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Concomitant chemo-radiotherapy for unresectable oesophageal cancer: A mono-institutional study on 40 patients

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ABSTRACT

Background/Aim: To analyse clinical response, overall (OS) and disease free survival (DFS) and toxicity in patients with unresectable oesophageal cancer treated by concomitant chemo-radiotherapy (CRT).

Materials and methods: Forty patients with stage IIa–IVa biopsy proven oesophageal carcinoma were treated with CRT. All patients were studied with endoscopy and CT and judged unresectable after multidisciplinary discussion. CRT consisted of 3 cycles of cisplatin 100 mg/m^2 or carboplatin 300 mg/m^2 on day 1 and 5-fluorouracil 1000 mg/m^2 as a continuous infusion of 96 h associated with concurrent 3D-conformal RT. By using 15 MeV X-rays, a total dose of 60–66 Gy was delivered with daily fractions of 1.8–2.0 Gy.

Results: Complete response (CR), partial response (PR) and no response (NR) were observed in 50%, 20% and 20% of cases, respectively. Of the 20 patients with CR, 15 developed loco-regional recurrent disease. OS and DFS rates at 3 and 5 years were 38%, 8%, 49% and 10%, respectively. Total radiation dose ≥60 Gy improved loco-regional control and complete response (CR vs. PR + NR; $p = 0.004$) influenced both DFS and loco-regional control. Grade 3 gastrointestinal and haematological acute toxicity occurred in 3/40 patients (7.5%). One patient developed grade 4 renal failure. Late toxicity was reported in 2/40 patients (5.0%), consisting of grade 3 radiation pneumonitis.

Conclusions: Concomitant CRT for unresectable oesophageal cancer can result in an acceptable loco-regional control with limited toxicity. Response after treatment and total radiation dose influenced the outcome.

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1. Background

Oesophageal cancer is a quite uncommon tumour entity accounting approximately for 1% of all malignancies and for 6% of gastrointestinal tumours.[1] The incidence of oesophageal cancer has risen in recent years in Western countries mainly in relation to an increased incidence of the adenocarcinoma of the lower oesophagus.[2] It is in principle a treatable tumour but rarely curable. Clinical presentation is often with advanced and unresectable disease, occurring the diagnosis in early stage (<T1b) in less than 10% of cases.[3] Three-year survival rates of patients with oesophageal cancer undergoing surgery alone in clinical trials range from 6% to 36%,[1] whereas 5-year survival rates of patients treated by radiotherapy alone are reported to be 0–10%.[4]

Combined modality therapy with chemotherapy and radiotherapy has become a standard treatment for oesophageal cancer over the last decade. International guidelines including the National Comprehensive Cancer Network[5] consider chemo-radiation to be an appropriate treatment option for stage II and III when unfit for surgery and for stage IVa in selected cases.

2. Aim

The aim of the present study is to analyse clinical response, overall survival (OS), disease free survival (DFS) and toxicity in patients with unresectable oesophageal cancer treated by concomitant chemo-radiotherapy.

3. Materials and methods

Between January 1994 and June 2010, 106 patients with oesophageal cancer were referred to the Department of Radiotherapy of the University Hospital "Maggiore della Carità" in Novara, Italy. Of these 106 patients, 20 were treated in pre- or postoperative setting, 46 received only palliative radiotherapy and 40 were treated by concomitant chemo-radiotherapy with a radical intent. These 40 patients were included in the present retrospective study that was approved by the local review committee. Thirty one patients (77.5%) were male and 9 female (22.5%) with median age of 66 years (range 52–79 years). Performance status assessed by the ECOG scale[6] ranged from 0 to 2 (median 1). At biopsy, 38/40 patients (95%) had squamous cell carcinoma and 2/40 (5%) adenocarcinoma. Other tumour characteristics are reported in Table 1. All cases were studied with endoscopy and computed tomography (CT)-scan and 17/40 (42.5%) also with positron emission tomography (PET)/CT imaging. The lymph nodes status was assessed by CT and, in case of nodal enlargement >1 cm, by eco-endoscopy and/or PET/CT. All cases were judged to be candidates for radical chemo-radiotherapy after multidisciplinary discussion. Chemotherapy consisted of 3 cycles of cisplatin 100 mg/m^2 or carboplatin 300 mg/m^2 on day 1 and 5-fluorouracil 1000 mg/m^2 as a continuous infusion of 96 h. Three dimension conformal radiotherapy was given concomitantly to chemotherapy by using 6–15 MeV X-rays starting during the first cycle. Gross tumour volume (GTV) was outlined on CT images in 23/40 cases (57.5%) and on PET/CT fused images in 17/40 cases (42.5%). For delineation on PET/CT images, a fixed threshold value of 40% of the maximum uptake in the lesion was adopted. Prescribed total dose was 46–50 Gy, possibly followed by a boost of up to 60–66 Gy with daily fractionation of 1.8–2.0 Gy/die. The highest dose levels were prescribed in the case of larger tumour volume and no severe toxicity during the first part of the treatment. Four–eight weeks after the end of chemo-radiotherapy, all patients underwent repeat endoscopy and CT-scan to assess tumour response. The 17 cases studied with PET/CT at diagnosis were re-scanned with PET/CT 3–4 weeks after treatment completion to asses metabolic tumour response. Follow-up was performed every 6 months during the first 3 years and then yearly by clinical assessment, blood test, endoscopy and CT-scan. Acute toxicity was scored by the National Cancer Institute-Common Toxicity Criteria Version 4.0 based on data recorded in the patients' charts and late toxicity was assessed by the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) late radiation morbidity scoring scheme.[7,8]

Table 1 – Main patient and tumor characteristics.

Characteristics	Patient number	%
Gender		
Male	31	77.5
Female	9	22.5
Performance status (ECOG)		
0	4	10
1	25	62.5
2	9	22.5
Tumor location		
Upper third	12	30
Middle third	18	45
Lower third	3	7.5
Multiple sites	7	17.5
Clinical stage		
IIA	15	37.5
IIB	1	2.5
III	21	52.5
IV	3	7.5

3.1. *Statistical analysis*

Actuarial OS and DFS were calculated by the Kaplan Meier method. Univariate analysis was performed by the Log Rank test for OS, DFS and loco-regional control (LRC) considering the following parameters: age, clinical stage, N-stage, grading, response to treatment, and radiation dose. A p-value < 0.05 was considered to be statistically significant. The correlation between total dose (≥60 Gy vs. <60 Gy) and clinical response (CR vs. PR + NR) was analysed by the χ^2 test.

4. Results

Of the 40 patients included in the present study, 36 (90%) completed the chemo-radiotherapy program. Two patients stopped chemotherapy after the first cycle for renal toxicity grade G3, but completed radiotherapy reaching the total dose of 60 Gy and the other two patients stopped chemotherapy after the second cycle: one at the radiation dose of 21.6 Gy for disease progression and the other one at the dose of 40 Gy

Table 2 – Univariate analysis (log-rank test).

	N. of patients	Overall survival	Disease free survival	Loco-regional control
Age (y)				
<65	21	$p = 0.61$	$p = 0.87$	$p = 0.80$
≥65	19			
Stage				
Stage IIA–IIB	16			
Stage III	21	$p = 0.28$	$p = 0.66$	$p = 0.65$
Stage IV	3			
N category				
N0	24	$p = 0.83$	$p = 0.31$	$p = 0.30$
N1	16			
Histological grading				
G < 3	22	$p = 0.30$	$p = 0.38$	$p = 0.29$
G = 3	18			
Response to treatment				
Complete response	20			
Partial response	8	$p = 0.11$	$p = 0.0006$	$p = 0.0003$
No response	8			
Complete response	20	$p = 0.32$	$p = 0.0001$	$p = 0.0001$
Partial response + no response	16			
Dose (Gy)				
<60 Gy	26	$p = 0.53$	$p = 0.06$	$p = 0.02$
≥60 Gy	14			

for cachexia. The dose actually delivered in the whole series ranged from 21.6 Gy to 66 Gy (median 54 Gy).

After chemo-radiotherapy, 20/40 patients (50%) showed a complete response (CR), 8/40 (20%), partial response (PR), and 8/40 (20%) no response (NR). The χ^2 test showed a trend for a possible statistical correlation between total dose and clinical response ($p = 0.067$). Four patients died before response assessment, three for disease progression and one for myocardial infarction. Of the 20 patients with CR, 15 (75%) developed loco-regional recurrence after 5–36 months (median 12 months) as first relapse of disease.

Follow-up time ranged from 3 to 60 months with a median of 21 months. Median survival time was 22.5 months. OS rates at 2, 3 and 5 years were 52%, 38% and 8%, respectively. DFS rates at 2, 3 and 5 years were 54%, 49% and 10%, respectively (Fig. 1). By univariate analysis, the clinical response after treatment influenced DFS: the 2-year DFS rate was 100% for patients with CR vs. 24% for patients with PR + NR ($p = 0.0001$). Clinical response and total radiation dose <60 Gy or ≥60 Gy improved LRC ($p = 0.02$) (Table 2) (Figs. 2–4).

Metastases were detected in 12/40 patients (30%): in 4 cases to the lymph nodes and in 8 cases to other distant sites including the lung, bone, liver and brain.

Acute toxicity, mainly gastrointestinal and haematological, occurred with grade 1–2 in 21/40 patients (52.5%) and with grade 3 in 3/40 patients (7.5%). Only one patient experienced grade 4 toxicity due to a renal failure after cisplatin administration. Late toxicity was reported in 2/40 patients (5.0%), consisting in both cases of grade 3 radiation pneumonitis (Table 3).

5. Discussion

When oesophageal cancer presents with unresectable disease, the general consensus is to treat it using a combined approach with chemotherapy and radiotherapy since the benefit of definitive chemo-radiation over radiation alone has been well documented.[9] The recommendation from literature studies, based on small but randomized experience, is to treat both squamous and adenocarcinoma cell histology in a similar way by using fluoropyrimidine plus another cytotoxic agent.[3,10–12]

Our series does not substantially differ from other literature series in terms of gender and age distribution, showing a prevalence of males and a median age of 66 years. Most cases arose from the upper and middle oesophageal third and presented with squamous cell carcinoma histology, whereas only 5% of cases were diagnosed with adenocarcinoma. The relatively low percentage of adenocarcinoma in our series compared with the tumour presentation from other series treated by surgery may be explained by the fact that the lower third location, where such histology typically arises, is more often approached by surgical resection. Seven cases

– Acute (CTCAE Version 4.0) and late toxicity (RTOG scale).

Acute toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Anemia	4	4	2	–
Leukopenia	2	3	–	–
Thrombocytopenia	8	2	–	–
Gastrointestinal				
Nausea	–	4	2	–
Vomiting	–	4	2	–
Hematemesis	1	–	–	–
Dysphagia-Esophagitis	–	5	1	–
Renal failure	–	–	1	1
Mucositis	–	1	2	–
Erythema	–	2	–	–
Late toxicity				
Angina	–	1	–	–
Radiation pneumonitis	–	–	2	–

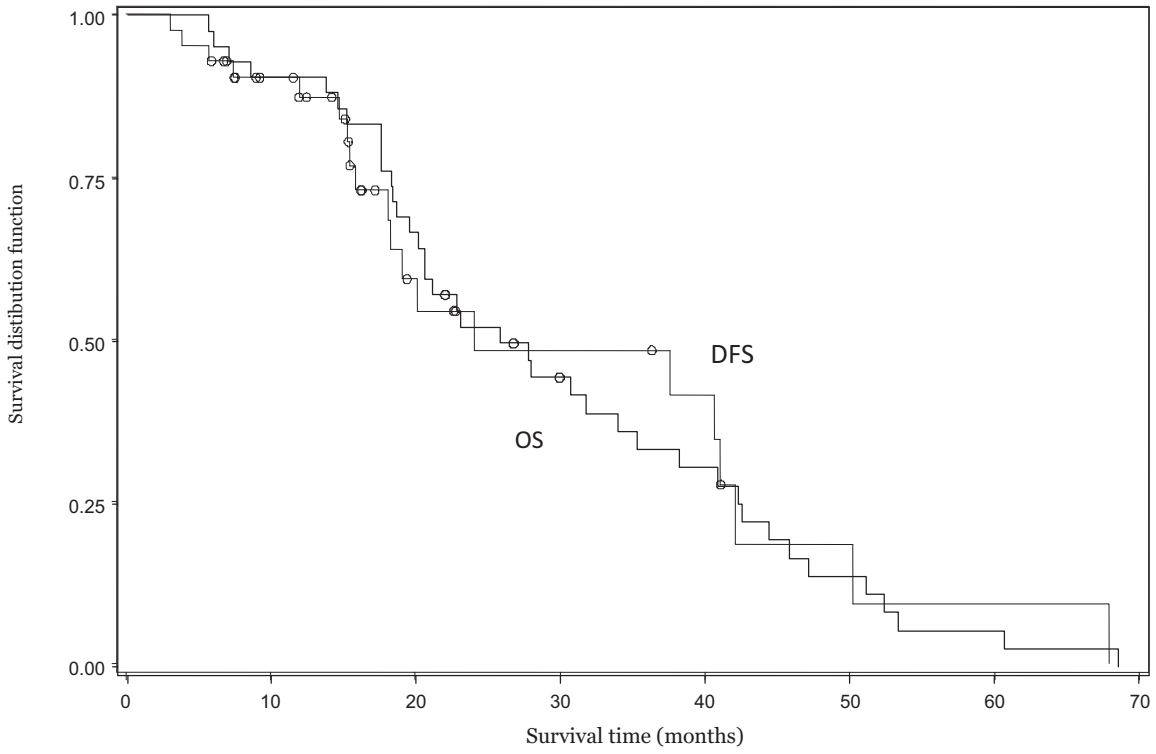

Fig. 1 – Overall survival (OS) and disease free survival (DFS).

(17.5%) presented with multiple locations in relation to a multicentre origin of the tumour. This aspect was reported also by Morita et al. who found an association of the loss of fragile histidine triad gene expression with alcohol induced carcinogenesis and multicentre tumour presentation.[13] Advanced clinical stage distribution of our series ranging from IIa to IVa was relatively less favourable compared with other studies that used a similar chemo-radiotherapy approach.[9,14,15]

Seventeen of our patients were studied also by PET/CT imaging that was used both for staging and for treatment planning purposes. In the recent years, PET/CT has been

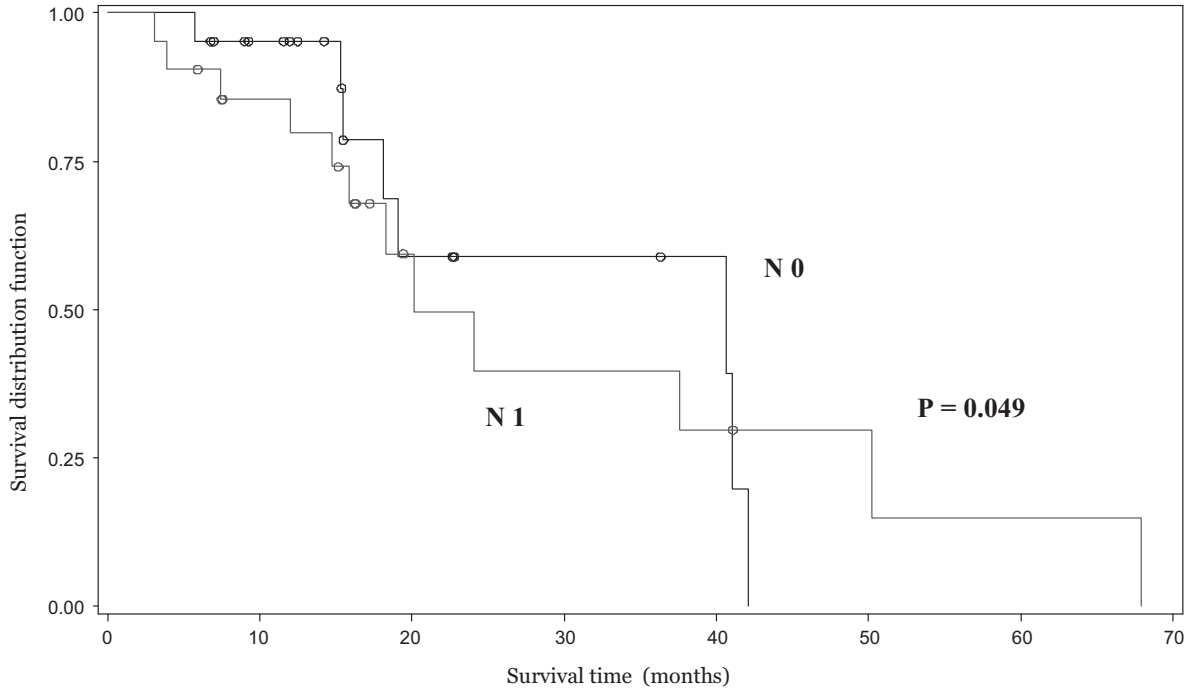

Fig. 2 – Node status and disease free survival (DFS).

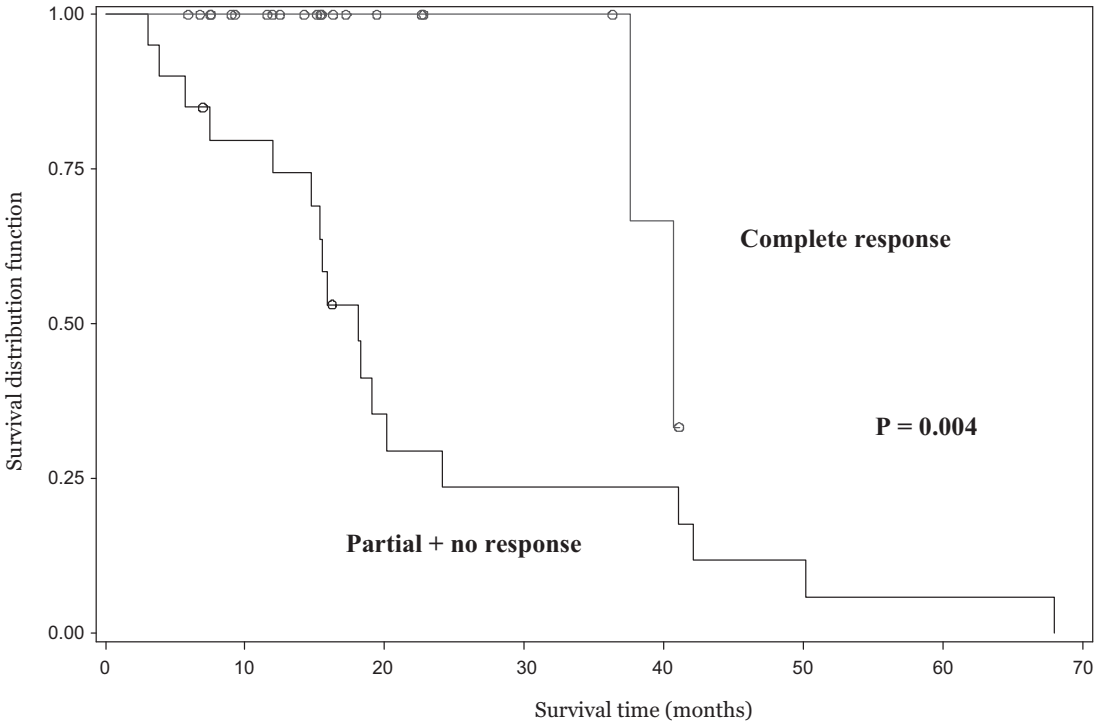

Fig. 3 – Response to treatment and disease free survival (DFS).

implemented for the identification and delineation of target volume as well as for the response assessment after treatment completion in several tumour locations but only a few of the recent literature studies have described the use of PET/CT in oesophageal cancer. Interestingly, FDG-PET performed after induction chemotherapy or before concomitant chemo-radiation may be useful in predicting a final tumour response[16] and FDG-PET after chemo-radiation may predict patients' prognosis.[17] In this regard, we are still following our patients who underwent PET/CT to understand whether this functional information can correlate with clinical outcome.

Treatment schedule was very similar over time for all our patients. Chemotherapy regimen was substantially the same, including cisplatin or carboplatin, mainly in relation to the patients' renal function. Nowadays, other new drugs like docetaxel, epirubicin, irinotecan and capecitabine, tested in various literature studies for preoperative or radical chemo-radiotherapy, failed to show a substantial improvement of prognosis of the disease.[3] The addition of target therapy to chemo-radiotherapy schemes seems to be a new promising approach that has been preliminarily tested in controlled clinical trails.[18] Radiotherapy was conducted with a similar 3D-conformal technical approach. The changes over time have been in the more detailed dosimetry documentation with dose-volume histograms since 1999 and the implementation of PET/CT imaging for assistance in target identification and delineation since 2005. The prescribed total dose was higher (60–66 Gy) than that reported in most literature studies and recommended in the NCCN guidelines.[5] As a matter of fact, a total dose of 45–50 Gy was prescribed to the target volume

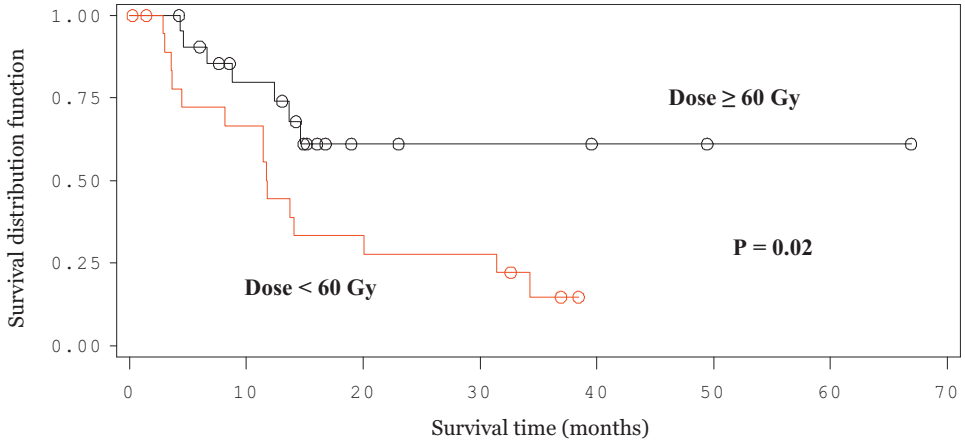

Fig. 4 – Dose and loco-regional control.

and, in case of large tumour volume, whenever possible, a boost dose was applied of up to 60–66 Gy in the attempt to increase local tumour control. In this regard, the majority of our patients (26/40, 65%) were able to effectively reach such a high dose level. In other literature series, high dose-rate brachytherapy was used to either intensify the dose or palliate symptoms.[19,20]

The overall response rate after chemo-radiation, assessed by endoscopy and CT, was 70% with 50% of CR. Other authors report response rates ranging from 38% to 96% with average CR rates of 60% and up to 96%. Interestingly, 11–79% (mean 32%) of pathological responses were reported after preoperative chemo-radiotherapy when radiation is usually given to a total dose of about 40–50 Gy and the response rates seem to be higher for treatment regimens that include a concomitant administration of radiation and platinum compounds.[14,15,21–24]

The median survival time (22.5 months) and the OS and DFS rates at 2, 3 and 5 years of 52%, 38% and 8% and of 54%, 49% and 10%, respectively, observed in our series, are basically in the range of the recent literature data, despite a relatively unfavourable patient selection that included mainly stage III and also stage IVa disease.[15,21,23–26] The most frequent pattern of relapse was loco-regional, accounting for 75% of cases who obtained CR after treatment. Such percentage is similar to that observed in some literature studies[9,14] but higher than that reported in others.[15,23,24] This difference may be related to the different stage distribution. Univariate analysis showed that clinical response after treatment correlated with DFS and clinical response and total radiation dose $\geq$60 Gy correlated with higher loco-regional control rate. Similarly, other literature studies showed that CR after treatment completion may influence favourably the outcome.[19] In our series, the histological grading <3 and the dose $\geq$60 Gy showed only a trend for better DFS, whereas some literature studies observed a statistical significance of these parameters.[25]

Acute toxicity was mainly of grade 1–2 (52%) and only in 4 cases (10%) was it of higher grade. Grade 3 late effects consisting of radiation pneumonitis occurred only in 2 cases (5%). Similar or higher toxicity rates were reported by other authors.[14,15,21]

The main limitations of our study are the retrospective design and the relatively small number of patients not allowing to perform a multivariate analysis. On the other hand, the treatment characteristics were substantially homogeneous over time and the median follow-up was adequate to observe and report long-term outcome.

6. Conclusions

This observational study showed that concomitant chemo-radiotherapy for unresectable oesophageal cancer is feasible and can result in an acceptable rate of local control with limited toxicity in a clinical series treated outside prospective controlled clinical trials. Loco-regional recurrence was the most frequent pattern of relapse and OS rates at 2, 3 and 5 years were similar to those of other literature series. The clinical response after treatment influenced DFS and the clinical response, and the use of high radiation doses improved loco-regional control.

Conflict of interest

None declared.

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