

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Role of positron emission tomography-computed tomography in the management of anal cancer

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/104108> since 2016-01-28T13:20:27Z

Published version:

DOI:10.1016/j.ijrobp.2011.10.048

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)



UNIVERSITÀ DEGLI STUDI DI TORINO

This Accepted Author Manuscript (AAM) is copyrighted and published by Elsevier. It is posted here by agreement between Elsevier and the University of Turin. Changes resulting from the publishing process - such as editing, corrections, structural formatting, and other quality control mechanisms - may not be reflected in this version of the text. The definitive version of the text was subsequently published in *Int. J. Radiation Oncol Biol Phys* 84, 1, 2012, DOI 10.1016/j.ijrobp.2011.10.048
<http://www.sciencedirect.com/science/article/pii/S0360301611034560>

You may download, copy and otherwise use the AAM for non-commercial purposes provided that your license is limited by the following restrictions:

- (1) You may use this AAM for non-commercial purposes only under the terms of the CC-BY-NC-ND license.
- (2) The integrity of the work and identification of the author, copyright owner, and publisher must be preserved in any copy.
- (3) You must attribute this AAM in the following format: Creative Commons BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/deed.en>),
<http://www.sciencedirect.com/science/article/pii/S0360301611034560>

Role of Positron Emission Tomography-Computed Tomography in the Management of Anal Cancer

- Massimiliano Mistrangelo, MD, PhD^{□,*,†}, Ettore Pelosi, MD[†], Marilena Bellò, MD[‡],
- Umberto Ricardi, MD[§], Enrica Milanesi, MD[□], Paola Cassoni, MD[¶], Massimo Baccega, MD^{□□}, Claudia Filippini, MD^{††}, Patrizia Racca, MD[□], Adriana Lesca, MD^{□□}, Fernando H. Munoz, MD[§], Gianluca Fora, MD[□], Andrea Skanjeti, MD[‡], Francesca Cravero, MD[□],
- Mario Morino, MD[□]

Purpose

Pre- and post-treatment staging of anal cancer are often inaccurate. The role of positron emission tomography-computed tomography (PET-CT) in anal cancer is yet to be defined. The aim of the study was to compare PET-CT with CT scan, sentinel node biopsy results of inguinal lymph nodes, and anal biopsy results in staging and in follow-up of anal cancer.

Methods and Materials

Fifty-three consecutive patients diagnosed with anal cancer underwent PET-CT. Results were compared with computed tomography (CT), performed in 40 patients, and with sentinel node biopsy (SNB) (41 patients) at pretreatment workup. Early follow-up consisted of a digital rectal examination, an anoscopy, a PET-CT scan, and anal biopsies performed at 1 and 3 months after the end of treatment. Data sets were then compared.

Results

At pretreatment assessment, anal cancer was identified by PET-CT in 47 patients (88.7%) and by CT in 30 patients (75%). The detection rates rose to 97.9% with PET-CT and to 82.9% with CT ($P=0.042$) when the 5 patients who had undergone surgery prior to this assessment and whose margins were positive at histological examination were censored. Perirectal and/or pelvic nodes were considered metastatic by PET-CT in 14 of 53 patients (26.4%) and by CT in 7 of 40 patients (17.5%). SNB was superior to both PET-CT and CT in detecting inguinal lymph nodes. PET-CT upstaged 37.5% of patients and downstaged 25% of patients. Radiation fields were changed in 12.6% of patients. PET-CT at 3 months was more accurate than PET-CT at 1 month in evaluating outcomes after chemoradiation

therapy treatment: sensitivity was 100% vs 66.6%, and specificity was 97.4% vs 92.5%, respectively. Median follow-up was 20.3 months.

Conclusions

In this series, PET-CT detected the primary tumor more often than CT. Staging of perirectal/pelvic or inguinal lymph nodes was better with PET-CT. SNB was more accurate in staging inguinal lymph nodes.

Summary

This study looked at pre- and post-treatment imaging in patients with anal cancer undergoing chemo-radiation and compared the results with pathologic findings. PET-CT had a high incidence of inguinal node false positives and sentinel node biopsy was more reliable. PET-CT assessment at 1-month follow-up had lower sensitivity and specificity than anal biopsy but PET-CT assessment at 3 months appeared more useful.

Introduction

Anal cancer remains a rare disease, but its incidence is increasing (1), mainly in association with human papillomavirus (HPV) infection. An estimated 5290 new cases (2100 men and 3190 women) of anal cancer were estimated to occur in the United States in 2009, accounting for approximately 1.91% of digestive system cancers. It has been estimated that 710 deaths due to anal cancer occurred in the United States alone in 2009 (2).

Since 1974, multimodality treatment as proposed by Nigro et al (3), which combines radiation and chemotherapy, has become the standard of care, with surgery reserved for salvage treatment following local failure. Local control rates of 60%-90% to are achievable in all tumor stages, with sphincter preservation in about 65% of cases. High tumor stage and regional nodal involvement are associated with a worse prognosis. Synchronous inguinal metastases occur in 10%-25% of patients (4) and constitute an independent prognostic factor for local failure and overall mortality according to a multivariate analysis in a phase III European Organization for Research and Treatment of Cancer trial (5). Metachronous metastases have been reported in 5%-25% of patients (4).

Clinical workup in the staging of anal cancer consists of digital rectal examination, anoscopy with biopsy of suspicious lesions, palpation of inguinal lymph nodes, tumor

marker assay, chest X-ray, rigid proctoscopy, total colonoscopy, rectal endosonography, and contrast-enhanced diagnostic computed tomography (CT) or magnetic resonance imaging (MRI).

Recently, ¹⁸F-labeled fluorodeoxyglucose-positron emission tomography-CT (FDG-PET-CT) has rapidly gained an expanding role in oncology, with mounting evidence for its effectiveness in the staging and management of various types of tumors. Since 2005, its use in anal cancer has been described 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 and 19. As suggested by Grigsby et al (18), the advantage of FDG-PET-CT is that it can address all 3 staging criteria of the tumor-node-metastasis (TNM) system in a single whole-body imaging procedure by demonstrating the extent of the primary tumor, detecting lymph node metastases, and revealing any sites of distant metastases. The 2007 National Comprehensive Cancer Network (NCCN) treatment guidelines included PET/CT as a part of the standard pretreatment workup of patients diagnosed with anal carcinoma (19). The new NCCN version, 2.2011, considers PET-CT scan for workup, even if its use for staging or treatment planning has not been validated (20). The authors suggested that PET-CT actually does not replace a diagnostic CT scan (20).

In this study, we performed PET-CT at diagnosis and then at 1 and 3 months after the end of chemoradiation therapy treatment in patients with anal cancer and then compared the pre- and post-treatment imaging data sets with follow-up anal biopsy findings in order to evaluate the role of PET-CT in staging and following up patients affected by anal cancer.

Methods and Materials

Patients

The study population consisted of 53 consecutive patients with anal cancer. The study was approved by the local ethics committee. The presenting symptoms were bleeding on defecation, sometimes associated with anal pain or the sensation of an anal mass. Proctological examination and anoscopy revealed an anal neoplasm. Biopsy demonstrated 33 squamous carcinomas and 20 basaloid carcinomas. Clinical workup consisted of digital rectal examination, anoscopy, rigid proctoscopy, total colonoscopy (32 patients), CT scan (40 patients), rectal endosonography (25 patients), sentinel lymph node biopsy (SNB) (41

patients), and tumor marker assay. Patients with perianal cancer were excluded from the study.

We designed a protocol consisting of a PET-CT performed before radiation therapy (RT) and CT treatment that provided adequate pretreatment staging. This protocol was prospectively performed and compared with SNB for inguinal node staging (possible in 41 patients). The pretreatment PET-CT was retrospectively compared with the CT scan. An additional PET-CT was performed at 1 and 3 months after the end of therapy. Those examinations were prospectively compared with anal biopsy results. All patients were informed about the procedure and gave their written informed consent. PET-CT image acquisitions and the techniques of SNB have been described previously 11 and 21.

Contrast-enhanced CT scans in addition to PET-CT and inguinal sentinel node biopsy (SNB) were performed, respectively, in 40 and 41 patients, and results were compared. On completion of pretreatment assessment, combined chemoradiation therapy treatment was initiated. Chemotherapy was administered according to the following schedule: fluorouracil, 1000 mg/m² on days 1-4 and on days 28-31, in combination with mitomycin C, 10 mg/m² on days 1 and 28. All patients receiving RT were treated with megavoltage therapy units: 30 patients were treated with 3-dimensional conformal RT, and 3 patients were treated with intensity modulated radiation therapy (average dose, 56.4 Gy; range, 45-59.4 Gy). The primary tumor received a dose of 54 Gy (45 Gy plus 9 Gy boosting dose). Nodal structures received 45 Gy in an elective fashion. For involved nodes up to 3 cm maximum in any direction, the primary involved node received 50.4 Gy. If involved nodes were >3 cm, the dose received was 54 Gy. Two patients received further treatment with brachytherapy (15 and 18 Gy, respectively) to treat minimal persistence of disease. At 1 and 3 months after the completion of chemoradiation therapy patients underwent rectal digital examination, anoscopy with biopsy, and PET-CT. PET-CT data and anal biopsy findings were then compared.

Statistical analysis

Data are presented as means \pm SD (or median and range) and rate with percentages for continuous and categorical variables, respectively. Differences in means were compared using a two-tailed Student *t* test. Chi-square or Fisher's exact test was used for categorical data as appropriate. Statistical significance was set at a *P* level of .05. Statistical analysis was performed using SAS software version 8.02 (SAS Institute, Cary, NC).

Results

Between October 2004 and December 2009, 53 consecutive patients with anal cancer were studied at our department. Patient characteristics are shown in Table 1.

Table 1.

Patient characteristics

Patient characteristic No. of patients (%)

Sex

Male	19 (35.8)
Female	34 (64.1)

Race

White	53 (100)
-------	----------

Age (y)

Median	56.6
Range	32-75
HIV seropositive	14 (26.4)

Histological subtype

Squamous	33 (62.3)
Basaloid	20 (37.7)

Localization

Anal canal	34 (64.1)
Anal margin	19 (35.8)

T stage

T1	5 (9.4)
T2	29 (54.7)
T3	15 (28.3)
T4	4 (7.5)

Detection of the primary tumor

Pretreatment PET-CT staging was performed in all 53 patients; biopsy results were positive for anal cancer in all cases. The primary tumor was visualized in the anal region in 47 patients (88.7%). Five patients were referred to our department after local excision of

the tumor. Histological examination revealed persistence of the tumor in the specimen margins in all 5 cases, whereas PET-CT was negative in all 5 cases. PET-CT was unable to detect the persistence of disease. In the remaining 48 patients, PET-CT confirmed an anal tumor in 47 patients (97.9%). The false-negative case was diagnosed as T1 anal cancer (20% of T1 patients).

CT revealed an anal tumor in 30 of 40 patients (75%, with 10 false-negative results). CT was negative in 4 of the 5 patients who had undergone tumor removal. These 5 patients had stage T2 disease. When they were excluded from analysis, the detection rate for CT was 82.9% (29/35 patients). In the remaining patients, CT was negative in 2/3 stage T1 patients (66.6% false negatives) and in 4/18 T2 patients (22.2% false negatives). CT correctly revealed the tumor in all T3 and T4 patients.

The detection rate of PET-CT vs CT in identifying the primary tumor was 97.9% vs 82.9% ($P=.042$, obtained using a chi-square test). Table 2 shows the detection rates for pretreatment PET-CT and CT, excluding the data subset identifying the surgically untreated tumor.

Table 2.

Anal cancer detected by pretreatment PET-CT and CT, excluding patients who had undergone surgical tumor removal

Stage	No. of patients/total found to be positive by PET-CT (%)	No. of patients/total found to be positive by CT (%)
T1	4/5 (80)	1/3 (33.3)
T2	24/24 (100)	14/18 (77.8)
T3	15/15 (100)	11/11 (100)
T4	4/4 (100)	3/3 (100)
Total	47/48 (97.9)	29/35 (82.9)

Detection of metastatic perirectal and pelvic nodes

Perirectal and/or pelvic nodes were revealed by PET-CT in 14 of 53 patients (26.4%) and by CT in 7 of 40 patients (17.5%).

Detection of metastatic inguinal nodes

PET-CT was positive for inguinal metastases in 12 of 53 patients (22.6%) (Fig. 1, Fig. 2 and Fig. 3) and negative in 41 of 53 patients (77.4%). CT was positive for inguinal metastases in 8 of 40 patients (20%).

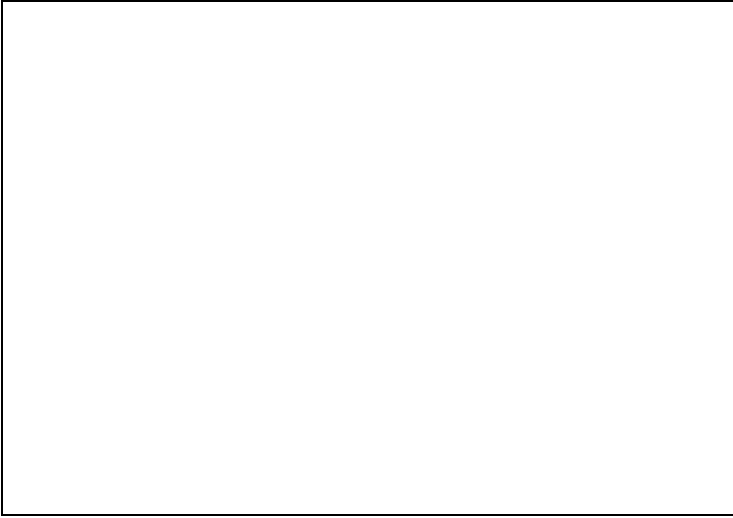


Fig. 1.
PET-CT scan showing inguinal lymph node metastases in a 76-year-old female patient.

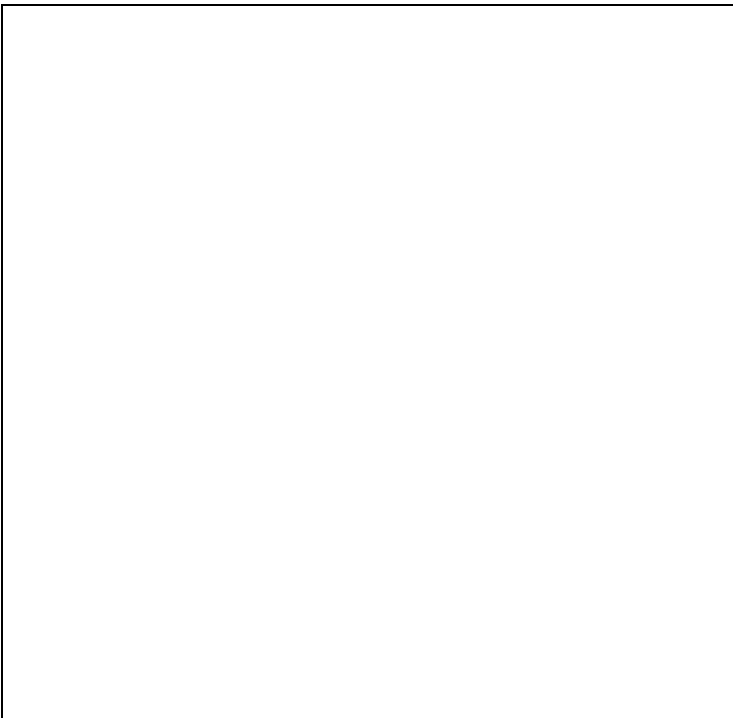


Fig. 2.
Inguinal metastases on PET-CT in a 76-year-old female patient.
Figure options

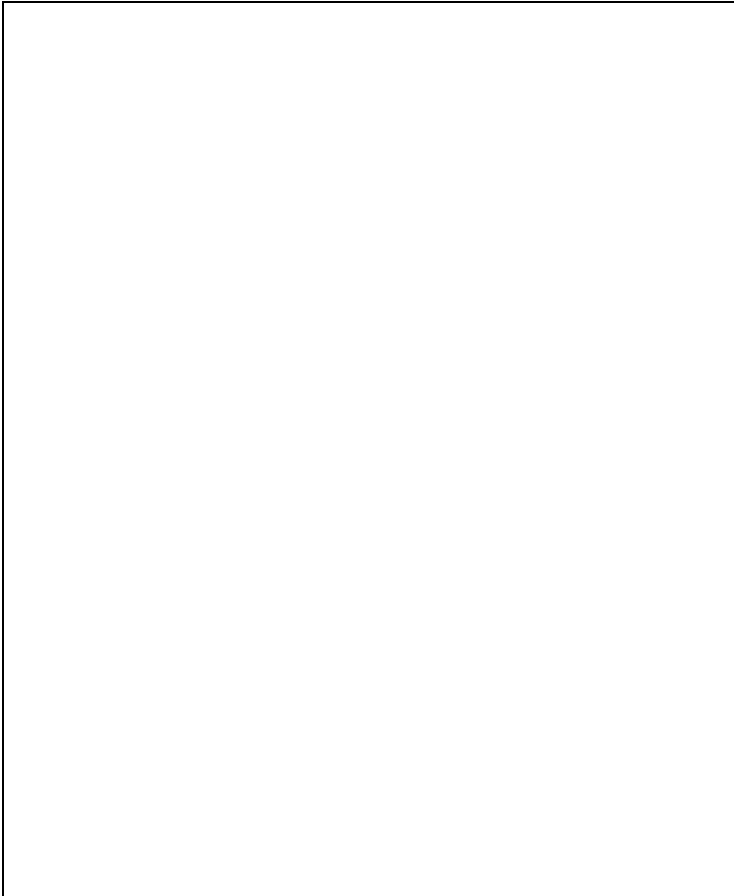


Fig. 3.

PET-CT in a 76-year-old female patient.

Figure options

Inguinal node staging was compared with the results of SNB, which was performed in 41 patients. Comparison between SNB and PET-CT findings showed that SNB confirmed the presence of inguinal metastases in only 8 cases, with 4 of 41 patients (9.7%) false positive and 2 of 41 patients (4.9%) false negative. Comparison between SNB and CT findings (34 patients) showed that SNB identified 4 of 34 patients (11.7%) false positive and 4 of 34 patients (11.7%) false negative.

Other findings

PET-CT was suggestive of suspected metastases to mediastinal lymph nodes in 1 of 53 patients (1.9%); a subsequent thoracoscopic biopsy revealed only fibrosis. CT revealed a renal neoplasm that PET-CT failed to detect in 1 of 40 patients (2.5%); an oncocytoma was found at surgery. CT revealed 2 cases (5% of 40 patients) of suspected invasion of the vagina (not confirmed by clinical examination) and 3 cases (7.5% of 40 patients) of suspected pulmonary metastases (not confirmed by PET-CT).

Pretreatment final staging

Tumors were staged according to the American Joint Committee on Cancer staging system (22). Tumor staging obtained with PET-CT and CT scans is shown in Table 3. PET-CT upstaged 15 patients (37.5%; 95% confidence interval [CI], 22.1-55.6) and downstaged 10 patients (25%; 95% CI, 10.1-39.9), compared to CT scans. Three of the patients upstaged by CT corresponded to the 3 cases of suspected pulmonary metastases not confirmed by PET-CT and follow-up in 2 cases or by biopsy and PET-CT in 1 case. Downstaging decreased to 16% when these 3 cases were excluded from the analysis. The radiation fields were changed in 5 patients (12.5%).

Table 3.

Pretreatment tumor staging by PET-CT and CT for all patients

Stage	No. of patients staged by PET-CT (N=53) (%)	No. of patients staged by CT (N=40) (%)
0	6 (11.3)	10 (25)
I	3 (5.6)	1 (2.5)
II	22 (41.5)	9 (22.5)
IIIA	2 (3.8)	8 (20)
IIIB	19 (35.8)	9 (22.5)
IV	1 (1.9)	3 (7.5)

Treatment

Patients were treated for anal cancer: 40 patients (75.5%) received combined chemoradiation therapy 1 patient (1.9%) RT alone, 7 patients (13.2%) surgery plus combined chemoradiation therapy and 5 patients (9.4%) surgery alone (T1 lesions of anal margin). The 7 patients mentioned above underwent a surgical excision of the anal mass by another surgeon, but the surgery was not complete, so chemoradiation therapy was indicated to radicalized uncompleted excision.

Follow-up at 1 month

PET-CT and anal biopsy were performed at 1 month after the end of treatment. PET-CT was performed in 43/53 patients: 1 patient died while receiving combined treatment; 5 patients were still under radiation and/or chemotherapy or in follow-up; and 4 patients did not return for PET-CT assessment.

Of these 43 patients, 35 patients (81.4%) were PET-CT negative; 5 patients (11.6%) were positive for the persistence of local disease; and 3 patients (7%) were positive for inguinal or lumboaortic lymph node metastases. PET-CT was positive for multiple abdominal, inguinal, thoracic, and neck nodes in 2 HIV-seropositive patients. All patients positive for suspected persistence of anal disease had received chemoradiation therapy treatment. Anal biopsy confirmed the persistence of disease in 3 patients, 2 of whom underwent abdominoperineal resection (APR) for the persistence of disease, and definitive histology confirmed the persistence of anal cancer after chemoradiation therapy. The third patient declined APR and subsequently underwent macrobiopsy of the suspected residual neoplastic area. The histological examination was negative for the persistence of disease, in contrast to the findings from both PET-CT and anal biopsy. At 44 months' follow-up, there was no persistence or recurrence of disease in this patient. The 2 patients found positive at PET-CT but negative at anal biopsy tested negative at later follow-up assessments (27 and 15 months, respectively) for the persistence or recurrence of disease without further therapy. The 2 patients found positive for multiple lymph nodes were negative for neoplastic disease during follow-up at 33 and 22 months, respectively. In the 2 cases of positive inguinal nodes detected by PET-CT, inguinal biopsy confirmed the presence of inguinal metastases in 1 patient and was negative in the other patient (1 false negative). Assessment at 1 month follow-up is shown in Table 4. In the detection of persistence of disease, PET-CT had a sensitivity of 66.6%, a specificity of 92.5%, a positive predictive value (PPV) of 40%, and a negative predictive value (NPV) of 97.4%. Anal biopsy had a sensitivity of 100%, a specificity of 97.5%, a PPV of 75%, and an NPV of 100%.

Table 4.

Results of follow-up assessment at 1 month

Assessment	PET-CT (N=43) (%)	Anal biopsy (N=43) (%)
Negative-anus	38 (88.4)	39 (90.7)
Persistence of anal disease	5 (11.6)	4 (9.3)
True positive	2	3
False positive	3	1
False negative	1	0
True negative	37	39
Multiple lymph node metastases	2 (4.6)	NE
Inguinal lymph node metastases	2 (4.6)	NE
True positive	1 (50)	NE

Assessment	PET-CT (N=43) (%)	Anal biopsy (N=43) (%)
False positive	1 (50)	NE
Lumboaortic lymph node metastases	1 (2.3)	NE

Abbreviation: NE = not evaluated.

Table options

Follow-up at 3 months

PET-CT and anal biopsy, performed by the same surgeon who specialized in colorectal surgery, were both performed in 40 patients at 3 months after the end of treatment. Biopsies were executed in the exact site of the original neoplasm and eventually in areas of induration of the anal canal. PET-CT was performed in 40 patients (2 patients had undergone APR, 11 patients dropped out or were in follow-up). PET-CT detected no persistence of local disease in 32 patients (80%). All patients with a PET-CT positive for persistence of local disease had previously received chemoradiation therapy treatment. Results are shown in Table 5. PET-CT revealed 1 false positive for persistence of disease (2.5%).

Table 5.

Results of follow-up assessment at 3 months

Assessment	PET-CT (N=40) (%)	Anal biopsy (N=40) (%)
Negative-anus	37 (92.5)	38 (95)
Persistence of anal disease	3 (7.5)	2 (5)
True positive	2	2
False positive	1	-
Multiple lymph node metastases	2 (5)	NE
Inguinal lymph node metastases	2 (5)	NE
Femoral metastases	1 (2.5)	NE

Abbreviation: NE = not evaluated.

Table options

The 2 HIV-seropositive patients with multiple lymph nodes were in follow-up and were negative for neoplastic disease. A patient with suspected femoral metastases, observed at PET-CT, underwent a biopsy that revealed a desmoid tumor. The 2 patients positive for inguinal metastases were positive in one case and negative in the other.

In the detection of persistence of disease, PET-CT had a sensitivity of 100%, a specificity of 97.4%, a PPV of 66%, and a NPV of 100%. Anal biopsy had a sensitivity of 100%, a specificity of 100%, a PPV of 100%, and a NPV of 100%.

Follow-up

The median duration of follow-up was 20.3 months (range, 1-60 month). During the follow-up period, 4 patients (7.5%) died: 1 due to toxicity related to radiation and chemotherapy treatment and 3 due to progression of disease. Ten patients (18.8%) experienced a recurrence in the same place of original disease: 2 patients were treated with brachytherapy; 3 patients with APR; 2 patients with chemotherapy (1 after declining APR, and 1 of whom was treated for pelvic and iliac lymph node recurrence); and 2 patients with surgery (1 R0 and 1 R1 resections after declining other treatments); and 1 patient was hospitalized for hepatitis C virus and HIV co infection.

Discussion

Patients affected by anal cancer were studied with PET-CT scans in order to evaluate the role of the scans in staging and superior detection of primary neoplasm and lymph node metastases but inferior ability to stage SNB in inguinal lymph nodes. The study also provided results of PET-CT in follow-up of these patients, showing that PET-CT performed 3 months after the end of combined chemoradiation therapy was useful in association with digital rectal examination, anoscopy, and biopsy results, in detection of persistence of the disease.

Accurate staging of anal cancer followed by optimal planning of combined chemoradiation therapy treatment can extend patient survival. Anatomical imaging techniques such as CT and MRI cannot evaluate tumor biology and behavior. PET-CT imaging is increasingly used to stage different malignant diseases (23). The advantage of PET-CT fusion imaging is its ability to correlate findings from anatomic and functional imaging modalities, lending it a more important role than diagnostic CT alone in the selection of proper treatment (13). Moreover, therapy-induced changes in tumors are related to changes in FDG uptake, and treatment response can be efficiently monitored by PET-CT, also considering the standardized uptake value (SUV) of FDG.

Data from our study indicate that PET-CT is clearly superior to CT in visualizing the biopsy-proven primary tumor, although the lack of sensitivity did not affect treatment. The primary anal tumor was revealed by PET-CT in 88.7% of patients and by CT in 75%. These percentages rise to 98% and 83% ($P=0.042$), respectively, when we excluded the 5 patients who had undergone surgical removal of the anal tumor but who had histologically

confirmed positive surgical margins. This suggests that both PET-CT and CT were unable to detect residual tumor after surgical excision. These data agree with previous observations: detection of the primary anal tumor varies from 82% (16) to 100% (10) for PET-CT vs 45% (16) to 76% (24) for CT.

In our series, pretreatment PET-CT upstaged 37.5% of patients and downstaged 25% of patients with anal cancer. These staging differences were higher than those reported by other studies, where upstaging was between 7% and 20% 6, 7, 9, 10 and 25, but comparable to those in the study by Bannas et al (16) (upstaging of 36% of patients) (16). The study by De Winton et al (10) was the only other one besides ours to report downstaging (8%).

PET-CT at diagnosis can also be used for radiation therapy treatment planning as it clearly defines sites of metabolically active tumor (16). Radiation treatment fields were changed in 12.6% of patients. This rate was lower than that reported elsewhere (range, 16%-35%) 7, 8, 9, 10 and 26. Only Vercellino et al (25) reported no change in treatment fields in their series of 44 patients.

In most studies, upstaging was related to better staging of metastases in perirectal, pelvic, and inguinal lymph nodes. As it defines nodal and metastatic disease, PET imaging can improve the staging of anal cancer (9). Mai et al (27) assumed that PET-positive lymph nodes in a setting of anal cancer as defined by SUV uptake raises the likelihood of lymph node involvement, which would warrant more aggressive treatment in patients with PET positive nodes.

The sensitivity of CT for detecting nodal metastases in the pelvic and inguinal regions is limited to 40%-68% (27). In contrast, PET-CT showed a higher specificity (80%-90%) and sensitivity (70%-90%) in the detection of nodal and distant metastases for several tumor types like non-small cell lung cancer and head-and-neck cancer (27). Also, in gynecologic cancer, PET can have a specificity of 90%-95% (28).

Cotter et al (7) reported that PET-CT upstaged inguinal nodes in 17% of patients. They also found a higher rate of PET-CT positivity for inguinal metastases in HIV-seropositive vs HIV-seronegative patients (44% vs 16%), while we observed a marginal difference in positive inguinal metastases between these 2 patient subgroups (28.5% vs 25%).

Otherwise, 5% of inguinal lymph node metastases detected with PET-CT were false positive by fine-needle aspiration cytology results (15) and up to 57% by histological confirmation of samples from SNB (11). Igaru et al (14) and Engledow et al (15) reported that inguinal lymph nodes positive by PET-CT were negative by fine-needle aspiration

cytology in 50% and by SNB in 5% of cases. Therefore, positive lymph nodes identified by PET-CT should be adequately studied with biopsy before changing RT plans. In this connection, the high incidence of inguinal metastases found on imaging compared with conventional staging tools should warn against unnecessary inguinal RT. Inguinal staging with SNB may explain the lower percentage of change in RT fields in our series compared to others.

PET-CT also was recently considered for follow-up of patients undergoing radiation and chemotherapy treatment in anal cancer. Kidd et al (29) reported that a higher SUV_{max} was associated with lymph node involvement at diagnosis. Those patients were also at higher risk of persistent disease on their post-treatment PET, if the study was performed less than 4 months after completing therapy. The authors suggested that SUV_{max} for FDG represents a potential new biomarker for anal cancer prognosis, as it is significantly associated with lymph node involvement at diagnosis, treatment response, and disease-free survival.

Post-treatment PET-CT is indicated to determine response to therapy, and it is highly predictive of long-term clinical outcomes (18). It can also be used to evaluate sites of recurrent disease. Few studies have examined clinical response to therapy, and clinical workup differs widely. Piperkova et al (13) suggested that PET-CT in anal cancer accurately identifies treatment response. Schwarz et al (12) reported that post-therapy FDG response was the most significant predictor of progression-free survival ($P=0.003$) and that it was more predictive of treatment outcome than either pretreatment tumor size ($P=0.08$) or nodal status ($P=0.40$). Persistent disease is indeed a predictor of poor clinical outcome (12).

In our study, PET-CT assessment at 1 month had a sensitivity of 66.6%, a specificity of 92.5%, a PPV of 40%, and a NPV of 97.4% for detecting persistence of anal disease. These data are not comparable to previous observations. Only Trautmann et al (6) reported results of PET-CT assessment at 1 month (persistence of disease of 66.6% of cases), suggesting that PET-CT at 1 month after the end of therapy is of little value in predicting the durability of response.

In contrast, anal biopsy at 1-month follow-up had higher sensitivity and specificity than PET-CT, even if assessment with biopsy of nonprogressive residual tumor at 1 month after treatment might be misleading because shortly after radiation, a nonviable cancer cell may look morphologically intact (30). Considering these aspects, biopsy sample for a nonprogressive residual tumor at 1 month after treatment should not be taken, as this can

lead to unnecessary abdominoperineal excision. These patients should be closely observed.

PET-CT assessment at 3 months had a sensitivity of 100%, a specificity of 97.4%, a PPV of 66%, and a NPV of 100%; anal biopsy had the same sensitivity but a better specificity than PET-CT. One limitation of our study is that the patient series was small, thus limiting its statistical power. Multicenter studies will be needed to confirm these results.

Conclusions

In our series, PET-CT detected the primary tumor more often than CT, but neither tool is indicated to reveal persistent disease after surgery. PET-CT proved useful in initial staging of perirectal/pelvic or inguinal lymph nodes. However, upstaging related to lymph nodes metastases might have been overestimated, as up to 31% of inguinal metastases identified by PET-CT are reportedly false positive. Currently, inguinal lymph nodes are better staged by sentinel node biopsy. PET-CT assessment at 1-month follow-up had lower sensitivity and specificity than anal biopsy. PET-CT assessment at 3 months more accurately evaluated the persistence or the recurrence of anal disease and thus allowed for better follow-up when combined with anal biopsy.

References

1.
 - L.A.G. Ries, D. Harkins, M. Krapcho, *et al.*
 - B.K. Edwards (Ed.), SEER incidence and US mortality, trends 1992-2002 in SEER Cancer statistics review, 1975-2003, National Cancer Institute, Baltimore, MD (2005), pp. 1–103
2.
 - A. Jemal, R. Siegel, E. Ward, *et al.*
 - Cancer statistics, 2009
 - CA Cancer J Clin, 59 (2009), pp. 225–249
3.
 - N.D. Nigro, V.K. Vaitkeicus, C.B. Basil
 - Combined therapy for cancer of the anal canal: a preliminary report
 - Dis Colon Rectum, 17 (3) (1974), pp. 354–356
4.
 - J.-P. Gerard, O. Chapet, F. Samiei, *et al.*

- Management of inguinal lymph node metastases in patients with carcinoma of the anal canal. Experience in a series of 270 patients treated in Lyon and review of the Literature
- Cancer, 92 (2001), pp. 77–84
- 5.
- H. Bartelink, F. Roelofsen, F. Eschwege, *et al.*
- Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups
- J Clin Oncol, 15 (5) (1997), pp. 2040–2049
- 6.
- T.G. Trautmann, J.H. Zuger
- Positron emission tomography for pre-treatment staging and posttreatment evaluation in cancer of the anal canal
- Mol Imaging Biol, 7 (2005), pp. 309–313
- 7.
- S.E. Cotter, P.W. Grigsby, B.A. Siegel, *et al.*
- FDG-PET/CT in the evaluation of anal carcinoma
- Int J Radiat Oncol Biol Phys, 65 (2006), pp. 720–725
- 8.
- C. Anderson, M. Koshy, C. Staley, *et al.*
- PET-CT fusion in radiation management of patients with anorectal tumors
- Int J Radiat Oncol Biol Phys, 69 (1) (2007), pp. 155–162
- 9.
- B.T. Nguyen, D.L. Joon, V. Khoo, *et al.*
- Assessing the impact of FDG-PET in the management of anal cancer
- Radiother Oncol, 87 (2008), pp. 376–382
- 10.
- E. de Winton, A.G. Heriot, M. Ng, *et al.*
- The impact of 18-fluorodeoxyglucose positron emission tomography on the staging, management and outcome of anal cancer
- Br J Cancer, 100 (2009), pp. 693–700
- 11.
- M. Mistrangelo, E. Pelosi, M. Bellò, *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, 77 (1) (2010), pp. 73–78
- 12.
- J.K. Schwarz, B.A. Siegel, F. Dehdashti, *et al.*
- Tumor response and survival predicted by post therapy FDG-PET/CT in anal cancer
- Int J Radiat Oncol Biol Phys, 71 (1) (2008), pp. 180–186
- 13.
- E. Piperkova, B. Raphael, M. Altinyay, *et al.*
- Impact of PET/CT on initial staging, restaging and treatment management of anal cancer: a clinical case with literature review
- J BUON, 11 (2006), pp. 523–527
- 14.
- A. Iagaru, R. Kundu, H. Jadvar, *et al.*
- Evaluation by 18 F-FDG-PET of patients with anal squamous cell carcinoma
- Hell J Nucl Med, 12 (1) (2009), pp. 26–29
- 15.
- A.H. Engledow, J.R.A. Skipworth, G. Blackman, *et al.*
- The role of 18FDG PETCT in the clinical management of anal squamous cell carcinoma
- Colorectal Dis, 13 (5) (2011), pp. 532–537
- 16.
- P. Bannas, C. Weber, G. Adam, *et al.*
- Contrast-enhanced [¹⁸F]Fluorodeoxyglucose-positron emission tomography/computed tomography for staging and radiotherapy planning in patients with anal cancer
- Int J Radiat Oncol Biol Phys, 81 (2) (2011), pp. 445–451
- 17.
- M. Krengli, M.E. Milia, L. Turri, *et al.*
- FDG-PET/CT imaging for staging and target volume delineation in conformal radiotherapy of anal carcinoma
- Radiat Oncol, 5 (2010), p. 10
- 18.
- P.W. Grigsby
- FDG-PET/CT: new horizons in anal cancer
- Gastroenterol Clin Biol, 33 (5) (2009), pp. 456–458
- 19.
- P.F. Engstrom, J.P. Arnoletti, A.B. Benson III, *et al.*
- NCCN clinical practice guidelines in oncology. Anal carcinoma
- J Natl Compr Canc Netw, 8 (1) (2010), pp. 106–120

20.

- Engstrom PF, Arnoletti JP, Benson AB III, et al. NCCN Clinical practice guidelines in oncology: anal carcinoma. vol 2.2011. 2. National Comprehensive Cancer Network. Available at: <http://bit.ly/iH4XWj>. Accessed March 30, 2012.

21.

- M. Mistrangelo, M. Bellò, A. Mobiglia, *et al.*
- Feasibility of the sentinel node biopsy in anal cancer
- Q J Nucl Med Mol Imaging, 53 (1) (2009), pp. 3–9

22

American Joint Commission on Cancer

- Anal canal
- AJCC cancer staging manual (6th ed.), Springer, New York (2002), pp. 125–130

23.

- P.J. Ell
- PET/CT in oncology: a major technology for cancer
- Chang Gung Med J, 28 (2005), pp. 274–283

24.

- A. Scherrerree, F. Reboul, D. Martin, *et al.*
- CT of malignant anal canal tumors
- Radiographics, 10 (3) (1990), pp. 433–453

25.

- L. Vercellino, V. de Paredes, V. Nataf, *et al.*
- Has FDG PET/CT an impact on the management of patients with anal carcinoma?
- Med Nucl, 34 (2010), pp. 96–102

26.

- S. Renaud, S. Guillermand, M.C. Eberlé-Pouzeratte, *et al.*
- Contribution of ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) in the management of anal carcinoma

- Med Nucl, 33 (2009), pp. 415–424

27.

- S.K. Mai, G. Welzel, B. Hermann, *et al.*
- Can the radiation dose to CT-enlarged but FDG-PET-negative inguinal lymph nodes in anal cancer be reduced?
- Strahlenther Onkol, 185 (2009), pp. 254–259

28.

- D.E. Cohn, F. Dehdashti, R.K. Gibb, *et al.*
- Prospective evaluation of positron emission tomography for the detection of groin node metastases from vulvar cancer
- Gynecol Oncol, 85 (2002), pp. 179–184

29.

- E. Kidd, F. Dehdashti, B.A. Siegel, *et al.*
- Anal cancer maximum F-18 fluorodeoxyglucose uptake on positron emission tomography is correlated with prognosis
- Radiother Oncol, 95 (2010), pp. 288–291

30.

- H.D. Suit, H.S. Gallager
- Intact tumor cells in irradiated tissue
- Arch Pathol, 78 (1964), pp. 648–651