Digestive and Liver Disease 51 (2019) 887–893

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Oncology

Early metabolic response to chemoradiotherapy by interim FDG PET/CT is associated with better overall survival and histological response in esophageal cancers

N. Hammoudi [a], C. Hennequin [a], L. Vercellino [b], A. Costantini [a], A. Valverde [c], P. Cattan [d], L. Quéro [a,*]

[a] Department of Radiation Oncology, Saint Louis Hospital, Paris, France
[b] Department of Nuclear Medicine, Saint-Louis Hospital, Paris, France
[c] Department of Surgery, Croix St Simon Hospital, Paris, France
[d] Department of Surgery, Saint Louis Hospital, Paris, France

ARTICLE INFO

Article history:
Received 8 August 2018
Accepted 10 December 2018
Available online 23 December 2018

Keywords:
Cancer
Local recurrence
Oesophageal
PET
Prognosis
Radiotherapy

ABSTRACT

Background: Early assessment of response to neoadjuvant chemoradiotherapy (CRT) is crucial in determining the most suitable treatment strategy in locally advanced oesophageal cancer (LAEC).
Aims: We evaluated the impact of early metabolic response during CRT on overall survival (OS) and histological response.
Methods: Patients with biopsy-proven oesophageal carcinoma underwent FDG PET/CT with evaluation of the standardized uptake value (SUV) before any treatment and during CRT after 20 Gy.
Results: 116 patients (Male: 66.4%, Median age: 63; squamous cell carcinomas (SCC): 70%) met inclusion criteria. Median OS was 21.7 months. There was a significant positive correlation between interim metabolic response and OS. In multivariate analysis, only metabolic response using the 50% cut-off value remained significantly associated with OS (IC95% = 0.28–0.73; p = 0.001). In this statistical analysis, surgery (p = 0.007) and T stage (p = 0.023) were also correlated with OS. There was a significant correlation between early metabolic response and local recurrence (Chi-squared test p = 0.0001).
Conclusions: Early metabolic response using FDG PET/CT is associated with better OS, disease-free survival, local control and pathological response in patients treated by CRT for LAEC.

1. Introduction

Oesophageal cancer includes two main histological subtypes: squamous cell carcinoma (SCC) and adenocarcinoma (ADC) [1] and represents the 6th leading cause of cancer-related mortality worldwide [2]. Its management is a major public health challenge. Its complete surgical resection without further therapy is the treatment of choice for limited local disease (i.e. T1–T2 N0M0) whereas in locally advanced oesophageal carcinomas (LAEC) this strategy cannot be considered as sufficient [3]. It has been shown that, patients with locally advanced disease who received preoperative treatment had increased R0 resection and survival rates [4,5]. However, there is still no standardized management for these patients.

It has been demonstrated that preoperative chemoradiotherapy (CRT) followed by surgery has improved the prognosis of patients with oesophageal cancers [6,7].

These results concerned the two main histological subtypes of oesophageal cancers. However, in patients with SCC, randomized controlled studies found equivalent overall survival (OS) whether the patients were treated with CRT or surgery [8,9].

The evaluation of response to neoadjuvant treatment classically combines computed tomography (CT) and an endoscopic evaluation either by conventional examination (esogastroduodenoscopy (EGD) or endoscopic ultrasonography (EUS)) [10]. Fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT has the ability to detect nodal and distant metastases with a greater sensitivity than anatomic imaging modalities [10]. This assessment, recommended by the European Society of Medical Oncology (ESMO) in patients who are candidates for oesophagectomy, has been evaluated with promising results after completion of chemotherapy or CRT in patients with locally advanced oesophageal carcinomas

* Corresponding author at: Department of Radiation Oncology, Saint Louis Hospital, 1, Avenue Claude Vellefaux, 75010 Paris, France.
E-mail address: laurent.quero@aphp.fr (L. Quéro).

https://doi.org/10.1016/j.dld.2018.12.006
1590-8658/

[11–13]. Some of these studies suggested that it could be an early surrogate for pathological response [14].

In recent years, multiple works have attempted to stratify patients as responsive and non-responsive with a non-invasive method in order to further adapt the treatment strategy. Interim FDG PET/CT could be one of these potential approaches [15].

Indeed, interim FDG PET/CT could have a major impact on patient management, firstly by predicting treatment outcome early in the patient management and secondly, by modifying the therapeutic strategy (i.e. modification of radiotherapy (RT) plan or surgery indication) in order to improve and optimize the patient's outcome.

In head and neck cancers [16] or in non-small cell lung cancer [17], FDG PET/CT is now considered as a very promising tool in the evaluation of response and prognosis. Concerning oesophageal cancers, data are more controversial. A recent meta-analysis by Cremonesi et al. [18] showed that individual therapeutic decisions based on interim FDG PET/CT, although promising, was inconsistent and depended on the methods used to perform the analysis. The heterogeneity of the populations studied in each cohort of the meta-analysis combined with the relative low number of patients included (only one study with more than 100 subjects) could have led to this disappointing result. New trials are needed in order to precisely define the importance of this early evaluation.

The objective of the present work was to determine the impact of decrease of the standardized uptake value (SUV) during the CRT course (at 20 Gy) on patient OS in a large cohort.

2. Patients and methods

From May 2006 to August 2016, an initial FDG PET/CT was performed before any treatment and a second FDG PET/CT during CRT at 20 Gy was planned for all patients treated for a LAEC (T3/T4 or N1/N2/N3) in our institution with upfront CRT. All patients were required to have biopsy-proven ADC or SCC of the oesophagus. Staging was established according to the TNM classification using the 7th edition of Union for International Cancer Control (UICC) TNM staging system, by physical examination, CT scans of the chest and abdomen, EGD and EUS. Patients with distant visceral metastases and with a performance status (PS) of 3 or more were excluded.

All chemotherapy regimens were permitted. After neoadjuvant treatment, an evaluation of tumor response by CT and EGD according to RECIST criteria was performed. Surgery was discussed during a multidisciplinary team meeting before the beginning of the chemoradiation therapy if the patient's medical status and disease allowed it. There was no difference regarding the therapeutic strategy between SCC and ADC histology. After CRT a second multidisciplinary meeting confirmed the indication of oesophagectomy if the criteria where still fulfilled. Surgery was performed in two high-volume centers for oesophagectomy.

3. Data collection

Data on patients' characteristics (gender, age, PS, weight loss at baseline before neoadjuvant treatment), tumor (staging, histology, location), initial FDG PET/CT (date, location, SUV concerning the primary lesion), treatment management (treatment dates, radiotherapy schedule and dose, type of chemotherapy, number of cycles of chemotherapy), post-medical treatment evaluation (CT, EGD), FDG PET/CT at 20 Gy (date, location, SUV concerning the primary lesion, metabolic response), surgery (date, histologic response) and follow-up (disease progression, death) were retrospectively collected.

The same physician reviewed all data sheets in order to make an uniform interpretation of this retrospective data.

4. ^{18}F FDG PET/CT imaging

Patients underwent whole-body FDG PET/CT before CRT (PET1) and at 20 Gy (PET2). This second FDG PET/CT was performed 2 weeks after the beginning of radiotherapy. Patients fasted for at least 6 h before they were injected with 18F-FDG (5 MBq/Kg body weight). The blood glucose level at the time of baseline FDG PET/CT study had to be <9 mmol/L for inclusion.

The baseline PET imaging could be performed in different institutions. The interim FDG PET/CT was performed at the same FDG PET/CT center location (Philips Gemini XL from May 2006 to August 2015 or Siemens mCT Flow since September 2015).

FDG PET/CT imaging was performed from the base of the skull to mid-thighs starting 60 min after FDG injection. CT parameters were 120 kV and 100 mAs. No contrast enhancement was used for the CT part. PET images were reconstructed iteratively using a three- dimensional, row action maximization likelihood algorithm. A semi-quantitative analysis using the SUV was performed. For the calculation of SUV at baseline FDG PET/CT and on interim FDG PET/CT, images were displayed on the Extended Brilliance^{TM} workstation (Philips Medical Systems). The SUV was measured by manually marking a circular region of interest (ROI) in the three planes (coronal, sagittal and axial) around the tumor (3D ROI). The maximum SUV (SUVmax) within the tumor was used for the study analysis. For this study, only SUVmax was used for prognostic and predictive calculations. The same nuclear medicine physician who was blind to the clinical, radiological and follow-up data interpreted the initial and interim PET images.

5. Chemoradiotherapy

All chemotherapy regimens were permitted. Data concerning the type of chemotherapy, number of cycles preceding the interim FDG PET/CT and doses were collected. Three-dimensional conformal radiation therapy was delivered with megavoltage equipment (6–18 MV) using a multiple field technique. All patients had 3D treatment planned. Patients were treated 5 days per week at 2 Gy per day. All fields were treated each day, and portal films were obtained from at least two fields per week or more often if needed. Treatment used a combination of anterior/posterior, oblique or lateral fields so that the dose did not vary by more than 5% over the entire target volume. The dose was prescribed according to the International Commission on Radiation Units and Measurements (ICRU) recommendations. Initial gross tumor volume (GTV) included primary tumor (GTV T) and involved lymph nodes (GTV N) on initial FDG PET/CT. Clinical Target Volume (CTV1) included the GTV T plus a margin of 5 cm above and below the primary oesophageal tumor, including GTV N and lymph node areas at risk. The mediastinal fat around the oesophagus was included in this CTV1. CTV2 consisted of the GTV T plus a margin of 2 cm above and below the primary tumor. A safety margin of 5 mm was added to CTV1 and CTV2 to obtain Planning Target Volume (PTV1) and PTV2. The prescribed doses for PTV1 and PTV2 were 40 and 66 Gy, respectively. CTV2 treatment was performed only in cases of exclusive CRT.

6. Surgery

Surgery was not systematically performed after CRT. It was scheduled before chemoradiation, only performed in medically fit patients for surgery with a low risk of post-operative complications and confirmed after CRT during a second multidisciplinary meeting if the criteria where still fulfilled. Moreover, patients should have a resectable disease on CT scan with a high probability of R0 surgery resection. Surgery was scheduled 4–6 weeks after completion of

CRT. Surgical modalities were decided according to tumor site, disease extent and surgeons' preferences. Standardized transthoracic en bloc oesophagectomy with lymphadenectomy was performed for all operated patients. We used the Mandard histological classification [19] to assess residual disease. We defined three different groups: complete histological response if there was no viable tumor cell or fibrosis with scattered tumor cells (TRG1 and TRG2), major response when only a few viable tumor cells were present in the tumor or in the nodes (TRG3) and poor response in the other cases (TRG4 or TRG5).

7. Follow-up

Patients were followed-up at 4-month intervals for the first year, at 6-month intervals for the next 2 years and annually thereafter. The follow-up evaluation consisted of physical examination, a complete blood count and liver function test. All patients had Thoraco-abdominal and pelvic CT Scan at 6-month intervals for the first 2 years and annually thereafter. Gastroscopy was performed in case of clinical symptoms. FDG PET/CT was not routinely performed in the follow-up of patients after treatment.

8. Statistical analysis

The main aim of this study was to evaluate the prognostic value of the decrease in SUV for progression-free survival (PFS) and OS. Regression of SUV was defined as: $[1-(SUV2/SUV1)] \times 100$. PFS and OS were measured from the date of the first day of treatment to the date of disease progression or death from any cause. Survival curves were calculated by using Kaplan–Meier survival analysis. The log-rank test was used to evaluate survival differences. Comparison of continuous variables was performed using the t-test. Sensitivity, specificity, positive predictive values and negative predictive values were calculated using standard formulas. Receiver operating characteristic (ROC) curve analysis was used to define the optimal cut-off. Accuracy was measured as area under the ROC curve. Cox regression analysis was used to perform a multivariate analysis, incorporating weight loss at baseline, T and N stages and the factors significantly associated with survival in univariate analyses. Chi^2 test was used to measure the correlation between metabolic response and local recurrence Statistical analyses were performed using Stata 9 software (College Station, TX: StataCorp LP).

9. Results

9.1. Patients and tumors characteristics

During the study period, 193 patients were evaluated for LAEC and 116 met the inclusion criteria (Fig. 1). A first FDG PET/CT evaluation was performed followed by a second interim examination. The baseline characteristics are listed in Table 1.

Two thirds of the patients were male (66.4%) with a median age at inclusion of 63-years (range 20–87). The large majority of patients had a PS of 0 or 1 (n = 101, 87%) and were almost equally distributed in three groups concerning their weight loss. Considering the tumor staging using the TNM classification, all patients had LAEC with an indication, according to the international recommendations, to preoperative CRT.

Seventy percent of patients had SCC and 30 percent had ADC. Their location was distributed as described in Table 1.

9.2. Therapeutic management

All patients first received a CRT regimen. Data concerning therapeutic management are listed in Table 1.

Table 1
Patiens characteristics.

Variable	N (%)
Gender	
Men	77 (66.4)
Women	39 (33.6)
Mean age (years) (range)	63 (20–87)
Performance status	
- 0	32 (27.6)
- 1	69 (59.5)
- 2	15 (12.9)
T Stage	
- 2	4 (3.5)
- 3	107 (92.2)
- 4	5 (4.3)
N stage	
N0	29 (25)
N+	87 (75)
Weight loss	
- <5%	32 (27.6)
- 5–10%	42 (36.2)
- >10%	42 (36.2)
Histology	
- Squamous cell carcinoma	81 (69.8)
- Adenocarcinoma	35 (30.2)
Tumour location	
- Upper third	20 (17.2)
- Middle third	57 (49.1)
- Lower third	39 (33.7)
Chemotherapy regimen	
- 5-Fluorouracil (5FU) — Cisplatin	77 (65.3)
- 5FU — Oxaliplatin	29 (24.6)
- Docetaxel — 5FU — Cisplatin	9 (7.6)
- 5FU — Carboplatin	3 (2.5)
Mean RT dose (Gy) (range)	
- Pre-operative RT	40 (38–42)
- Exclusive RT	66 (32–70)
Surgery	
Yes	42 (36.2)
No	74 (63.8)
Pathological response	n = 42
Complete (TRG 1–2)	19 (45.2)
Major (TRG 3)	2 (4.8)
Minor (TRG 4–5)	21 (50)
Mean SUV1 (range)	13.6 (3.4–47)
Mean SUV2 (range)	6.5 (0–20)
Mean metabolic response (range)	48% (30–100)
Metabolic response ≥30%	
Yes	84 (72.4)
Not	32 (27.6)
Metabolic response ≥50%	
Yes	56 (48.3)
No	60 (51.7)
Metabolic response ≥70%	
Yes	28 (24.1)
No	88 (75.9)
Progression	
Yes	73 (62.9)
No	43 (37.1)
Death	
Yes	78 (67.2)
No	38 (32.8)

Concerning radiotherapy, median interval time between the first FDG PET/CT and the first day of treatment was of 32 days (range 0–77). The median radiotherapy dose was 40 Gy (range 38–42) for patient receiving neoadjuvant therapy and 66 Gy (range 32–70) for patients receiving definitive treatment respectively. Two-third of patients received 5FU-Cisplatine chemotherapy and one-quarter of patients received FOLFOX chemotherapy.

Only forty-two patients (36.2%) (30 SCC and 12 ADC) were able to had surgery after chemoradiotherapy due to patients' comorbidities, age, performance status, weight loss, tumor location (patients with cervical location were excluded) and chemoradiotherapy tolerance. Among patients who underwent surgery, 19 had complete

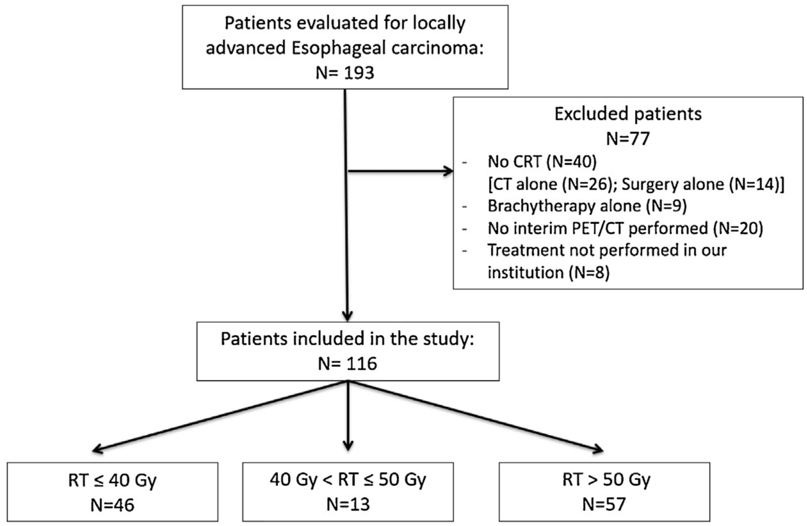

Fig. 1. Flow chart.

histological response, 2 had major response and 21 had poor response.

9.3. Overall survival (OS) and progression-free survival (PFS)

In the whole cohort, mean follow-up was of 27 months (standard deviation: 24,5 months). In patients living at the end of the follow-up, it was of 41,2 months (standard deviation: 29,5 months). Median OS was 21.7 months with 1- and 3-year OS of 71.9% and 35.4% respectively (Fig. 2). Median PFS was 14.4 months with 1- and 3-years PFS of 58.7% and 31.7% respectively (Fig. 3).

In univariate analysis, a good PS at baseline was significantly associated with a greater 3-year OS: 39.7% for PS 0, 29.7% for PS 1 and 7% for PS 2 respectively ($p = 0.03$).

In univariate analysis, surgery was also associated with better overall survival: Among operated patients, median OS was 41.3 months with a 1- and 3-year OS of 88% and 31% respectively. Among non-operated patients, median OS was 14.5 months, with 1- and 3- year OS of 58% and 18% respectively. The difference between operated and non-operated patients was statistically significant ($p = 0.001$).

No other classic prognostic factor was significantly associated with OS.

In multivariate analysis, including TNM classification, weight loss at baseline and the two factors significantly associated with better overall survival in univariate analysis (surgery and PS), surgery ($p = 0.007$ IC95% (0.26–0.81)) and T stage ($p = 0.023$ IC95% (1.09–3.49)) but not PS were correlated with OS.

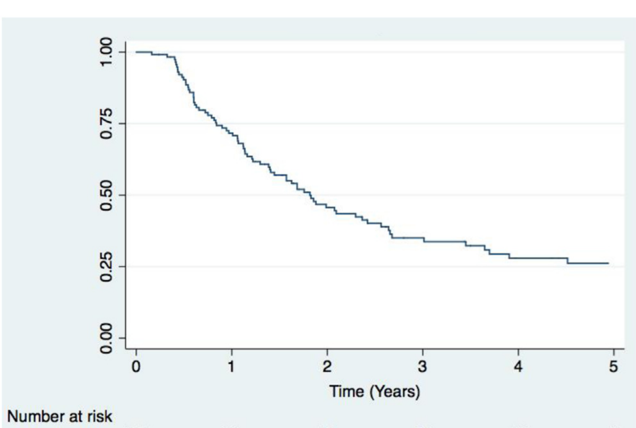

Fig. 2. Overall survival.

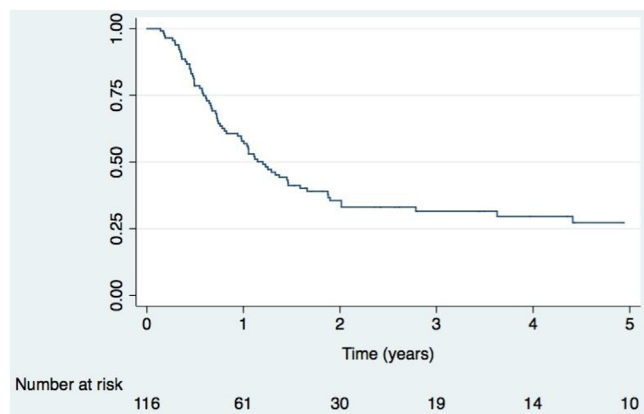

Fig. 3. Progression free survival.

9.4. Patterns of relapse

Ninety-four patients have relapsed after treatment: 49 patients had a local recurrence and 45 patients had a metastatic recurrence. Among those patients, 23 had both local and metastatic recurrence. In case of recurrence, patients were treated by salvage brachytherapy or chemotherapy. No patient had salvage surgery for local recurrence.

9.5. Prognostic value of metabolic response

Interim FDG PET/CT was performed at a mean dose of 21 Gy (Median 20 Gy, Standard Deviation 3.76 Gy) At baseline, the mean SUVmax (SUV1) of the primary oesophageal tumor was 13.6 (range 3.4–47). At interim FDG PET/CT, the mean SUVmax (SUV2) was 6.5 (range 0–20). The mean metabolic response was 48% when considering both SCC and ADC. Using the mean as cut-off value, SUV1 level had no prognostic value: 3-year OS was 18.6% and 24.7% for patients with SUV1 lower and higher than 13.6 respectively ($p = 0.96$).

To establish a correlation between metabolic response and outcome, cut-offs of 30, 50 and 70% of regression of SUV were evaluated. According to these cut-off values, the metabolic response

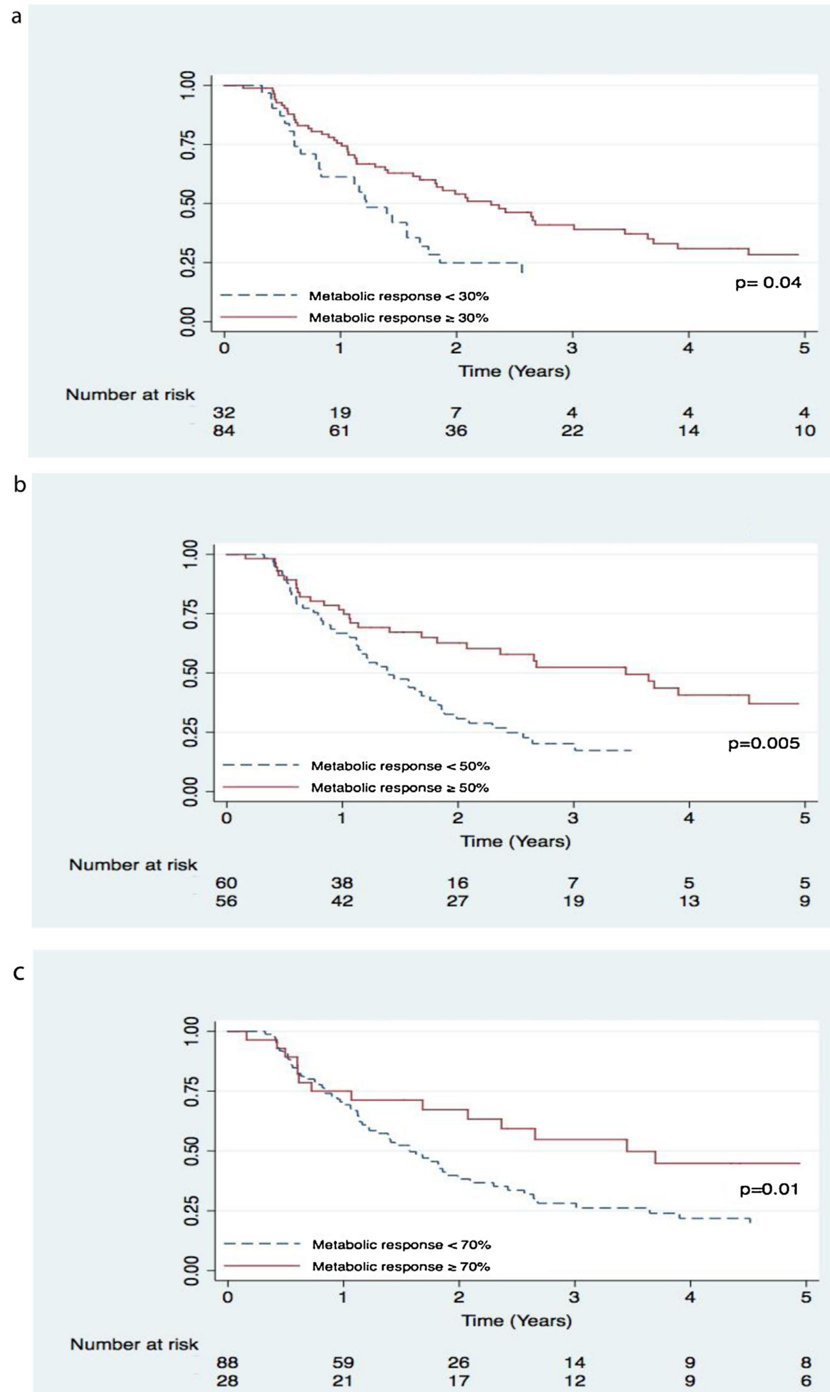

Fig. 4. Overall survival according to metabolic response.

rates were: 72.4% (84/116), 48.3% (56/116) and 24.1% (28/116 patients) respectively. There was a significant positive correlation between interim metabolic response and OS: the 3-year OS of good metabolic responders, for a threshold SUVmax decrease of respectively 30%, 50% and 70%, were 41.1%, 52.5% and 54.8% as compared to 20.9%, 19.9% and 28.6% for poor metabolic responders ($p = 0.04$, $p = 0.005$ and $p = 0.01$ respectively) (Fig. 4). The same features were observed for PFS. Regarding 3-year survival as the end point, sensitivity, specificity, positive and negative predictive values for the three cut-off values were calculated. According to the ROC curve, the best cut-off value was 50% (AUROC was 0.631 and 0.69 for OS and PFS respectively). Indeed, the 3-year OS of good responders was 52.5% compared to 19.9% for poor responders ($p = 0.005$).

In multivariate analysis, integrating metabolic response to the Cox model previously described (including TNM classification, weight loss at baseline and the two factors significantly associated with better overall survival in univariate analysis (surgery and PS)), the only cut-off value remaining significantly associated with OS ($p = 0.001$) was of 50% (Table 2).

There was a significant correlation between early metabolic response and local recurrence but not between early metabolic response and metastatic recurrence. Twenty-six percent of good metabolic responders had a local recurrence vs 58% of poor

Table 2
Multivariate analysis – correlation with OS.

Variable	Hazard ratio	Standard error	p	95% confidence interval
Surgery	0.46	0.13	0.007	(0.26–0.81)
Performance status	1.17	0.26	0.485	(0.75–1.81)
T stage	1.96	0.58	0.023	(1.10–3.49)
Weight loss	0.98	0.15	0.878	(0.73–1.31)
Rep50	0.45	0.11	0.001	(0.28–0.73)

metabolic responders (Chi-squared test p = 0.0001). Fifty percent of good metabolic responders had a metastatic recurrence vs 45% of poor metabolic responders (Chi-squared test p = 0.203).

When separating the 116 patients into two groups according to their primary tumor histology, OS was significantly associated with metabolic response for both ADC (p = 0.01) and SCC (p = 0.03) using the cut-off value of 50%.

We also studied if performing both FDG PET/CT (at baseline and interim points) in the same or different FDG PET/CT facility location influenced the correlation with OS. Using the cut-off value in SUV change of 50%, we did not find any significant difference (respectively p = 0.76 and p = 0.6) (Supplementary Fig. 1).

In patients who underwent surgery, metabolic and histological responses were correlated using the cut-off value of 70% (Pearson ratio: 6.0935; p = 0.048). When pooling patients with complete and major histological responses, these results were more significant (Pearson ratio: 5.1593; p = 0.023).

10. Discussion

Our study showed that early response to CRT by interim FDG PET/CT was associated with better survival in locally advanced oesophageal cancer. Interestingly this result remained significant whether the two FDG PET/CTs were performed in the same or different institutions.

By using either a 30%, 50% or 70% decrease in SUVmax as cut-off values, metabolic response was significantly correlated to a better 3-year OS.

In patients who underwent surgery, we also showed that when using a cut-off value of 70%, metabolic and histological responses were correlated with a strong significant Pearson ratio.

The relevance of an interim FDG PET/CT evaluation during CRT for LAEC remains controversial. A study including 100 patients with locally advanced ADC did not show any correlation between FDG PET/CT after CRT and histological tumor regression or OS [20]. The recent meta-analysis published by Cremonesi et al. analyzing 13 studies and 697 patients, did not find any correlation between the interim variation of FDG PET/CT and the pathological complete response and/or the clinical outcome [18]. However, in this review, the study population was heterogeneous with utilization of different treatment protocols and utilization of different methods of analysis to assess the prognostic and predictive value of the interim FDG PET/CT. Moreover, a recent work, presented during ESMO 2018, found that early metabolic response was associated with both improved PFS and low local recurrence rate [21]. Our present cohort of 116 patients recruited a high number of patients (the second highest one in the literature to our knowledge) in a single institution. We showed that this approach was feasible in current practice and had a potential relevance in early prediction of OS. Our results were first given globally in SCC and ADC patients but we found the same trends when separating patients regarding their tumor histology.

CRT alone may be indicated in patients with either locally advanced ADC or SCC [22].

RTOG 94-05 (INT 0123) randomized trial failed to show that high-dose radiotherapy (64.5 Gy) delivered with concurrent chemotherapy had any advantage over standard-dose radiotherapy (50.4 Gy) delivered with concurrent chemotherapy in patients treated for oesophageal cancer [23]. However, considering the high local failure rates after 50 Gy for patients treated by exclusive CRT [24], we think that high-dose radiotherapy delivered with concurrent chemotherapy should be the optimal treatment. Indeed, some retrospective studies have reported encouraging results after high dose radiotherapy in combination with chemotherapy for locally advanced oesophageal cancer [25–27]. Two randomized trials evaluating exclusive chemoradiotherapy (CRT) versus preoperative chemoradiotherapy have used high dose radiotherapy (65–66 Gy) as standard RT treatment arm [8,9]. A recent publication compiling an analysis of non-randomized patients in the FFCD 9102 phase 3 trial with no clinical response after induction CRT, or with contraindication to follow any attributed treatment, showed that OS did not differ between responders to induction CRT (operated or not) and patients who had salvage surgery after clinical failure of chemoradiation [21]. Our data shows that patients who were operated had a significantly better 3-year OS than non-operated ones (31% versus 17.6%; p = 0.001).

Interim FDG PET/CT evaluation was also correlated with histological response after surgery as previously suggested in other works [28]. These results emphasize the potential interest of performing surgery in patients with locally advanced oesophageal cancers. Interim FDG PET/CT could also be useful in predicting the histological response in those patients. However, a randomized study would be helpful in order to clarify the ideal management of these patients. After induction CRT, interim FDG PET/CT would define poor and good responders. Patients should then be randomly assigned to surgery or continuation of CRT taking into account the histological type of the primary lesion. Comparing the OS of these subgroups could confirm the usefulness of interim FDG PET/CT. Barbour et al. reported the results of AGITG DOCTOR multicentric randomized trial which evaluated the impact of metabolic response at day 15 after 1 cycle of neoadjuvant CF (Cisplatin, Fluorouracil) chemotherapy to tailor therapy in patients treated for oesophageal and gastro-oesophageal junction adenocarcinoma. Early metabolic responders received a second cycle of CF chemotherapy then oesophagectomy. Early metabolic non-responders (SUVmax decreasing by $\geq$35% from baseline to day 15 PET) were centrally randomised 1:1 to 2 cycles of DCF (Docetaxel, Cisplatin, Fluorouracil) chemotherapy or DCF + concurrent 45 Gy radiotherapy then oesophagectomy. The addition of docetaxel and radiotherapy in metabolic non-responders group augmented major histological response rate (63% vs 20%), PFS rate at 36 months (46% vs 31%) and decreased local recurrence rate (11% vs 32%) in comparison with preoperative DCF alone [29].

In our study, we found no correlation between weight loss at baseline and OS. The importance of nutritional parameters variations during CRT had previously been correlated with a worse impact on response and survival [30]. We could explain these surprising results by the systematic nutritional management of patients in our institution with frequent use of enteral or parenteral nutrition in order to normalize nutritional parameters. In our study, performance status was not a prognostic factor contrary to surgery. The fact that most of patients in our study had good PS (0–1) could explain that we did not find PS as a prognostic factor by lack of statistical power. Indeed, only 13% of the patients had PS 2. Moreover, PS was not the only reason for which surgery could not be performed in some patients. Local extension of the disease could also explain some exclusion from surgery.

Our study had several limitations. First, the evaluation of tumor-specific metabolic changes might be blurred by the post-radiation inflammatory effect. Changes in SUV induced by CRT reflect the decrease in viable cell fraction but are also influenced by many other phenomena, including recruitment of inflammatory cells (macrophages and activated leucocytes). A rigorously validated method for tumor delineation on post-treatment scans is therefore required for optimal results. These additional methods of metabolic assessment should be investigated in the setting of early prediction of response during CRT in oesophageal cancer. Moreover, if the location of the interim FDG PET/CT was always the same, the first examination could be performed in different centers. However, we did not find any significant differences in our results regarding the location of the first FDG PET/CT. These findings showed that this possible bias did not interfere with our results. All chemotherapy protocols were allowed, leading to potential bias due to the differences between chemotherapy regimens. In this "real-life" retrospective study, this bias could hardly be avoided. However, almost all the patients included in our study (more than 90%) received either 5FU-Cisplatine or 5FU-Oxaliplatin chemotherapy which have comparable outcomes in this indication. Due to the retrospective nature of the study, physicians could take into account the results of interim FDG PET-CT particularly in patients with poor metabolic response for whom salvage surgery could be proposed.

11. Conclusion

Early metabolic response using FDG PET/CT is associated with better OS, disease-free survival, local control and pathological response in patients with LAEC.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.12.006.

References

[1] Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D, Committee EG. Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v50–7.

[2] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.

[3] Mariette C, Piessen G, Triboulet JP. Therapeutic strategies in oesophageal carcinoma: role of surgery and other modalities. Lancet Oncol 2007;8:545–53.

[4] Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in oesophageal cancer. J Clin Oncol 2009;27:5062–7.

[5] Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 2011;12:681–92.

[6] van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for oesophageal or junctional cancer. N Engl J Med 2012;366:2074–84.

[7] hapiro J, van Lanschot JJB, Hulshof M, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015;16:1090–8.

[8] Bedenne L, Michel P, Bouche O, Milan C, Mariette C, Conroy T, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 2007;25:1160–8.

[9] Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 2005;23:2310–7.

[10] van Westreenen HL, Westerterp M, Bossuyt PM, Pruim J, Sloof GW, van Lanschot JJ, et al. Systematic review of the staging performance of 18F-fluorodeoxyglucose positron emission tomography in oesophageal cancer. J Clin Oncol 2004;22:3805–12.

[11] Dai T, Popa E, Shah MA. The role of (1)(8)F-FDG PET imaging in upper gastrointestinal malignancies. Curr Treat Options Oncol 2014;15:351–64.

[12] Elimova E, Wang X, Etchebehere E, Shiozaki H, Shimodaira Y, Wadhwa R, et al. 18-fluorodeoxy-glucose positron emission computed tomography as predictive of response after chemoradiation in oesophageal cancer patients. Eur J Cancer 2015;51:2545–52.

[13] Vallbohmer D, Holscher AH, Dietlein M, Bollschweiler E, Baldus SE, Monig SP, et al. [18F]-Fluorodeoxyglucose-positron emission tomography for the assessment of histopathologic response and prognosis after completion of neoadjuvant chemoradiation in oesophageal cancer. Ann Surg 2009;250:888–94.

[14] Harada K, Wang X, Shimodaira Y, Sagebiel T, Bhutani MS, Lee JH, et al. Early metabolic change after induction chemotherapy predicts histologic response and prognosis in patients with oesophageal cancer: secondary analysis of a randomized trial. Target Oncol 2018;13:99–106.

[15] Monjazeb AM, Riedlinger G, Aklilu M, Geisinger KR, Mishra G, Isom S, et al. Outcomes of patients with oesophageal cancer staged with [(1)(8)F]fluorodeoxyglucose positron emission tomography (FDG-PET): can postchemoradiotherapy FDG-PET predict the utility of resection? J Clin Oncol 2010;28:4714–21.

[16] Min M, Lin P, Lee MT, Shon IH, Lin M, Forstner D, et al. Prognostic role of metabolic parameters of (18)F-FDG PET-CT scan performed during radiation therapy in locally advanced head and neck squamous cell carcinoma. Eur J Nucl Med Mol Imaging 2015;42:1984–94.

[17] Cremonesi M, Gilardi L, Ferrari ME, Piperno G, Travaini LL, Timmerman R, et al. Role of interim (18)F-FDG-PET/CT for the early prediction of clinical outcomes of Non-Small Cell Lung Cancer (NSCLC) during radiotherapy or chemo-radiotherapy. A systematic review. Eur J Nucl Med Mol Imaging 2017;44:1915–27.

[18] Cremonesi M, Garibaldi C, Timmerman R, Ferrari M, Ronchi S, Grana CM, et al. Interim (18)F-FDG-PET/CT during chemo-radiotherapy in the management of oesophageal cancer patients. A systematic review. Radiother Oncol 2017;125:200–12.

[19] Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of oesophageal carcinoma. Clinicopathologic correlations. Cancer 1994;73:2680–6.

[20] Elliott JA, O'Farrell NJ, King S, Halpenny D, Malik V, Muldoon C, et al. Value of CT-PET after neoadjuvant chemoradiation in the prediction of histological tumour regression, nodal status and survival in oesophageal adenocarcinoma. Br J Surg 2014;101:1702–11.

[21] Vincent J, Mariette C, Pezet D, Huet E, Bonnetain F, Bouche O, et al. Early surgery for failure after chemoradiation in operable thoracic oesophageal cancer. Analysis of the non-randomised patients in FFCD 9102 phase III trial: chemoradiation followed by surgery versus chemoradiation alone. Eur J Cancer 2015;51:1683–93.

[22] Lagergren J, Smyth E, Cunningham D, Lagergren P. Oesophageal cancer. Lancet 2017;390:2383–96.

[23] Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for oesophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002;20:1167–74.

[24] Zhang Z, Liao Z, Jin J, Ajani J, Chang JY, Jeter M, et al. Dose-response relationship in locoregional control for patients with stage II-III oesophageal cancer treated with concurrent chemotherapy and radiotherapy. Int J Radiat Oncol Biol Phys 2005;61:656–64.

[25] Hennequin C, Gayet B, Sauvanet A, Blazy A, Perniceni T, Panis Y, et al. Impact on survival of surgery after concomitant chemoradiotherapy for locally advanced cancers of the oesophagus. Int J Radiat Oncol Biol Phys 2001;49:657–64.

[26] Nayan N, Bhattacharyya M, Jagtap VK, Kalita AK, Sunku R, Roy PS. Standard-dose versus high-dose radiotherapy with concurrent chemotherapy in oesophageal cancer: a prospective randomized study. South Asian J Cancer 2018;7:27–30.

[27] Suh YG, Lee IJ, Koom WS, Cha J, Lee JY, Kim SK, et al. High-dose versus standard-dose radiotherapy with concurrent chemotherapy in stages II-III oesophageal cancer. Jpn J Clin Oncol 2014;44:534–40.

[28] Lordick F, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol 2007;8:797–805.

[29] Barbour A, Walpole E, Mai G, Barnes L, Watson D, Ackland S, et al. Progression-free survival and recurrence results for AGITG DOCTOR. Pre-op cisplatin, 5FU & DOCetaxel +/?radioTherapy after poOR early response. Ann Oncol 2018;29, viii205–70. Abstract 618.

[30] Di Fiore A, Lecleire S, Gangloff A, Rigal O, Benyoucef A, Blondin V, et al. Impact of nutritional parameter variations during definitive chemoradiotherapy in locally advanced oesophageal cancer. Dig Liver Dis 2014;46:270–5.