Overview on Gastric Cancer

Chapter 5

Role of postoperative chemoradiotherapy in the therapeutic management of adenocarcinomas of the stomach and oesogastric junction

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Abstract

The available data in the literature show that for gastric adenocarcinoma or gastroesophageal junction adenocarcinoma, postoperative chemoradiotherapy improves disease-free survival after surgery with D0 or D1 lymph node dissection (and perhaps D2) as well as in case of positive node or R1 resection. With the publications of perioperative chemotherapy trials, the role of postoperative radiotherapy in the therapeutic arsenal of gastric adenocarcinoma or gastroesophageal junction adenocarcinoma becomes difficult to define. Postoperative radiotherapy is indicated in case of R1 resection.

1. Introduction

Surgery is the reference treatment of resectable forms of gastric adenocarcinomas [1]. The margins of resection constitute an essential prognostic factor [1]. After surgery type R0 and in the absence of adjuvant therapy, the survival rate is only 20 to 30% and that of locoregional recurrences is 40 to 60% [1]. These recurrences are mainly noted for tumors classified T3 and those accompanied with nodal extension (N +), which is frequent and can reach 80% of cases [1,2]. On the other hand, invaded margins (R1 or R2) are reported in 15 to 30% of cases [1,2]. To improve the results of surgery, adjuvant treatments have been studied [3].

2. Review of the Literature

The Macdonald Randomized Trial (INT0116) compared surgery and surgery followed by radiotherapy and chemotherapy for adenocarcinomas of the stomach and oesogastric junction [4]. The number of assessable patients was 556. All patients had an R0 surgery and a lymph

node dissection (D1 in36% of cases, D2 in 10% of cases and D0 in 54% of cases). The tumor was classified T3 in two-thirds of the cases, with invaded nodes in 84% of cases. Adjuvant therapy included FUFOL-type chemotherapy (5-fluorouracil-folinic acid) and radiotherapy of the tumor bed and regional lymph node. Total dose was 45 Gy delivered at the rate of 2Gy/ fraction, 5 fractions/ week. This irradiation was concomitant with chemotherapy. It was interposed between the second and the third cure. Because of the toxicity, only 64% of the patients had the entire therapeutic procedure. The arm with adjuvant therapy was superior to surgery in terms of the probability of overall survival (50% 41%) and progression-free survival (48% vs. 31%) at 3 years [4]. Two criticisms were made for this trial. The first concerns the quality of surgery. Indeed, several authors consider that by performing alymph node dissection less than D1, it leave certainly some invaded nodes in place and therefore the surgery is not complete [4,5]. The second concerns acute toxicity. Indeed, haematological toxicity grade 3 related to chemotherapy was reported in 54% of cases. Grade 3 gastrointestinal toxicity was observed in 33% of cases [4,5].

Updating the results of this trial confirmed the benefit of chemoradiotherapy and its persistence at 10 years [6]. This Was observed regardless of the type of lymph node dissection, especially if it was D0 or D1. There was no benefit for women with cancer of diffuse intestinal type [6]. The benefit of postoperative chemoradiotherapy after D1 lymph node dissection was also demonstrated by the Dutch Gastric Cancer Group [7]. In this study, the benefit was significant in terms of local recurrence and not significant for survival. This trial did not reveal benefit from the therapeutic association in case of D2 lymph node dissection. However, in the case of surgical margins of type R1, the probability of survival at 2 years and the rate of recurrence were best with postoperative treatment (respectively 66% against 29% and 6% against 26%) [7]. Kim et al., In their non-randomized comparative study, showed a gain in overall survival and survival without recurrence at 5 years in favor to postoperative chemoradiotherapy for patients with adenocarcinomas of the stomach with D2 lymph node dissection [8]. The Phase III Artist Trial Comparing Postoperative Chemotherapy and chemoradiotherapy after surgery (R0) with a D2 lymph node dissection, failed to show a difference significant difference between the two arms in terms of survival. However, the study of patient subgroups showed in case of invaded nodes an improvement in probability of disease-free survival at 3 years in favor of chemoradiotherapy (71% versus 76%, $p = 0.04$) [9].

A meta-analysis showed the superiority of chemoradiotherapy compared with postoperative chemotherapy in terms of local disease control after surgery with D2 dissection [10].

The data available in the literature thus show that for the adenocarcinomas of the stomach and the oesogastric junction, postoperative chemoradiotherapy prolongs survival without disease after surgery and D0 or D1 and probably D2, as well as in the presence of lymph node invasion histologically proven and in case of invaded resection margines (R1). The benefit of

this treatment is a gain of overall survival for some authors.

With the publications of perioperative chemotherapy trials, the role of radiotherapy in the therapeutic arsenal of gastric adenocarcinomas becomes difficult to specify. Three randomized trials compared perioperative chemotherapy and exclusive surgery, which are the trial of medical research council adjuvant gastric infusional chemotherapy (MAGIC), the trial of the" Federation francophone de cancerologie digestive" (FFCD 9703) trial and the European organization for Research and treatment of cancer (EORTC 40954) [11-13]. The MAGIC trial included 503 patients with unreserved non metastatic gastric carcinoma.The study randomized patients to receive perioperative chemotherapy, epirubicin, cisplatin, and fluorouracil (ECF) vs. surgery alone. The chemotherapy consisted of 3 cycles of preoperative and 3 cycles of postoperative treatment. It showed a gain in percentage of resections R0, progression-free survival and overall survival, knowing that only 49.5% of the patients had the three courses of chemotherapy [11]. The trial of FFCD included 224 patients. It showed also significant improvement in the rate of R0 resection, progression and overall survival [12]. The EORTC trial included 144 patients with a T3 or T4 carcinoma, with or without node invasion. These patients had D2 lymph node dissection in 95% of cases. It showed onlya significant increased rate of R0 resection [13].

In CROSS trial, patients with potentially resectable esophageal or oesogastric junction cancer (3/4 adenocarcinomas, majority distal esophageal, 11% oesogastric junction) were randomized to preoperative CRT using weekly paclitaxel plus carboplatin plus concurrent radiotherapy (41.4 Gy over 5 weeks) or surgery alone. The R0 resection rate was higher with chemoradiation therapy (92% vs. 69%). At a median follow-up of 32 months, median OS was significantly better with preoperative treatment [14].

A meta-analysis of individual data from 14 trials including patients with adenocarcinoma of the esophagus, stomach or oesogastric junction was published [15]. It studied the impact of perioperative chemotherapy compared to surgery alone and showed a survival gain related to perioperative chemotherapy (32% vs. 23%) [15].

The results of these various trials have led to a change in the therapeutic standards for resectable adenocarcinomas of the stomach and the generalization of the practice of perioperative chemotherapy which has become the reference [16-17]. However, the treatment strategies remain different, depending on the country, especially in Western countries [8,15-17]. The absence of a study comparing perioperative chemotherapy with surgery followed by chemoradiotherapy makes the accuracy of the indication of postoperative chemoradiotherapy difficult at the present time. Nevertheless after surgery of type R1, the authors agree on the need for postoperative radiotherapy [18-19].

Stiekema and al studied a series of 409 patients who underwent R1 surgery for gastric

adenocarcinoma. Forty patients received chemotherapy (according to the Macdonald protocol.) The others did not receive adjuvant therapy. The latter were older (Median of 70 years versus 57 years, p <0.001) and had diffuse adenocarcinoma in 43% of cases (versus 80%, p <0.001). There was no significant difference in pT Nor pN the median overall survival time was 13 months in the absence of postoperative treatment and 24 months in the chemoradiotherapy group (p = 0.003) [19]. Trials are under way to clarify the role of radiochemotherapy before or after surgery using peri or preoperative chemotherapy [20-25].

3. Conclusion

Postoperative radiotherapy retains a place in the treatment of adenocarcinomas of the stomach and the oesogastric junction for patients who have not received perioperative chemotherapy if the tumor is stage II or III and the general and nutritional state allows it. It must be discussed in case of N1 stage lymph node invasion after D1 lymph node dissection. The place of postoperative chemo-radiotherapy after a D2 lymph node dissection, remains controversial. Postoperative chemoradiotherapy should be offered to patients who have undergone perioperative chemotherapy in case of invaded surgical margins.

4. References

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