Impact of radiation schedule and chemotherapy duration in definitive chemoradiotherapy regimen for esophageal cancer

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SUMMARY

Impact of radiotherapy (RT) schedule on local response and duration of the 5-fluorouracil/cisplatin (5 FU/CDDP) chemotherapy (CT) on more still questioning in chemoradiotherapy (CRT) regimen in esophageal carcinoma.

Aim — Evaluate two RT schedules and two different CT durations by a retrospective comparison of the CRT regimens used by two centres between 1994 and 2000.

Methods — In centre I (regimen I), patients received 2 CT concomitantly to a continuous RT (50 Gy/25 fractions/5 weeks). In centre II (regimen II), patients received 6 CT, 3 were concomitant to a split course RT (20 Gy/10 fractions x 3 courses) and 3 CT were delivered after CRT.

Results — A total of 129 patients were included, 74 in centre I and 55 in centre II respectively. Main patient characteristics were similar between the two groups. Clinical complete response to CRT was significantly more frequent in regimen I (83.8% vs 65.4%; P = 0.02). The median overall survival (OS) was 20 months in regimen I and 22 months in regimen II (NS). During follow-up, responder patients to CRT in regimen II experienced significant fewer metastasis (51.6% vs 27.8%; P = 0.03) with a trend to an increased 5-year survival (19.4% vs 11.3%) and OS (26.5 vs 21.0 months) (NS). Grade 3-4 toxicities were not different.

Conclusion — Clinical complete response to CRT was significantly more frequent with a continuous RT whereas additional CT after CRT significantly reduced metastasis occurrence. CRT regimen in esophageal carcinoma may be more effective using a continuous RT schedule and additional CT courses after CRT completion.

RÉSUMÉ

Impact du schéma de radiothérapie et de la durée de la chimiothérapie dans la radiochimiothérapie exclusive du cancer de l’œsophage

Frédéric DI FIORE, Stéphane LECLEIRE, Marie-Pierre GALAIS, Olivier RIGAL, Brigitte VIÉ, Isabelle DAVID, Hadji HAMIDOU, Bernard PAILLOT, Jacques-Henri JACOB, Pierre MICHEL

(Gastroenterol Clin Biol 2006;30:845-851)

Introduction

Esophageal cancer is a frequent gastrointestinal malignancy with 32 332 new cases per year in Europe [1]. In France, esophageal carcinoma is the third most frequent digestive tract cancer with approximately 5 000 new cases per year. This incidence is particularly high in NorthWest regions of France including Normandy where our two centres are located (Rouen, Caen).

[2]. The prognosis of patients with esophageal cancer is mainly correlated with tumour parietal infiltration, lymph node and distant metastasis with an overall 5-year survival rate less than 10% [1]. Staging at diagnosis revealed that more than 50% of patients exhibited a locally advanced esophageal carcinoma defined either as tumour with peri-esophageal tissue penetration (T3), or contiguous structure invasion (T4) and/or lymph-node involvement (N+) [3, 4]. Currently, one of the therapeutic options for patients with locally advanced esophageal carcinoma is a definitive concomitant chemoradiotherapy (CRT) regimen described by Herskovic et al. [5] (Figure 1). During the past decade, several investigators have reported successful results in treatment of LAOC with a CRT regimen including the 5-fluorouracil/cisplatin (5FU/CDDP) chemotherapy (CT) combination associated either with or without surgery [6-10]. Furthermore, recent phase III trials have reported equivalent results between...
The aim of the present study was to evaluate the impact of two RT schedules on the clinical complete response to CRT and the impact of two CT durations on metastatic occurrence in patients with locally advanced esophageal carcinoma through a retrospective comparison of the CRT regimens used in two centres with frequent collaboration and similar clinical care. Both centres used the CRT regimen in their routine practices as the first-line treatment in non operated patients.

Material and methods

Patient population

Patients with locally advanced esophageal carcinoma who were registered in each centre between the January 1994 and December 2000 were screened for this study. The following criteria were used to selected patients: a histologically confirmed esophageal carcinoma (squamous cell carcinoma or adenocarcinoma); a first-line treatment with a definitive CRT regimen using the 5 FU/CDDP CT and a concomitant external radiation; a performance status (OMS) grade 2 or less; satisfactory haematological function (leucocytes count $\geq 3000$ $\text{mm}^{-3}$, platelet count $\geq 100000$ $\text{mm}^{-3}$) and good renal function (creatinine serum level $\leq 100$ micromole/l). Patients were excluded if they had a previous history of carcinoma during the three years, if they had synchronous metastasis or if they exhibited a major complication i.e. heart disease, pulmonary fibrosis, or a second carcinoma at other site.

For each selected patient, we routinely collected all baseline clinical and tumour characteristics including age, sex, OMS performance status, dysphagia Atkinson score and weight loss at the start of treatment, median tumour length, esophageal location, histopathology findings and tumour stage. Observance and toxicity related to treatment was assessed in both groups.

Tumour stage

The 1983 AJCC staging system was used in this study according to recommendations recently published [8]. Tumour evaluation was based on esophagoscopy, barium esophagography, chest and abdominal computed tomography (CT-scan), endoscopic bronchoscopy and esophageal ultrasonography whenever if feasible.

Treatment schedule (figure 1)

In centre I, patients were treated with a CRT (regimen I) including a continuous RT ($50$ Gy) concurrent to 2 CT courses (2 concomitant + 2 after the CRT), by continuous infusion on days 1 to 5 (week 1), 28 to 33 (week 5) and 56 to 61 (week 9) and CDDP ($75$ mg/m$^2$ on days 1, 29 and 32 (week 5)) and 5FU ($1000$ mg/m$^2$/day delivered by continuous infusion on days 2 to 5 (week 1) and 29 to 32 (week 5)) and CDDP ($100$ mg/m$^2$ on days 1 and 28). No additional CT courses were delivered after CRT completion in regimen I.

In centre II, patients were treated with a CRT (regimen II) including a split course RT ($20$ Gy/10 fractions x 5 weeks) concurrent to 3 CT courses of 5-FU ($1000$ mg/m$^2$/day delivered by continuous infusion on days 1 to 5 (week 1), 28 to 33 (week 5) and 56 to 61 (week 9)) and CDDP ($75$ mg/m$^2$ delivered on days 1, 28 and 56). Three additional CT courses were delivered after the CRT completion in regimen II and consisted of 5-FU ($1000$ mg/m$^2$/day continuous infusion delivered during five days) and CDDP ($100$ mg/m$^2$ on day 1) with a 2-week break between each course.

In both centres, the target volume of RT was the macroscopic tumour and enlarged lymph nodes if any, surrounded by 5-cm proximal and distal margins and a 2-cm radial margin. The target was extended to the inferior cervicale area in cases of tumours located above the carina. The specified dose was delivered at the intersection of the central axis of the beams, according to international guidelines. The irradiation technique was applied in anterior and posterior opposed fields. At 40 Gy, the radiation portals were reduced to shield the spinal cord and to encompass the primary tumour with a 2-3 cm craniocaudal margin.

Evaluation of clinical response and toxicity to CRT

Evaluation of the clinical response to CRT included endoscopy and CT-scan evaluation in both centres 8-10 weeks after CRT completion. Patients were considered to have clinical complete response to CRT if no residual tumour was detected at endoscopy and if no occurrence of metastatic disease was identified on CT-scan evaluation. Toxicity related...
to the treatment was evaluated using the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2.0). Toxicity was assessed in each patient in both centres at day 1 of each CT course.

Follow-up

The exact dates of relapse and death were assessed by reviewing each patient's follow-up based on clinical data, endoscopy and CT scan. Histopathological confirmation of the recurrence was not routinely required. Follow-up was performed either until death or for the purpose of this study until September 2005.

Statistical analysis

Analysis was performed in September 2005 when all data were censored. All collected data were compared between each centre using the chi-square test. Mann-Whitney tests were used to compare quantitative or ordinal variables. Survival curves were established using Kaplan-Meier method, and were compared with the log-rank test. Two-side P-values equal or less than 0.05 was considered to indicate statistical significance.

Data from patients who had been lost to follow-up were censored at the time of last evaluation. The starting point for the analysis of overall survival and for progression-free survival was the date of CRT initiation. Disease-free survival (DFS) was calculated from the date of endoscopy evaluation after the CRT.

Results

Patients characteristics

A total of 129 patients with a locally advanced esophageal carcinoma were selected for the study based on the inclusion criteria, 74 from centre I and 55 from centre II respectively.

The characteristics of selected patients are listed in table I. The two groups were remarkably similar regarding all baseline clinical and tumour characteristics. In both regimens, the majority of patients had a good performance status and the dysphagia score before treatment reflected their ability to eat a normal or semisolid diet in approximately 90% of patients. Although 48.8% of patients in both centres were estimated with no lymph node involvement on CT-scan, only 15 patients (11.6%) were estimated to present with a T1-T2 N0 tumour. These latter patients were treated with a definitive CRT as regards age and/or comorbidities.

Safety and toxicity

Toxicities per patient are shown in table II. There was no death related to CRT in both regimens and the rate of patients who had toxicities grade 3 or 4 was not different between the two groups. Patients who required a dose modification to the planned CT schedule were more frequent with regimen II than regimen I (44 patients (80%) compared to 19 patients (26%) respectively (P < 0.001) but the majority of these dose modifications (84%) in regimen II were only observed after the second CT course. Similarly, only 1/74 patients in regimen I received the CT treatment with a delay of more than 1 week as compared to 19 patients (34%) treated with regimen II (P < 0.001), majority of them (58%) after the third CT course.

In regimen I and regimen II respectively, patients received 99% and 76% of the planned total dose of 5FU and 98% and 77% of the planned total dose of CDDP. The mean delivered radiation dose was 49.9 Gy in regimen I and 56.6 Gy in regimen II.

Patient outcome

The median follow-up duration was 20 months (range 2-114) for the whole series. On September 2005, 8/129 patients (6.2%) were still alive. The median follow-up of the surviving patients was 77 months (range 56-114). Only eleven patients were lost to follow-up during the study. The median follow-up of these patients was 45.1 months (range 2-68). For the entire series, the median overall survival was 20 months (range 2-114) and the 5-years survival was 11.6%.

Clinical response and metastatic occurrence during the follow-up according to CRT regimen (table III)

A total of 62/74 patients (83.8% (95%CI: 77-93%)) with regimen I achieved a clinical complete response to CRT as compared to 36 patients (65.4% (95%CI: 52-78%)) with regimen II (P = 0.02).

In these responder patients, metastasis occurred in 32/62 (51.6% (95%CI: 45-69%)) with regimen I as compared to 10/36 (27.8% (95%CI: 10-38%)) with regimen II (P=0.03). The rate of local disease recurrence was not significantly different between the two regimens.

Survival according to CRT regimen (table III)

The median overall survival was 20 months in centre I and 22 months in centre II, respectively (NS) (figure 2a). The 5-year survival rate was 10.7% in regimen I as compared to 12.7% in regimen II, respectively (NS).

Our results however showed that there was a trend in median overall survival improvement for responder patients to CRT in regimen II (26.5 months, range 3-114) as compared to responder patients in regimen I (21 months, range 5-70), however non statistically significant (figure 2b) (table III).

Discussion

Herskovic’s CRT regimen is considered the standard treatment for non operated patients with locally advanced esophageal carcinoma but this CRT regimen has rarely been strictly applied. Therefore, questions still remain debated concerning this CRT regimen and several authors described variations in the treatment schedule [5,11,18-21]. Indeed, the choice between split course and continuous RT schedule for optimal local response is still debated. On the other hand, the accurate benefit of the additional 5 FU/CDDP CT courses delivered after the CRT completion is not well documented.

As regards our specific retrospective study design, we were able to evaluate the impact of the RT schedule on local response and the impact of duration of CT in metastasis occurrence. Thus, our analysis focused on response rate to CRT and on metastasis occurrence in responder patients to CRT. The few patients who had been lost to follow-up and the very close similarity in all clinical and tumour baseline characteristics between the two groups allowed us to perform a comparison between the two CRT regimens, despite the retrospective and non-randomized design of our study.

Literature search indicated a complete response rate to CRT ranging from 65 to 85% whatever the CRT design [5, 22, 23]. Our findings suggest that patients treated with a RT delivered in a continuous course (regimen I) more frequently achieved a complete clinical response to CRT than patients treated with a split-course technique (regimen II) (respectively 83.8% vs 65.4%; P = 0.02). Despite the fact that the 6 planned CT courses were delivered before the response to CRT assessment in regimen II, our results suggest that the complete clinical response to CRT was less frequent in patients treated with a split-course irradiation.

Jacob et al. particularly addressed the response rate of patients with esophageal carcinoma treated by a CRT regimen...
Progression-free survival was not different between responder patients to CRT in the two regimens. However, our results showed that patients who responded to CRT and were treated with additional CT courses (regimen II) experienced fewer metastatic disease as compared to responder patients treated with CRT alone (regimen I) [16]. The significant decrease in metastatic disease frequency in responder patients in regimen II underlined the potential benefit of additional CT courses.

Table I. – Patient characteristics.
Caractéristiques des malades.

<table>
<thead>
<tr>
<th></th>
<th>CENTRE I</th>
<th>CENTRE II</th>
<th>P</th>
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<tbody>
<tr>
<td>Mean age</td>
<td>61.9</td>
<td>60.8</td>
<td>ns</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>9/1</td>
<td>9/1</td>
<td>ns</td>
</tr>
<tr>
<td>Performance status (OMS) grade</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>17 (23.2)</td>
<td>18 (32.8)</td>
<td>ns</td>
</tr>
<tr>
<td>1</td>
<td>47 (64.4)</td>
<td>30 (50.4)</td>
<td>ns</td>
</tr>
<tr>
<td>2</td>
<td>9 (12.4)</td>
<td>7 (12.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Dysphagia (Atkinson score)</td>
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<td></td>
<td></td>
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<td>0</td>
<td>12 (16.3)</td>
<td>13 (23.6)</td>
<td>ns</td>
</tr>
<tr>
<td>1</td>
<td>36 (48.6)</td>
<td>30 (54.5)</td>
<td>ns</td>
</tr>
<tr>
<td>2</td>
<td>18 (24.4)</td>
<td>11 (20.0)</td>
<td>ns</td>
</tr>
<tr>
<td>3</td>
<td>5 (6.7)</td>
<td>1 (1.8)</td>
<td>ns</td>
</tr>
<tr>
<td>4</td>
<td>3 (4)</td>
<td>0</td>
<td>ns</td>
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<td>Weight loss ≥ 10% at CRT initiation</td>
<td>18 (24)</td>
<td>13 (24)</td>
<td>ns</td>
</tr>
<tr>
<td>TNM</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>T 1-2</td>
<td>15 (20.3)</td>
<td>13 (23.7)</td>
<td>ns</td>
</tr>
<tr>
<td>3-4</td>
<td>59 (79.7)</td>
<td>42 (76.3)</td>
<td>ns</td>
</tr>
<tr>
<td>N 0</td>
<td>38 (51.4)</td>
<td>25 (45.5)</td>
<td>ns</td>
</tr>
<tr>
<td>1</td>
<td>36 (48.6)</td>
<td>30 (54.5)</td>
<td>ns</td>
</tr>
<tr>
<td>M 0</td>
<td>74 (100)</td>
<td>55 (100)</td>
<td></td>
</tr>
<tr>
<td>Esophageal location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper one-third</td>
<td>26 (35.2)</td>
<td>14 (25.5)</td>
<td>ns</td>
</tr>
<tr>
<td>Middle one-third</td>
<td>27 (36.5)</td>
<td>25 (45.5)</td>
<td>ns</td>
</tr>
<tr>
<td>Lower one-third</td>
<td>21 (28.3)</td>
<td>16 (29.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Mean tumour length (cm)</td>
<td>4.9 (1-10)</td>
<td>4.8 (2-12)</td>
<td>ns</td>
</tr>
<tr>
<td>Mean tumour diameter (cm)</td>
<td>1.7 (1.7-5.8)</td>
<td>1.6 (0.5-6.5)</td>
<td>ns</td>
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<tr>
<td>Histopathology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>67 (90.5)</td>
<td>52 (94.5)</td>
<td>ns</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>7 (9.5)</td>
<td>3 (5.5)</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns : not significant

according to the RT schedule. In this randomized study, a continuous RT (50 Gy/25 fractions/5 weeks) was compared to a split course RT (20 Gy/5 fractions x 2 courses weeks 1, 5), both schedules associated to 5 FU/CDDP CT at weeks 1, 5, 8 and 11 [16]. This study found no significant difference between the two RT schedules in complete response rate (respectively 59% vs 48%; NS), although there was a trend for a better response to CRT with a continuous RT schedule [16]. Although our results suggested significant more response rate to CRT with a RT delivered in continuous course, the impact of the RT schedule for the definitive CRT regimen remains to be more accurately assessed.
of the additional CT in an attempt to reduce the metastatic occurrence.

The median overall survival ranged from 9 to 26 months in patients with locally advanced esophageal carcinoma treated with definitive CRT [5,9,29,30]. Our series shows similar results with a median overall survival of 20 months and 22 months in regimen I and II respectively, whatever the response status to CRT. However, our results suggest that there was a trend to an

Table II. – Significant treatment toxicities per patient (%).

<table>
<thead>
<tr>
<th></th>
<th>CENTRE I</th>
<th>CENTRE II</th>
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<tbody>
<tr>
<td></td>
<td>N=74</td>
<td>N=55</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Haematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Thrombopenia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mucositis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alopecia</td>
<td>3</td>
<td>-</td>
</tr>
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</table>

ns : not significant

Table III. – Outcome of patients who responded to CRT.

<table>
<thead>
<tr>
<th></th>
<th>CENTRE I</th>
<th>CENTRE II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=(62%)</td>
<td>N=(36%)</td>
</tr>
<tr>
<td>Recurrences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local alone</td>
<td>10 (16.1)</td>
<td>11 (30.5)</td>
</tr>
<tr>
<td>Metastatic alone</td>
<td>15 (24.2)</td>
<td>7 (19.4)</td>
</tr>
<tr>
<td>Local and metastatic</td>
<td>17 (27.4)</td>
<td>3 (8.3)</td>
</tr>
<tr>
<td>Total local</td>
<td>27 (43.5)</td>
<td>15 (41.6)</td>
</tr>
<tr>
<td>Total metastatic</td>
<td>32 (51.6)</td>
<td>10 (27.8)</td>
</tr>
<tr>
<td>Median survival</td>
<td>21 (5-70)months</td>
<td>26.5 (3-114) months</td>
</tr>
<tr>
<td>Median disease-free survival</td>
<td>12 (0-77) months</td>
<td>16 (0-109) months</td>
</tr>
<tr>
<td>Median progression-free survival</td>
<td>15 (4-46) months</td>
<td>20 (3-71) months</td>
</tr>
<tr>
<td>Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year</td>
<td>51 (82.2)</td>
<td>32 (88.8)</td>
</tr>
<tr>
<td>2-year</td>
<td>27 (43.5)</td>
<td>21 (58.3)</td>
</tr>
<tr>
<td>3-year</td>
<td>20 (32.2)</td>
<td>13 (36.1)</td>
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<tr>
<td>4-year</td>
<td>14 (22.6)</td>
<td>10 (27.7)</td>
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<tr>
<td>5-year</td>
<td>7 (11.3)</td>
<td>7 (19.4)</td>
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</tbody>
</table>

ns : not significant
results show that complete clinical response to CRT was significantly more frequent with a continuous RT, whereas additional CT after CRT significantly reduced metastatic occurrence with a trend, however not significant, in survival improvement. Therefore, our results suggest that the optimal CRT regimen in locally advanced esophageal carcinoma could be considered more effective using a continuous RT schedule and additional CT courses. Further randomized trials designed on these specific issues could be useful for the CRT regimen optimization.

ACKNOWLEDGEMENTS - The authors thank Richard Medeiros, Rouen University Hospital medical Editor, for his valuable advice in editing the manuscript.

REFERENCES


