reference
18 F-FDG	78% (67-87%)	81% (69-91%)	Prediction of pathological response to preoperative chemoradiotherapy in patients with primary rectal cancer	(Kunawudhi et al., 2016)
	90.3% (85.5-94%)	80% (67-89.6%)	Detection of recurrent colorectal cancer in patients with elevated CEA	(Garland et al., 2014)

than 7 cm3 had a better prognosis (Gauthé et al., 2017)

Nevertheless, FDG PET/CT can be a useful tool to evaluate treatment response in anal cancer (Nguyen et al., 2008a; Mistrangelo et al., 2012a; Schwarz et al., 2008b; Trautmann and Zuger, 2005). Early identification of patients with partial response using PET/CT may suggest the need for early salvage therapy before significant spread to distant sites occurs (Saboo et al., 2013; Schwarz et al., 2008b). A metabolic partial response at the site of primary anal cancer on post RT-CHT PET/CT is predictive of significantly decreased 2-year PFS as compared with metabolic complete response (22% vs 95%, respectively; $p < 0.0001$) (Schwarz et al., 2008b). In a study by Day et al. of 48 patients who underwent FDG PET at baseline and after RT-CHT, the 2-year PFS was found to be 95% for patients with metabolic CR, 71% for those with metabolic PR, and 0% for those with no response ($p < 0.0001$) (Day et al., 2011).

1.4.2. Radiation Oncology point of view

RT-CHT is the standard oncological approach for anal cancer patients. According to the T and N stage the nodal elective dose ranged from 30 to 42 Gy (for early stage), followed by a boost to macroscopic disease (involved nodes/region) until a total dose of 50.4-54-60 Gy is appropriate, in sequential or simultaneous integrated boost RT techniques (Ajani et al., 2008; Kachnic et al., 2013).

The elective target delineation has been assessed by consensus on contouring (Myerson et al., 2009; Ng et al., 2012), while the accurate pretreatment staging is crucial for the definition of GTVs and the proper prescription dose (Muirhead et al., 2015).

Several studies of RT or RT-CHT, have investigated the role of PET-CT in the target definition and treatment planning. PET-CT is a useful supplement in target definition with PET-CTVs smaller then CT-CTVs (Nguyen et al., 2008b; Mai et al., 2009; Krengli et al., 2010b; Bannas et al., 2011b; Buijsen et al., 2012; Mistrangelo et al., 2012b; Zimmermann et al., 2017; Rusten et al., 2017; Anderson et al., 2007), while similar GTVs were observed from the comparison of MRI and PET-TC contouring (Mistrangelo et al., 2012b). Most of the studies focused on the impact of FDG-PET-CT disease staging with special regard to treatment planning. The identification of additional involved nodes in unsuspected pelvic/inguinal nodes resulted in RT plans modification as the PET-CT upstaged nodes/region have to be included in the high dose volume (with a sequential or concomitant boost); in the studies reviewed (Nguyen et al., 2008b; Mai et al., 2009; Krengli et al., 2010b; Bannas et al., 2011b; Sveistrup et al., 2012; Mistrangelo et al., 2012b; Zimmermann et al., 2017), these changes in RT planning occurred in the 12.5–23% of cases.

Take home message: 18-FDG-PET/CT may provide diagnostic useful information for anal canal cancer, due to its high FDG avidity (up to 98%). PET-CT is a useful supplement in target definition for delineating smaller volume compared to CT alone and similar GTVs in comparison of MRI.

1.5. Rectal cancer

1.5.1. Nuclear medicine point of view

PET/CT has emerged as a promising option for the diagnostic work-up of colorectal cancer (CRC), evaluating features at presentation associated with a high risk of metastases (e.g. high levels of CEA or wide extramural vascular invasion). Its value for primary tumor mass assessment and LN status is not proven, although it may be useful in RT target delineation (Glynne-Jones et al., 2017). As recommended by the WHO and due to possible artifact, FDG PET/CT preferably should be performed no earlier than 7 weeks after neoadjuvant radiochemotherapy (nRT-CHT) and 8 weeks after early surgery (Niccoli-Asabella et al., 2014).

According to literature, PET/CT can be a useful tool for assessing therapy response to nRT-CHT, leading to changes in management plan in 3,2–50% of patients (Kunawudhi et al., 2016; Li et al., 2014; Avallone et al., 2012), with a sensitivity of 88.88% and a specificity of 92.86% (Murcia Duréndez et al., 2013 Table 5). Furthermore, several PET parameters both qualitative and quantitative, are potentially valuable imaging biomarkers in the evaluation of response to therapy and prognostication, according to tumor response grade (TRG) (Tagliabue, 2013; Kwak et al., 2012; Ozkan et al., 2012; Maffione et al., 2013; Memon et al., 2014; Liao et al., 2014; Whaley et al., 2014).

Moreover, FDG PET/CT has been shown to be superior to conventional imaging in evaluating recurrence of CRC (Garland et al., 2014; Lu et al., 2013), even regardless of the CEA levels.As showed by Sanli et al., among patients with normal CEA levels, the sensitivity and specificity of FDG PET/ CT for evidence of recurrence were 100% and 84.0%, respectively; of the patients with elevated CEA levels, the corresponding values were 97.1% and 84.6%, respectively (Sanli et al., 2012). Moreover, PET/CT has showed superior value than conventional imaging in detecting intrahepatic (most common site of metastases in CRC) and extrahepatic metastases (Niekel et al., 2010; Kuehl et al., 2008; Kinkel et al., 2002). Regarding to lymph nodes metastases, a recent meta-analysis by Lu et al. found sensitivity and specificity of 43% and 88%, respectively, recommending PET/CT as addendum to other modalities in case of equivocal findings (Lu et al., 2012).

1.5.2. Radiation Oncology point of view

The guidelines for CTV delineation in pre-operative CRChave been recently updated in the international consensus (Roels et al., 2006; Joye et al., 2015; Valentini et al., 2016; Joye et al., 2016). The role of FDG-PET for GTV identification is crucial, representing a useful and powerful tool to accurately determine the largest tumor dimension (Wang et al., 2013; Gwynne et al., 2012; Ciernik et al., 2005). Several studies have investigated the comparison of RT volumes obtained from different imaging technique. PET volumes seem to be bigger than CT volumes but smaller than MRI volumes (Paskeviciute et al., 2009; Bassi et al., 2008; Brændengen et al., 2011; Roels et al., 2009; Buijsen et al., 2011); PET provides the best correlation with the tumor pathologic specimen compared to MRI and CT in rectal cancer (Nijkamp et al., 2012) and it is responsible of changing apported to the treatment plan in 24–46% cases (Bassi et al., 2008; Brændengen et al., 2011). When automatically segmented, it was reported a reduction of interobserver variation in GTV definition (Roels et al., 2009; Buijsen et al., 2011; Nijkamp et al., 2012; Chiti et al., 2010; Patel et al., 2007; Krengli et al., 2010c; Buijsen et al., 2012).

Moreover, the potential role of radiation dose intensification with simultaneous integrated boost guided by 18-FDG-PET/CT in nRT-CHT for locally advanced rectal cancer has not been completely validated. Preliminary results of a prospective study of Alongi et al. did not confirm some advantages in terms of primary tumor downstaging/downsizing on PET volume compared to conventional schedules reported in historical series. The role of 18-FDG-PET/CT in neoadjuvant rectal cancer management needs to be confirmed in further investigations (Alongi et al., 2017)

New tracers are also investigated (FLT and FMISO) (Roels et al., 2008) and compared; no pathological correlation was carried out and this would be helpful in validating this technique further.

PET seems to be promising in target determination, but there are several methodological issues that need to be addressed, including the method for tumor volume segmentation and the selection of optimal tracer for rectal cancer.

Take home message: FDG-PET/CT can be used to evaluate features at presentation, therapy response and it could be useful in assessing the oncological outcomes of CRC.

2. Conclusion

PET/CT imaging produces a sensible change in RT volume definition, proving also a potential value in predicting clinical outcome after primary treatment (Albano et al., 2018). The present review assembles

Table 6
Advantages and disadvantages of PET/CT in target volume definition of pancreatic, prostate, gynecological, rectal and anal cancers.

Advantages	Disadvantages
Pancreatictumors	
pancreatic tumours are FDG-avid	Lack of pathologicalconfirmation
Optimal tumor delineation and contrast, distinguishing the primary tumour from the duodenum	
Correlate with prognosis	
Prostate tumors	
Identify patients who may benefit of dose escalation	lack of evidence from clinical trials
Biological analog and sensitive to areas of potential recurrence	decreaseduptake in neoplasmswithlower proliferative indices
More specific to tumoral cellular proliferation than inflammatory- type changes	
Gynecologicalcancers	
Delineate avoidance targets	Segmentation algorithms could have an impact on the MTV and this could bring uncertainties in PET/CT guidance of tumor RT
better staging and definition of disease	
Brachytherapytretment planning	
Rectal/anal Cancer	
high FDG avidity (up to 98%)	Other trackers than FDG are still under evaluation.
useful supplement in target definition for delineating smaller volume compared to CT	

the comprehensive literature data to evaluate whether PET/CT may offer a valuable impact for the definition of the BTV for RT planning of pancreas, gynecological cancer, prostate, rectal and anal cancer, highlighting strengths and weakness (Table 6). RT target definition based on molecular and functional imaging is steadily increasing and represents a large step to “personalize RT planning” in a “multidisciplinary oncological approach way” (Alongi et al., 2019.

Compliance with ethical standards

None.

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Conflict of interest

The authors declare that they have no conflict of interest.

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