

ORIGINAL ARTICLE

**FDG-PET/CT–based restaging may alter initial management decisions and clinical outcomes in patients with locally advanced pancreatic carcinoma planned to undergo chemoradiotherapy**

Erkan Topkan<sup>a</sup>, Cem Parlak<sup>a</sup>, Ali Fuat Yapar<sup>b</sup>

<sup>a</sup>Baskent University Adana Medical Faculty, Department of Radiation Oncology, Adana, Turkey; <sup>b</sup>Baskent University Adana Medical Faculty, Department of Nuclear Medicine, Adana, Turkey

Corresponding address: Erkan Topkan, MD, Department of Radiation Oncology, Baskent University, Adana Medical Faculty, Kisla SaglikYerleskesi, 01120, Adana, Turkey.  
Email: docdretopkan@gmail.com

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**Abstract**

The impact of [<sup>18</sup>F]fluorodeoxyglucose-positron emission tomography (PET)/computed tomography (CT) restaging on management decisions and outcomes in patients with locally advanced pancreatic carcinoma (LAPC) scheduled for concurrent chemoradiotherapy (CRT) is examined. Seventy-one consecutive patients with conventionally staged LAPC were restaged with PET/CT before CRT, and were categorized into non-metastatic (M<sub>0</sub>) and metastatic (M<sub>1</sub>) groups. M<sub>0</sub> patients received 50.4 Gy CRT with 5-fluorouracil followed by maintenance gemcitabine, whereas M<sub>1</sub> patients received chemotherapy immediately or after palliative radiotherapy. In 19 patients (26.8%), PET/CT restaging showed distant metastases not detected by conventional staging. PET/CT restaging of M<sub>0</sub> patients showed additional regional lymph nodes in 3 patients and tumors larger than CT-defined borders in 4. PET/CT therefore altered or revised initial management decisions in 26 (36.6%) patients. At median follow-up times of 11.3, 14.5, and 6.2 months for the entire cohort and the M<sub>0</sub> and M<sub>1</sub> cohorts, respectively, median overall survival was 16.1, 11.4, and 6.2 months, respectively; median locoregional progression-free survival was 9.9, 7.8, and 3.4 months, respectively; and median progression-free survival was 7.4, 5.1, and 2.5 months, respectively (*P* < 0.05 each). These findings suggest that PET/CT-based restaging may help select patients suitable for CRT, sparing those with metastases from futile radical protocols, and increasing the accuracy of estimated survival.

**Keywords:** *Locally advanced pancreatic carcinoma; restaging PET/CT; management decision change; chemoradiotherapy; survival outcome.*

**Introduction**

Radical chemoradiotherapy (CRT) has an established role in the treatment of medically fit patients with unresectable locally advanced pancreatic cancer (LAPC)<sup>[1]</sup>. Despite aggressive CRT, however, outcomes in LAPC remain dismal, with annual incidence and mortality rates being almost equal<sup>[2,3]</sup>. Due to the high locoregional and distant recurrence rates after definitive CRT, accurate staging of these patients is crucial in selecting those who may benefit from aggressive treatment, sparing those with metastases (M<sub>1</sub>) from futile and potentially toxic

treatment protocols. In addition, administration of CRT to these M<sub>1</sub> patients and those with locally advanced but non-metastatic (M<sub>0</sub>) tumors due to inaccurate staging may eventuate in unintentional under- or overestimation of treatment outcomes.

Traditional staging work-up in LAPC includes abdominal ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), and endoscopic US<sup>[4]</sup>. Although these methods are valuable in assessing primary tumors (T), they are not satisfactory for the determination of nodal (N) or distant metastatic (M)

stages, and may result in the understaging of patients. Functional imaging with [ $^{18}\text{F}$ ]fluorodeoxyglucose (FDG)-positron emission tomography (PET) has been shown to be a useful adjunct in diagnosing pancreatic tumors<sup>15–71</sup>. Integration of FDG-PET with anatomic CT results in improved spatial resolution, making the combination useful for the detailed assessment of T stage in primary and restaging settings. The major benefit of PET/CT is its greater ability to detect distant metastases (DM), and to discriminate between malignant and benign lesions that are equivocal on CT<sup>181</sup>. Although the liver and peritoneum are the most frequent metastatic sites in patients with LAPC, approximately one-third of these metastases smaller than 1 cm are missed by conventional CT and MRI<sup>181</sup>. A recent meta-analysis showed that PET/CT had the highest pooled sensitivity (91%) in detecting peritoneal metastases compared with CT and MRI<sup>191</sup>. Moreover, PET/CT accuracy in assessing primary tumors, local regional staging, and restaging in patients with pancreatic cancer has been reported to be 91%, 85%, and 92%, respectively<sup>161</sup>, suggesting that PET/CT may improve conventional staging in LAPC.

In addition to the relative resistance of pancreatic tumor cells to chemotherapy and radiation therapy (RT), the inadvertent downstaging of M<sub>1</sub> disease to LAPC may contribute to the poor survival outcomes in patients with LAPC. Surgical studies have demonstrated that, despite extensive preoperative staging with conventional imaging tools, 25–30% of patients previously regarded as resectable had metastases at the time of laparotomy<sup>110,111</sup>. One important limitation of laparotomy is its ability to assess only intra-abdominal structures. The addition of whole-body FDG-PET/CT to conventional staging procedures has been shown to change management strategies in 36–41% of patients with pancreatic cancer by providing more accurate staging<sup>1121</sup>. We therefore hypothesized that restaging with PET/CT before CRT may increase the accuracy of LAPC staging, obviating the use of potentially toxic and unnecessary CRT in M<sub>1</sub> patients, and correcting the underestimation of survival rates in patients with true LAPC. To test this hypothesis, conventionally staged LAPC patients were restaged with PET/CT before CRT, and the effects of PET/CT on the initial treatment decisions and clinical outcomes were assessed.

## Materials and methods

### *Study population*

The study population consisted of 71 consecutive patients diagnosed with surgically proven unresectable LAPC from June 2007 to March 2011. Disease extent was determined by laparotomy/laparoscopy and by imaging modalities, including contrast-enhanced abdominal CT, MRI, and/or MRCP. All patients were restaged with PET/CT, performed for RT planning (RTP). Disease was

considered unresectable if CT or staging laparoscopy revealed a low likelihood of complete resection and/or involvement of the superior mesenteric artery/celiac trunk and encasement or evidence of narrowing or thrombus within the superior mesenteric/portal vein. Inclusion criteria included age 18–70 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, presence of measurable or evaluable lesions, no contraindications for PET/CT imaging, adequate bone marrow reserve (Hb  $\geq$ 10 g/dL, white blood cell count  $\geq$ 4,000/ $\mu\text{L}$ , and platelet count  $\geq$ 100,000/ $\mu\text{L}$ ), adequate hepatic function (aspartate and alanine aminotransferase  $<$ 5 times the upper limit of normal), and adequate renal function (serum creatinine  $<$ 2 mg/dL). Patients with a previous history of chemotherapy or abdominal RT were excluded. All patients provided written informed consent signed before the start of treatment, and the study protocol, which was in accordance with the Declaration of Helsinki and the Rules of Good Clinical Practice, was approved by our Institutional Ethics Committee.

### *Restaging with PET/CT*

According to institutional protocol<sup>1131</sup>, PET/CT scans were performed within 10 days of treatment. For each patient, contrast-enhanced CT and FDG-PET scans were assessed by a nuclear medicine physician experienced in tumors of the pancreatobiliary system, who was blinded to the results of conventional staging. Categorization of areas of FDG uptake as malignant was based on their location, intensity, shape, size, and visual correlation with CT images to differentiate physiologic from pathologic uptake. Patients suspected of having DM with widespread metastatic deposits (involvement of more than one organ or multiple lesions in the same organ) were diagnosed radiologically with metastatic pancreatic cancer; by contrast, pathologic confirmation was required in patients with solitary lesions.

### *Treatment*

Image registration and RTP were performed using an Eclipse 7.5 (Varian Medical Systems, Palo Alto, CA, USA) RTP system. Two experienced radiation oncologists, with the assistance of a nuclear medicine physician, defined the target volumes by consensus and contoured the gross tumor volume (GTV) and the planning target volume (PTV) on contrast-enhanced CT/PET/CT fusion images. The volumes of all organs at risk (OAR) were contoured from the CT scans due to the inherent difficulty of detecting edges on PET scans. For each patient, the GTV included the primary tumor and apparently involved lymph nodes on CT ( $\geq$ 1 cm in short axis) and/or PET images (pathologic FDG uptake irrespective of size). PTV was defined as GTV + 1.5 cm in each direction except for intersecting OAR restrictions, to allow for

microscopic extension, organ motion, and set-up errors. Elective nodal irradiation was not performed.

The radiation field design, dose of RT, and OAR constraints have been described<sup>131</sup>. In brief, patients with M<sub>0</sub> disease received an RT protocol using 18 MV photon energy linear accelerators. A dose of 50.4 Gy (1.8 Gy/fraction) was prescribed to encompass the defined PTV with isodose lines between 95% and 107%. Dose-volume histograms were generated to assess target volume coverage and OAR doses. Patients with M<sub>1</sub> disease received palliative irradiation (PRT) to a total of 30 Gy (3 Gy/fraction).

All M<sub>0</sub> patients received continuously infused 5-fluorouracil (225 mg/m<sup>2</sup>/day) throughout the course of RT, followed after the completion of RT by 2–6 courses of maintenance gemcitabine (1000 mg/m<sup>2</sup> intravenously on days 1 and 8 every 21 days). Patients with proven M<sub>1</sub> disease received systemic chemotherapy either during or after PRT, depending on symptom status.

### Toxicity assessment

Toxicity was assessed, scored, and reported according to CTC 3.0 (Common Toxicity Criteria) weekly or more frequently during CRT, every 3 months for the first 2 years, and every 6 months thereafter.

### Response evaluation and follow-up

Response to treatment was assessed by restaging PET/CT scans 12 weeks after the end of CRT in accordance with the response criteria defined by the EORTC 1999 guidelines<sup>141</sup>. The 12-week time interval for the first follow-up PET/CT was the shortest possible time mandated by our national health insurance policy, rather than being evidence based. Thereafter, all patients were monitored every 8–12 weeks by blood count/chemistry, serum CA 19-9 concentrations, and PET/CT. If indicated, patients also underwent abdominal US and/or CT, chest CT, or cranial MRI.

### Statistical analysis

The primary end point was the assessment of the usefulness of restaging PET/CT before CRT on initial management decisions and clinical outcomes, including locoregional progression-free survival (LRPFS), progression-free survival (PFS), and overall survival (OS). Patients were therefore categorized, based on PET/CT findings, into M<sub>0</sub> (true LAPC) and M<sub>1</sub> groups. LRPFS was defined as survival without local/regional failure, and was calculated as the time from the first day of treatment to the day of local/regional failure or death/last visit. PFS was defined as the time from the first day of treatment to the day of any type of disease progression or death/last visit, and OS was defined as the time from the first day of treatment to the date of death/last visit. Survival was analyzed by the Kaplan-Meier method, and a Cox proportional hazard model was used to evaluate the

**Table 1 Pretreatment patient characteristics**

Characteristics	All patients (N=71)	M <sub>0</sub> patients (n=52)	M <sub>1</sub> patients (n=19)	P value
Age (years)				
Median	57.3	57.5	56.8	
Range	39–69	39–69	44–62	0.57
Gender (%)				
Male	54 (76.1)	40 (76.9)	14 (73.7)	
Female	17 (23.9)	12 (23.1)	5 (26.3)	0.52
ECOG performance (%)				
0	12 (16.9)	10 (19.2)	2 (10.5)	
1	41 (57.7)	31 (59.6)	10 (52.6)	0.35
2	18 (25.4)	11 (21.2)	7 (36.8)	
Chief complaint				
Pain	39 (54.9)	29 (55.7)	10 (52.6)	
Weight loss	21 (29.6)	16 (30.7)	5 (26.3)	
Loss of appetite	5 (7.0)	2 (3.9)	3 (15.8)	0.48
Jaundice	4 (5.6)	3 (5.8)	1 (5.3)	
Other	2 (2.9)	2 (3.9)	0 (0)	
Tumor location (n, %)				
Head	58 (81.7)	42 (80.8)	16 (84.2)	
Body	13 (18.3)	10 (19.2)	3 (15.8)	0.52
T and N category (n, %)				
T4N0	35 (49.3)	27 (51.9)	8 (42.1)	
T4N1	36 (50.7)	25 (48.1)	11 (57.9)	0.32

ECOG, Eastern Cooperative Oncology Group

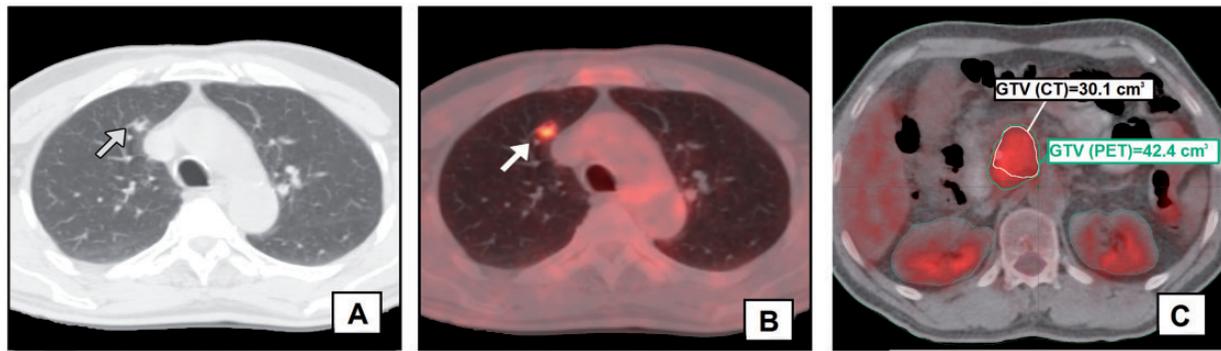
relationship between different variables and survival. *P* values ≤0.05 were considered statistically significant.

## Results

Pretreatment patient demographics are summarized in Table 1. Because of DM detected by PET/CT, 19 of the 71 patients (26.8%) could not receive intended CRT. Rather, they received chemotherapy, either immediately (*n* = 10) or after 30 Gy (3 Gy/fraction) PRT (*n* = 9). Indications for PRT were pain in 7 patients, and biliary obstruction in 2. Sites of DM were the liver in 8 patients, peritoneal surfaces in 6, liver and peritoneal surfaces in 4, and bone in 1.

In the remaining 52 patients, PET/CT confirmed the M<sub>0</sub> status determined by conventional staging. However, PET/CT revealed CT-occult regional lymphatic involvement in 3 patients (5.8%) and a primary tumor volume larger than that determined by CT in 4 (7.7%), with all 7 requiring enlargement of the radiation field beyond that of CT-defined borders (Fig. 1). Thus, PET/CT restaging resulted in changed or revised management decisions in 26 of the 71 (36.6%) patients (Table 2).

All patients with LAPC were able to receive their prescribed doses of concurrent CRT. Grade 2 or 3 toxicity was observed in 13 (25%) patients, including non-hematologic toxicities in 7 (13.4%), hematologic toxicities in 3 (5.8%), and both in 3 (5.8%). Five patients (9.6%) required unplanned treatment breaks, for an average of 4.2 days (range 2–7 days), but all were able to complete



**Figure 1** A typical patient with PET/CT-detected lung metastasis unapparent on CT images (A, B); Alteration of GTV size by PET/CT-based versus CT-based target volume delineation.

**Table 2** Impact of PET/CT restaging on treatment intent, treatment modality, and radiation portal size

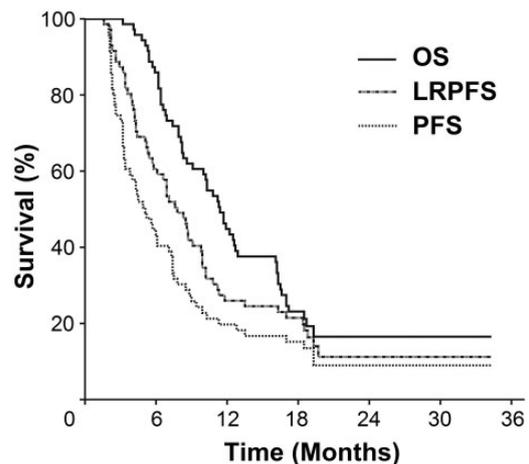
Characteristic	n (%)
Treatment intent (N=71)	
Curative	52 (73.2)
Palliative	19 (26.8)
Treatment modality (N=71)	
Chemoradiotherapy	52 (73.2)
Chemotherapy	10 (13.9)
Radiotherapy + chemotherapy	9 (12.9)
Radiation portal size (N=52)	
Not changed	45 (86.5)
Enlarged	7 (13.5)

their CRT course after symptomatic care. The main reasons for these breaks were diarrhea in 3 patients and leukopenia in 2; 3 (5.8%) required hospitalization.

Over the long term, 3 (5.8%) patients developed grade 3 gastric outlet obstruction, at 8.7, 10.9, and 12.6 months, respectively, after CRT. Although late toxicity cannot be excluded as a cause, the simultaneous evidence of disease progression in all 3 patients, at 6.8, 7.6, and 8.5 months, respectively, suggested that these symptoms were probably associated with progressive disease. Two additional patients (3.8%) experienced grade 2 gastric ulcers at 10.6 and 14.7 months, respectively, which were managed with medication.

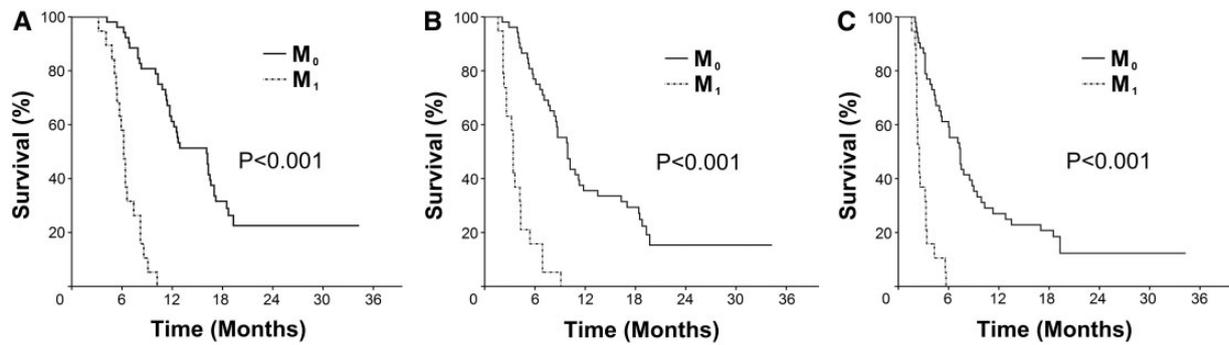
Median follow-up times for the entire,  $M_0$  and  $M_1$  cohorts were 11.3 months (range 3.2–34.3 months), 14.5 months (range 4.2–34.3 months), and 6.9 months (range 3.2–10.2 months), respectively. At the time of analysis, 9 (17.3%) patients in the  $M_0$  group were disease free. None of the  $M_0$  patients experienced regional failures as initial or ultimate sites of progression, whereas 17 of the 19  $M_1$  patients experienced regional failures. Similarly, local recurrences were significantly more common in the  $M_1$  group than in the  $M_0$  group (94.7% vs 48.1%;  $P=0.03$ ).

At the time of this analysis, 57 (80.3%) patients were dead; the 14 survivors were from the radically treated  $M_0$



**Figure 2** Survival curves for whole study population.

group. OS, LRPFS, and PFS curves for the entire study cohort are shown in Fig. 2. Median OS, LRPFS, and PFS in the 71 patients were 11.4 months (95% confidence interval (CI) 9.9–12.9 months), 7.8 months (95% CI 6.0–9.6 months), and 5.1 months (95% CI 3.6–6.6 months), respectively. The estimated 1- and 2-year OS rates were 43.4% and 16.5%, respectively; 1- and 2-year LRPFS rates were 24.5% and 11.2%, respectively; and 1- and 2-year PFS rates were 18.2% and 9.0%, respectively. Median OS (16.1 months [95% CI 12.4–19.7 months] vs 6.2 months [95% CI 5.7–6.7 months],  $P<0.001$ ), LRPFS (9.9 months [95% CI 8.2–11.6 months] vs 3.4 months [95% CI 3.1–3.7 months],  $P<0.001$ ), and PFS (7.4 months [95% CI 5.8–9.0 months] vs 2.5 months [95% CI 2.2–2.8 months],  $P<0.001$ ) were significantly higher in the  $M_0$  group than in the  $M_1$  group (Fig. 3). The 1- and 2-year OS rates in the  $M_0$  group were 56.8% and 23.1%, respectively; the 1- and 2-year LRPFS rates were 37.8% and 16.6%, respectively; and the 1- and 2-year PFS rates were 31.7% and 11.9%, respectively. By contrast, none of the patients in the  $M_1$  group was alive at 1 year.



**Figure 3** Comparative survival analyses between  $M_0$  and  $M_1$  cohorts. (A) Overall survival; (B) progression-free survival; (C) local regional progression-free survival.

Although the cohort size of the  $M_1$  group was relatively small, we assessed the possible impact of PRT on outcomes by stratifying this group into 2 subgroups, PRT+ ( $n = 10$ ) and PRT– ( $n = 9$ ). OS, however, did not differ in these 2 groups, (6.1 vs 5.8 months;  $P = 0.76$ ).

## Discussion

We have shown here that restaging PET/CT in patients with LAPC altered disease stage, changed initial management decisions, or mandated revision of RT portals in more than one-third of patients scheduled to undergo CRT. PET/CT restaging detected previously undetected DMs in 26.8% of these patients, sparing them from futile CRT, as well as enlarging RT portals beyond CT borders in an additional 13.5% of these patients. The longer median survival in the  $M_0$  group (16.1 months) than in the  $M_1$  group (6.2 months) and the entire cohort (11.4 months) indicates the importance of accurate staging on more reliable estimations of outcomes in patients with LAPC.

The current treatment of choice for patients with technically unresectable LAPC is sequential or concurrent CRT<sup>[15]</sup>. However, despite significant advances in staging procedures and treatment modalities, the locoregional and distant control rates of 32 to 58% and <20%, respectively, and median survival times  $\leq 1$  year are unsatisfactorily low<sup>[2,10]</sup>. These disappointing results may possibly be related to limited radiosensitization or antitumor efficacy of current chemotherapeutic agents, the insufficiency of conventional 45–54 Gy doses, and/or difficulties with precise definition of target volumes by conventional imaging methods. An additional factor may be the unintentional inclusion of patients with metastases in LAPC trials because of difficulties with accurate staging<sup>[10,11]</sup>. Of the 71 conventionally staged LAPC patients, 19 (26.8%) had DM on restaging PET/CT, shifting treatment intent from cure to palliation. Seven additional patients were found to have CT-occult regional lymphatic involvement or a larger primary tumor size than that determined by CT, resulting in the revision of RT portals, increasing the rate of management

modifications to 36.6%. Eventually, more than one-quarter of patients were spared from useless and potentially toxic radical CRT and were immediately referred for chemotherapy. In another 13.5%, geographic misses were avoided by revising RT portals, which may have favorably altered their outcomes.

The rates of staging discordance and the need for change in initial management decisions reported here are very similar to those reported in other studies comparing PET/CT with conventional staging in patients with pancreatic carcinoma<sup>[12,16,17]</sup>. PET/CT was found to change management in 36–41% of patients by providing more accurate staging<sup>[12]</sup>. Most studies on staging discrepancies between PET/CT and conventional imaging modalities have been found to favor PET, particularly PET/CT. CT assessment of 21 patients with metastatic pancreatic cancer identified DMs in 10 (47.6%) patients, whereas PET revealed liver metastases not identified or equivocal on CT and/or clinically unsuspected DMs in 7 (33.3%) additional patients<sup>[18]</sup>. In a study of 9 patients with proven metastases, PET detected DMs in 9 (77.8%), whereas CT could only detect 3 (33.3%)<sup>[17]</sup>. Other studies have yielded similar results<sup>[11,19,20]</sup>. The greater ability of PET, relative to CT and/or MRI, to detect metastatic deposits may be due to its relatively higher resolution (0.5 cm vs 1 cm) and functional advantages in discriminating between benign and malignant lesions. These results emphasize the importance of accurate staging in selecting and managing these patients.

Another important and pioneering finding of the present study was the demonstration that unintentional fallacious staging could result in significant misinterpretation of survival outcomes in patients with LAPC. Theoretically, for any type of tumor, staging failures may decrease or increase reported outcomes if patients are down- or upstaged, respectively. To evaluate the importance of staging accuracy, we compared the outcomes in 3 groups of patients with LAPC: the entire study cohort of 71 patients, representing conventional staging, the 52 patients found to be true LAPC based on restaging PET/CT results, and the 19 patients with

DM identified on PET/CT and confirmed pathologically. We found that median survival of the entire cohort was poorer than that of the true LAPC group (11.4 vs 16.1 months), indicating that the survival of the entire cohort was reduced by the inclusion of  $M_1$  patients, who had a median survival of only 6.2 months. Although the significant survival difference between our  $M_0$  and  $M_1$  cohorts is not a novel finding, the reduction in survival of the entire cohort caused by the unintentional inclusion of  $M_1$  patients highlights the importance of stage migrations resulting from more comprehensive staging procedures in LAPC patients, mostly in the form of upstaging, in reliably predicting the prognosis of these patients.

Lack of RT or a lower dose may have had an impact on the survival of  $M_1$  patients. We could not determine whether the absence of RT or the use of lower palliative doses (30 Gy in 10 fractions; biologically equivalent dose  $(BED)_{10} = 36$  Gy) rather than potentially more effective 50.4 Gy ( $BED_{10} = 60.5$  Gy) influenced survival. This may be determined by randomized controlled trials or meta-analyses. However, to test the potential influence of PRT on outcomes, we compared survival in  $M_1$  patients stratified by PRT status, observing almost identical median OS in the PRT+ and PRT- cohorts (6.1 vs 5.8 months;  $P = 0.76$ ). Although few patients were included in these subgroups, this finding indicates that accurate staging is more important than treatment modalities in predicting patient survival.

In conclusion, the results presented here demonstrate the importance of PET/CT restaging of LAPC patients in selecting patients for aggressive CRT and sparing those with metastases from useless radical treatment protocols. In addition, PET/CT restaging may point to the need for radiation fields enlarged beyond CT borders, indicating the need for more sophisticated imaging tools to define target volumes precisely in patients scheduled for CRT. Our findings show that unintentional fallacious staging may be a potential source of relatively poor survival after radical CRT in LAPC.

### Conflict of interest

The authors have no personal or commercial conflicts of interest to declare.

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