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Clinical Trial

Continuation versus discontinuation of first-line chemotherapy in patients with metastatic squamous cell oesophageal cancer: A randomised phase II trial (E-DIS)☆

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KEYWORDS
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Abstract ***Purpose:*** The role of chemotherapy has not been established in the treatment of metastatic squamous cell oesophageal cancer (mESCC).
Patients and methods: E-DIS is a discontinuation trial, aimed at estimating efficacy, quality of life and safety of chemotherapy continuation (CT-CONT) in patients with mESCC who are free from progression after a selection phase of chemotherapy. The primary end-point was overall survival.
Results: Sixty-seven patients were randomised. The 9-month survival rate was 50% (85% confidence interval [CI]: 37–62%) and 48% (85% CI: 35–60%) in the CT-CONT arm and in the chemotherapy discontinuation (CT-DISC) arm, respectively. The time until definitive deterioration of the global health status (European Organisation for Research and Treatment of Cancer [EORTC] core quality of life questionnaire) was 6.6 months (95% CI: 3.3–12.4) for the CT-CONT arm and 4.2 months (95% CI: 2.9–6.3) for the CT-DISC arm, with a hazard ratio ($HR_{CT\text{-}DISC/CT\text{-}CONT}$) = 1.44 (95% CI: 0.82–2.53). We observed a beneficial trend in favour of CT-CONT (HR > 1) for most dimensions, including an improvement for three dimensions (dysphagia, eating and oesophageal pain) of the EORTC Oesophageal Cancer Module QLQ-OES18.
Conclusion: CT-CONT provides an overall survival rate that is similar to CT-DISC. E-DIS trial provides valuable data to support shared decision-making between physicians and patients regarding CT-CONT/DISC.

1. Introduction

Oesophageal cancer ranks eighth on the list of the most common cancers worldwide, with an estimated 456,000 new cases in 2012 [1]. Oesophageal squamous cell carcinoma (ESCC) represents a majority of all cases of oesophageal cancer globally, and it is particularly prevalent in Eastern Asia, Eastern Africa and South America. ESCC is mainly related to the use of tobacco and alcohol [1]. Overall, this cancer is a deadly disease with a mortality-to-incidence ratio of 0.88 [1]. Fifty percent of these patients present with synchronous metastases at the time of diagnosis, and most patients who present initially with localised disease eventually develop metachronous metastases [2]. The 3-year survival rate for patients with metastatic oesophageal cancer is less than 1% [3].

The role of chemotherapy has not yet been fully established in the treatment of metastatic ESCC (mESCC) [4]. Many cytotoxic drugs promote tumour shrinkage [5–17] but, until now, there has been no randomised trial that provides unequivocal evidence for a clinical benefit with chemotherapy. For example, the European Organisation for Research and Treatment of Cancer (EORTC) reported the results of a randomised phase II trial that compared the activity of cisplatin (CDDP) with or without 5-fluorouracil (FU) in 88 patients with mESCC [7]. Although a greater response rate was observed with the combination, this was achieved without any overall survival (OS) benefit and at the expense of substantially increased toxicity, including deaths due to toxicity. Recently, the combination of chemotherapy and epidermal growth factor receptor monoclonal antibodies failed to improve the efficacy over chemotherapy alone [18,19]. Guidelines from the European Society of Medical Oncology (ESMO) recommend supportive care or chemotherapy as options in such settings [20]. Surprisingly, some physicians are convinced that patients with mESCC may benefit from chemo. This attitude leads to the delivery of treatments with unproven benefit with side-effects and unjustified costs.

The E-DIS trial (ClinicalTrials.gov identifier: NCT01248299) was a randomised discontinuation trial that was offered to patients with mESCC who were free from progression after a 6-week selection phase of FU/platinum-based chemotherapy. This study was designed to estimate the OS of patients with mESCC who continued chemotherapy (CT-CONT arm).

2. Patients and methods

2.1. Patient population and study design

The multicentre E-DIS study selected patients before starting a first-line FU/platinum-based chemotherapy. Key selection criteria included histologically confirmed mESCC, measurable disease, age greater than 18 years and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2. Prior chemotherapy was permitted only if it was delivered as a neoadjuvant treatment. The choice of the FU/platinum-based regimen was left to physician's decision among the

following ones: FU–CDDP, FU–CDDP–docetaxel, FU–folinic acid–CDDP (LVFU2-CDDP) and FU–folinic acid–oxaliplatin combination (FOLFOX). Chemo dosing is detailed in Appendix Table S1 and in Table 1. Patients free from progression after 6 weeks of treatment were assigned equally to either continue the same chemotherapy or discontinue chemotherapy. In the CT-CONT arm, the study treatment continued until there was disease progression, unacceptable toxicity or a patient or physician decision to terminate the treatment. In the CT-DISC arm, chemotherapy could be resumed after disease progression. On-demand supportive care was offered to any patient. The protocol complied with the recommendations of the 18th World Health Congress (Helsinki, Finland, 1964) and its subsequent amendments, good clinical practice guidelines and other legal requirements. The protocol, including all amendments, was reviewed and approved by the CPP Nord-Ouest III ethics committee on August 22, 2013. Patients provided written informed consent before enrolment in the study.

2.2. Efficacy and safety assessments

The primary end-point was OS, defined as the time interval from the date of random assignment to the date of death from any cause. Secondary end-points included progression-free survival (PFS), Quality of life (QoL), safety and medical costs. Tumour assessment was performed 6 weeks and 12 weeks after the randomisation

Table 1
Baseline characteristics of the 67 patients who were included in the randomised part of the study, by the treatment group.

Patients characteristics	CT-CONT N = 34		CT-DISC N = 33	
Age in years, median (range)	64.5	(43–81)	63	(50–72)
Gender				
Male	25	74%	29	88%
Female	9	26%	4	12%
ECOG performance status				
0-1	30	88%	31	94%
2	4	12%	2	6%
No dysphagia	16	50%	17	52%
Normal albumin	22	65%	21	66%
Metachronous metastasis	21	62%	18	55%
Time interval between initial diagnosis and first diagnosis of metastases, in months, median (range)	10.9	(0–151)	6.5	(0–41)
Previous locoregional therapy	20	59%	19	58%
Number of metastatic sites				
>1	22	65%	14	42%
Main metastatic sites[a]				
Lung	16	47%	20	61%
Liver	15	44%	10	30%
Nodes	25	74%	19	58%
Bones	3	9%	0	0%
Others	8	24%	6	18%
Previous chemotherapy in the neoadjuvant setting	18	53%	19	58%
Chemotherapy regimen				
FU–CDDP[b]	0/34	0%	1/33	3%
FU–CDDP–docetaxel[c]	0/34	0%	3/33	9%
LVFU2–CDDP[d]	8/34	24%	4/33	12%
FOLFOX[e]	26/34	76%	25/33	76%
Response after 6 weeks of chemotherapy				
Complete response	0		1	3%
Partial response	12	35%	9	27%
Stable disease	20	59%	21	64%
Progressive disease	2	6%	0	
Missing data			2[f]	6%

CT-DISC, chemotherapy discontinuation; CT-CONT, chemotherapy continuation; Eastern Cooperative Oncology Group performance status.

[a] One patient can have several metastatic sites.

[b] FU–CDDP: FU 1000 mg/m^2 as a continuous infusion over 96 h plus CDDP 100 mg/m^2 day 1 or 2, every 4 weeks.

[c] FU–CDDP–docetaxel: docetaxel 75 mg/m^2 on day 1, CDDP 75 mg/m^2 on day 1 and FU 750 mg/m^2 as a continuous infusion over 120 h, every 4 weeks.

[d] LVFU2–CDDP: FU–folinic acid–CDDP, with CDDP 50 mg/m^2, folinic acid 200 mg/m^2 and bolus FU 400 mg/m^2 on day 1 followed by FU 2400 mg/m^2 as a continuous infusion over 46 h, every 2 weeks.

[e] FOLFOX: FU-folinic acid-oxaliplatin combination with oxaliplatin 85 mg/m^2, folinic acid 200 mg/m^2 and bolus FU 400 mg/m^2 on day 1 followed by FU 2400 mg/m^2 as a continuous infusion over 46 h, every 2 weeks.

[f] For two patients, known as non-progressive at 6 weeks, detailed information about the tumour response at 6 weeks is not available.

date and every 12 weeks thereafter. PFS was assessed according to Response Evaluation Criteria in Solid Tumours 1.1. QoL was assessed using the EORTC QoL core questionnaire (QLQ-C30) [21] and with the oesophagus-specific questionnaire (QLQ-OES18) [22] at the baseline and every 6 weeks thereafter until 42 weeks after randomisation. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria, version 4.0. Patients were observed until death or until 48 months after study entry.

2.3. Statistical considerations

The sample size was calculated to ensure a precision of 12.5% to estimate the 9-month OS rate with a two-sided 85% confidence interval (85% CI) in the CT-CONT arm. Assuming a 9-month OS rate of 56% [18], 31 patients were required in each arm. The CT-DISC arm served as an internal control. With an anticipated 70% eligibility rate for randomisation after 6 weeks of CT, 88 patients were required in the selection part of the trial to randomise 62 patients. In 2013, we found that the actual eligibility rate for the randomised part was only 58%. The protocol was thus amended to select 106 patients. Randomisation was performed using a minimisation method controlling for the following factors: previous chemotherapy (no vs yes), dysphagia (Atkinson grade 1–2 vs 3–4) and EQ-5D visual analogue scale (<40 vs ≥ 40).

Statistical analyses of efficacy end-points were performed per randomised arm by the intention-to-treat approach. Survival estimates were calculated per treatment arm using the Kaplan–Meier method from the date of random assignment. An unplanned and exploratory *post hoc* analysis was performed to estimate OS curves in CT-DISC patients according to whether they received postprogression chemotherapy. All randomised patients were included in the QoL analysis. For functional scales, QLQ-C30 and QLQ-OES18 scores were considered as a definitive deterioration if the score decreased by more than 10 points compared with the score at randomisation and without later improvement superior to 10 points compared with the baseline. For symptom scales, a definitive deterioration was defined as an increase of 10 points or more without subsequent decrease. For each dimension of the QoL questionnaires, the time until definitive deterioration (TUDD) was defined as the time from randomisation to the first observation of a definitive deterioration of the corresponding score or death. Patients alive without reported definitive deterioration were censored at the date of the last follow-up visit. Patients without any QoL questionnaires were censored at randomisation [23]. TUDD was estimated using the Kaplan–Meier method. The impact of treatments on the different dimensions of the QoL was estimated by hazard ratios ($HR_{CT\text{-}DISC/CT\text{-}CONT}$) of QoL deterioration using Cox models. As QoL questionnaires could be missing during follow-up, leading to a possible overestimation of the TUDD, we also performed a sensitivity analysis considering the following imputations in the absence of a definitive deterioration of the QoL score: the date of definitive deterioration was imputed 3 weeks after the date of the last completion of the QoL questionnaire if the patient died more than 2 months later or if the patient was alive without subsequent QoL and patients having completed all QoL questionnaires planned in the study were censored at the date of the last QoL questionnaire plus 3 weeks.

In the CT-CONT arm, treatment-related AEs were analysed considering the maximum grade per patient and per type of AE.

3. Results

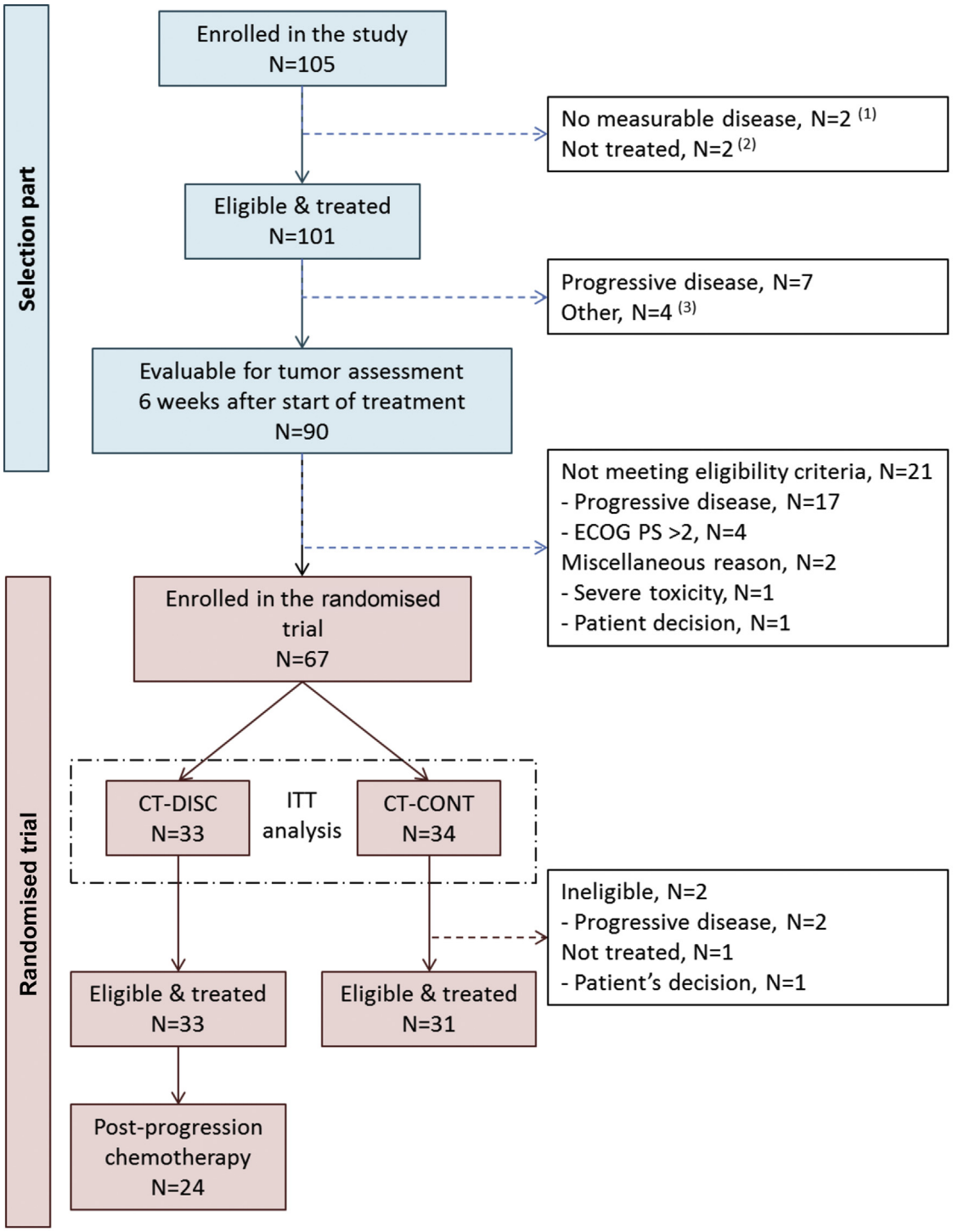
Between January 2011 and February 2015, 105 patients were recruited in the selection phase of the study. The patient distribution in the trial is illustrated in Fig. 1. Ninety patients were eligible for tumour assessment, and 69 were found to be disease-controlled with an ECOG performance status of 0–2. Among them, 67 patients were randomly assigned, 34 to continue chemotherapy and 33 to discontinue chemotherapy. At the time of the final data extraction, the median follow-up for the randomised patients was 36.9 months.

3.1. Patient and treatment characteristics

The baseline characteristics and details of the treatments that were administered before and after randomisation are given in Appendix Table S1 and in Table 1, respectively. The two treatment groups were well balanced with regard to the baseline characteristics of randomised patients and of eligible and treated patients (data not shown). Among the 31 eligible and treated patients in the CT-CONT arm, seven (23%) received LVFU2–CDDP and 24 (77%) received FOLFOX. In the CT-DISC group, 24 patients resumed chemotherapy after having progressed, while eight patients did not (missing data for one patient).

3.2. Efficacy

At the time of the analysis, 53 deaths had been reported, 51 after disease progression, one due to hepatic encephalopathy after 3.5 months and one from an unknown cause after 0.7 months, both in the CT-DISC arm. The estimated 9-month survival rate was 50% (85% CI: 37–62%) and 48% (85% CI: 35–60%) in the CT-CONT and the CT-DISC groups, respectively. The median OS rate was 8.5 months (95% CI: 6.6–12 months) and 8.8 months (95% CI: 5.9–13.4 months) for the CT-CONT and CT-DISC arm, respectively. The



(1) Two patients with an adenocarcinoma were withdrawn from the study after enrolment because they were classified as non-eligible (no measurable disease at study entry).
(2) Two patients were not treated due to poor general health status.
(3) Four patients had no tumor evaluation 6 weeks after start of treatment, due to patient's decision, no compliance, concurrent disease, and poor performance status.

Fig. 1. CONSORT diagram. ITT, intention to treat; ECOG PS, Eastern Cooperative Oncology Group performance status; CT-DISC, chemotherapy discontinuation; CT-CONT, chemotherapy continuation.

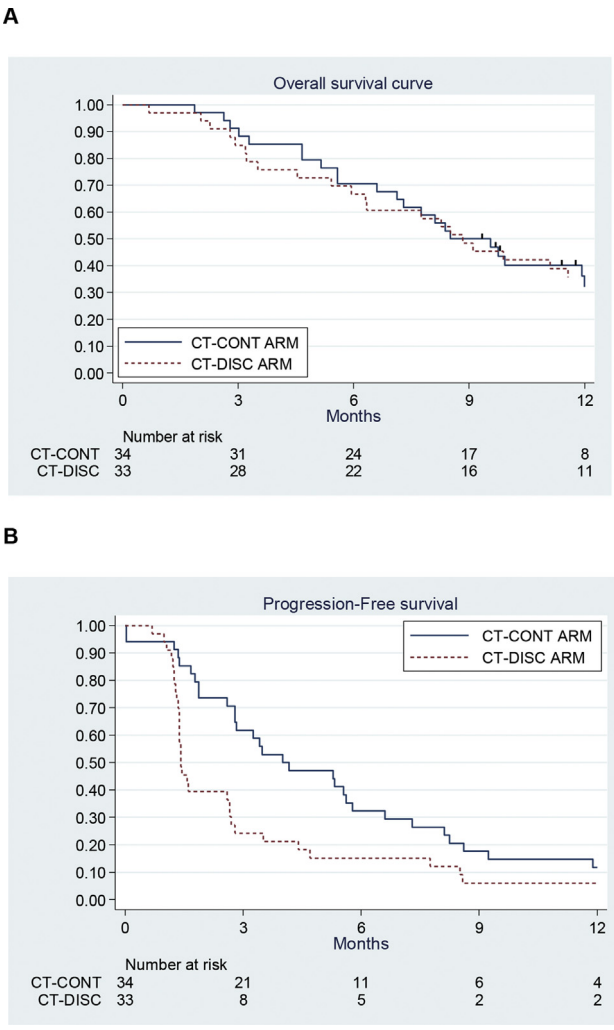


Fig. 2. Kaplan–Meier survival curves for (A) overall survival and (B) progression-free survival according to the treatment arm allocated by randomisation (intention-to-treat). CT-DISC, chemotherapy discontinuation; CT-CONT, chemotherapy continuation.

median PFS was 4 months (95% CI: 2.8–5.8 months) and 1.4 months (95% CI: 1.4–2.7 months) for the CT-CONT and CT-DISC arm, respectively. Kaplan–Meier survival curves are shown in Fig. 2. As illustrated in Fig. 3, the median OS was 9.9 months (95% CI: 6.3–16.9 months) and 3.5 months (95% CI: 2–15.4 months) for the 24 patients (24/33, 72.7%) in the CT-DISC group who received some postprogression chemotherapy and for the eight patients who did not, respectively.

3.3. Quality of life

QLQ-C30 and QLQ-OES18 domain scores showed no systematic differences between treatment arms at randomisation (data not shown). The median TUDD by the treatment arm and HR for each dimension of both QoL questionnaires are displayed in Table 2 and Fig. 4.

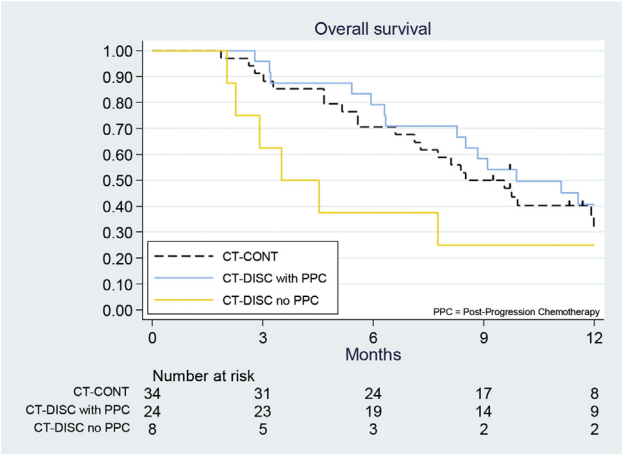


Fig. 3. Kaplan–Meier estimates of overall survival for patients who discontinued chemotherapy (n = 33), according to whether (n = 24, blue curve) or not (n = 8, yellow curve) they received postprogression chemotherapy. The dotted curve is the survival curve of patients (n = 34) who were randomly assigned to continue chemotherapy. CT-DISC, chemotherapy discontinuation; CT-CONT, chemotherapy continuation.

We observed a trend for a benefit in favour of the CT-CONT arm (HR > 1) for most dimensions, with a significant difference for three dimensions of the QLQ-OES18: dysphagia with a median TUDD of 7.3 months (95% CI: 4.2–12.0) and 2.9 months (95% CI: 1.4–4.4) for the CT-CONT and CT-DISC arm, respectively, leading to an estimated HR of 1.98 (95% CI, 1.15–3.4), p-value = 0.014; eating with a median TUDD of 7.7 months (95% CI: 5.6–9.5) and 2.9 months (95% CI: 2.0–5.9), respectively, with HR = 1.75 (1.02–3.02), p-value = 0.044 and pain with a median TUDD of 8.1 months (95% CI: 5.6–12.0) and 2.4 months (95% CI: 1.4–3.2), respectively, with HR = 2.52 (1.43–4.43), p-value = 0.001. The results appeared stable in the sensitivity analysis (Appendix Table S3).

3.4. AEs and other assessments

There were no treatment-related deaths during the study. As detailed in Appendix Table S2, toxicity was mild and without unexpected AEs. The results of the medical cost analyses will be reported elsewhere.

4. Discussion

Analysis of the primary end-point for this multicentre, randomised, discontinuation phase II trial in patients with mESCC who continued chemotherapy after having been disease-controlled with an FU/platinum regimen indicated a 50% of 9-month survival rate. Patients who had been assigned to CT-DISC had a 48% of 9-month survival rate. The median OS and median PFS were 8.5

Table 2
Quality of life analysis: median time until definitive deterioration (TUDD) by the treatment group and HR for each dimension of the quality of life questionnaires (QLQ-C30 and QLQ-OES18).

Dimension	Median TUDD in months (95% CI)		$HR_{CT-DISC/CT-CONT}$ (95% CI)
	CT-CONT arm	CT-DISC arm	
QLQ-C30 questionnaire			
Global health status	6.6 (3.3–12.4)	4.2 (2.9–6.3)	1.44 (0.82–2.53)
Physical	7.3 (5.6–9.4)	5.4 (2.9–8.5)	0.96 (0.56–1.64)
Role	5.6 (3.1–8.1)	4.5 (3.2–8.3)	1.01 (0.59–1.72)
Emotional	7.1 (4.2–11.9)	5.6 (3.2–7.8)	1.38 (0.80–2.37)
Cognitive	7.8 (3.3–12)	4.1 (2.8–8.5)	1.40 (0.80–2.42)
Social	5.6 (3.0–8.1)	6.2 (4.2–8.8)	0.88 (0.51–1.53)
Fatigue	5.6 (2.8–9.6)	4.4 (2.9–6.4)	1.28 (0.73–2.22)
Nausea	7.8 (3.3–9.8)	5.4 (2.8–8.8)	1.30 (0.75–2.24)
Pain	5.6 (2.8–7.0)	2.9 (2.1–6.3)	1.09 (0.64–1.86)
Dyspnoea	7.3 (4.2–11.9)	4.4 (2.8–7.8)	1.45 (0.84–2.50)
Insomnia	7.3 (3.3–11.9)	5.4 (2.0–7.8)	1.46 (0.84–2.55)
Appetite loss	7.1 (5.2–12.0)	4.5 (2.9–7.8)	1.45 (0.82–2.58)
Constipation	7.3 (5.2–11.9)	5.7 (2.8–9.9)	1.26 (0.73–2.18)
Diarrhoea	6.6 (3.3–9.9)	4.5 (2.9–8.5)	1.23 (0.70–2.16)
Financial difficulties	8.1 (5.6–12.4)	6.3 (3.2–9.9)	1.30 (0.74–2.27)
Pain alone	5.6 (3.0–7.3)	5.4 (2.8–8.3)	1.03 (0.60–1.77)
QLQ-OES18 questionnaire			
Dysphagia	7.3 (4.2–12)	2.9 (1.4–4.4)	1.98 (1.15–3.40)
Eating	7.7 (5.6–9.5)	2.9 (2.0–5.9)	1.75 (1.02–3.02)
Reflux	7.8 (4.7–11.9)	3.2 (1.4–7.8)	1.63 (0.93–2.85)
Pain	8.1 (5.6–12.0)	2.4 (1.4–3.2)	2.52 (1.43–4.43)
Trouble swallowing	7.8 (5.2–11.9)	6.3 (3.2–9.1)	1.39 (0.81–2.41)
Choked when swallowing	7.1 (4.2–9.9)	5.4 (3.0–6.9)	1.29 (0.75–2.22)
Dry mouth	6.8 (3.3–9.8)	5.9 (3.1–9.9)	0.98 (0.57–1.67)
Taste	7.3 (5.2–9.5)	4.4 (2.9–7.8)	1.19 (0.70–2.03)
Coughing	8.1 (5.6–9.9)	6.3 (3.2–8.8)	1.17 (0.69–1.98)
	7.3 (3.3–9.5)	5.7 (3.2–8.3)	0.98 (0.58–1.66)

CT-DISC, chemotherapy discontinuation; CT-CONT, chemotherapy continuation; HR, hazard ratio; CI, confidence interval.

and 4.0 months in the CT-CONT arm and 8.8 and 1.4 months in the CT-DISC arm, respectively. Although one could have anticipated a better OS for patients in the CT-CONT arm that, actually, had been selected on the basis of early control of their disease, our survival results are of the same order of magnitude to those previously reported with FU/platinum regimens in contemporary randomised studies [17–19]. E-DIS was not designed to detect a superiority of one arm over the other. Nevertheless, the two OS curves are so close and intertwined that one cannot claim a difference in OS. To understand why patients who discontinued chemotherapy had the same OS as patients who continued chemotherapy until progression, we examined the outcome of CT-DISC patients. First, most of these patients (72.7%) received subsequent chemotherapy at progression. As a consequence, most patients in the CT-DISC arm experienced a transient chemotherapy break rather than permanent discontinuation. Second, the shape of the OS curve for patients who resumed chemotherapy appeared better than the OS curve for patients who did not receive postprogression chemotherapy in the CT-DISC arm. Third, the OS curve for patients who resumed chemotherapy resembled those for patients who had been randomly allocated to the CT-CONT arm (Fig. 3). Taken together, these features suggest that chemotherapy might have some favourable impact on the OS. However, we acknowledge that our observation is tentative as the number of patients was low and as we cannot rule out a selection bias, i.e., a

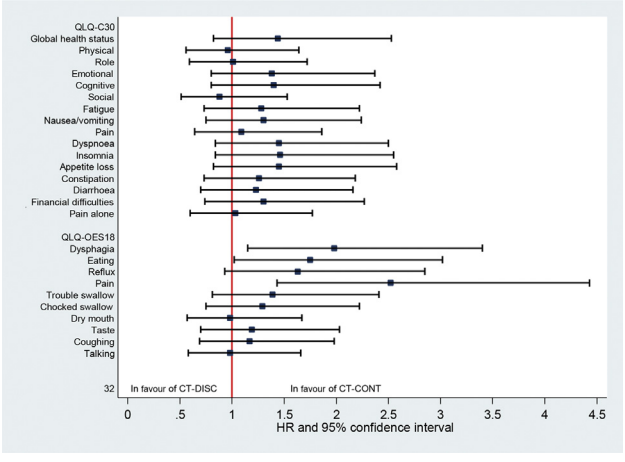


Fig. 4. Relative treatment effect on the quality of life end-points (a forest plot of the hazard ratio on definitive deterioration of quality of life). CT-DISC, chemotherapy discontinuation; CT-CONT, chemotherapy continuation; HR, hazard ratio.

poor performance status may have resulted in some patients not resuming chemotherapy.

In this study, most patients (77%) received FOLFOX and 23% received LVFU2–CDDP. The latter, a biweekly regimen combining CDDP, bolus FU and infusional FU over 2 days, is regarded as a convenient way to deliver FU and CDDP and a safer regimen than the monthly FU–CDDP regimen with FU given as a continuous infusion over 4 or 5 days [24]. Oxaliplatin is a platinum derivative that has a more favourable toxicity profile than CDDP, and FOLFOX has been previously investigated in the treatment of mESCC with comparable efficacy but with better safety than FU–CDDP [15]. Actually, FOLFOX is becoming popular in daily practice because it has been shown to be equivalent to FU–CDDP in terms of efficacy in locally advanced settings [25,26].

CT-CONT is associated with a significant delay in the worsening of some major symptoms such as dysphagia, eating and oesophageal pain (Fig. 4). The results of the sensitivity analysis performed to control a possible overestimation of the TUDD in the primary analysis of QoL were stable. Indeed, the study of the Qol has special relevance when life expectancy is short and when the benefit, if any, of some treatment can be perceived as modest. Consequently, it is satisfactory to observe an apparent benefit of the QoL in patients who continued chemotherapy.

Because of its limitations, E-DIS should be interpreted carefully. First, we acknowledge that part of our intervention was not standardised enough. At the onset of our trial, there was no clear evidence that chemotherapy provided a clinical benefit to patients with mESCC, and the ESMO guidelines suggested that either the best supportive care or palliative chemotherapy should be considered in this setting [20]. Consequently, we decided to accept all types of FU/platinum-based regimens as selection treatments. In 2009, at the time when the protocol was being written, we asked trial participants to provide on-demand supportive care to patients, regardless of the treatment arm to which they were assigned. Actually, we cannot certify that this supportive care was standardised adequately to avoid hypothetical differences between the two arms of this open-label trial, leading to a possible risk of systematically overestimating the net clinical benefit of the control arm, as has been recently suggested [27], although we were referring to national recommendations that were supposed to be followed similarly in the two arms of this trial. Second, the main apparent benefit of CT-CONT relies on QoL analysis, which was a secondary endpoint, with multiple comparisons and is subject to possible bias. Finally, E-DIS was designed as a non-comparative trial; therefore, all HRs are exploratory.

In conclusion, chemotherapy until progression provides an OS rate that is numerically similar to chemotherapy interruption in patients with mESCC who had been disease controlled with a 6-week selection course of an FU/platinum regimen. E-DIS provides valuable data to support shared decision-making between physicians and patients regarding CT-CONT/DISC.

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Conflict of interest statement

None declared.

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Appendix A. Supplementary data

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