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Adjuvant chemoradiation for gastric carcinoma: State of the art and perspectives

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ABSTRACT

An estimated 990,000 new cases of gastric cancer are diagnosed worldwide each year. Surgical excision, the only chance for prolonged survival, is feasible in about 20% of cases. Even after surgery, the median survival is limited to 12 to 20 months due to the frequency of locoregional and/or metastatic recurrences. This led to clinical trials associating surgery with neoadjuvant or adjuvant treatments to improve tumor control and patient survival. The most studied modalities are perioperative chemotherapy and adjuvant chemoradiotherapy. To date, evidence has shown a survival benefit for postoperative chemoradiotherapy and for perioperative chemotherapy. Phase III trials are ongoing to compare these two modalities. The aim of this review is to synthesize current knowledge about adjuvant chemoradiotherapy in the management of gastric adenocarcinoma, and to consider its prospects by integrating modern radiotherapy techniques.

Contents

Abbreviations: 5FU, 5-fluorouracil; 5FU-LV, 5-fluorouracil leucovorin; CRT, chemoradiotherapy; CT, chemotherapy; DCF, Doxorubicin Cisplatin 5-fluorouracil; ECF, Epirubicin Cisplatin 5-fluorouracil; ECX, Epirubicin Cisplatin Capecitabin; FOLFOX, 5-fluorouracil oxaliplatin; FUFOL, bolus 5-fluorouracil followed by leucovorin over 15 minutes; LV, leucovorin; IMRT, intensity modulated radiation therapy; RT, radiation therapy; XELOX, capecitabin oxaliplatine.

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Background

Despite a worldwide decline in incidence, gastric cancer remains the 4th most common cancer (incidence of approximately 1,000,000/year) and the 2nd most common cause of cancer death worldwide (approximately 750,000 per year) [1]. In 90% of cases, its histology is adenocarcinoma, either of the intestinal type (predominant in the elderly, decreasing incidence) or of diffuse type (mainly in elderly women, increasing incidence). Stromal, endocrine, or lymphoma tumors are not included in this review.

There is a 10-fold variation in incidence between the highest and lowest risk populations [2]. The highest incidence rates are observed in East Asia, East Europe, and South America, while the lowest rates are found in North America and most parts of Africa [1]. Helicobacter pylori infection, smoking, salt and nitrate-rich foods are the most important risk factors [2]. The interactions between dietary factors, environmental conditions, and the development of gastric cancer are also well described, with a number of clearly identifiable dietary exposures strongly associated with gastric cancer induction and prevention [2].A family history is found in 10% to 30% of cases. However, hereditary factors are rare and affect only 1% to 3% of patients (Lynch syndrome, hereditary diffuse cancer secondary to a mutation of E-cadherin, mutation of BRCA) [1]. Finally, a history of partial gastrectomy also increases the risk of developing gastric cancer, usually 10–15 years after the surgery [1].

Early publications on the use of adjuvant chemoradiotherapy (CRT) for gastric cancer date back to the early 1980s. They reported series of patients treated postoperatively with radiation therapy from 20 Gy to 50 Gy with concurrent 5-fluorouracil (5FU) [3–5]. In Intergroup 0116 phase III trial published in 2001 by MacDonald et al., 556 patients with gastric or gastroesophageal junction cancers were randomized after complete resection between observation and postoperative CRT [6]. The radiation therapy dose was 45 Gy in 25 fractions and 5 weeks. This treatment provided a significant benefit in terms of overall survival (36 months versus 27 months, HR = 1.4, 95%CI = 1.1–2.0, p = 0.005) and relapse-free survival (30 months versus 19 months, HR = 1.5, 95%CI = 1.2–1.9, p < 0.001). This benefit was confirmed after a follow-up of more than 10 years [7]. Results of controlled prospective studies of adjuvant radiotherapy for gastric cancer are summarized in Table 1. Gastroesophageal junction (GEJ) adenocarcinomas will not be specifically addressed in this review, as these tumors are sometimes treated as gastric cancer and other times as oesophageal cancer. For example, patients with GEJ tumors were included in Intergroup 0116 and TOPGEAR, but not in ARTIST studies.

Post-operative CRT had been the standard adjuvant treatment of resected gastric adenocarcinoma until the publication of the MAGIC trial [8]. In this UK phase III trial, 503 patients were randomized between surgery alone versus perioperative chemotherapy with three cycles of ECF (epirubicin, cisplatin, 5FU) pre-surgery and post-surgery. Patients who received perioperative chemotherapy had a significantly higher 5-year overall survival rate than those who did not (36% versus 23%, HR = 0.75, 95% CI = 0.60–0.93, p = 0.009). Since then, this regimen has become the standard of care in Europe, eclipsing adjuvant CRT.

To date, except for HER2, there are no established evidence-based biomarkers predictive of tumour response to targeted agents, and the majority of patients do not yet benefit from molecularly directed therapies [9]. Classic biomarkers for gastric cancer diagnosis include carcinoembryonic antigen and cancer antigen 19-9, while microRNA and DNA hypomethylation are proposed as novel biomarkers. Modern biomedical research has explored many potential gastric cancer biomarker genes by utilising serum protein antigens, oncogenic genes or gene families through improving molecular biological technologies, such as microarray, RNA-Seq and the like [10]. Excluding classical biomarkers, those determining prognosis and the progression of gastric cancer focus on targeting microRNAs, epigenetic alterations and genetic polymorphisms [11]. Recently, the small noncoding microRNAs (miRNAs) have been suggested to be critical regulators in the oncogenesis pathways and to serve as useful clinical biomarkers [10].

We aim to summarize current knowledge and practices concerning adjuvant CRT for gastric cancer (excluding GEJ cancer patients) and to propose recommendations concerning the technical modalities of radiation therapy and the choice of concurrent chemotherapy.

Radiation therapy: technique, modalities

Dose

Historically, the radiation therapy dose used in clinical studies, including Intergroup 0116, was 45 Gy delivered in 25 fractions of 1.8 Gy in 5 weeks [6]. Subsequent trials have mainly used this dose of 45 Gy until the development of new radiation therapy techniques such as 3-dimensional conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT).

In the Korean phase III ARTIST trial, 458 patients were randomized between adjuvant chemotherapy with six cycles of cisplatin and capecitabine (XP) versus two cycles of XP followed by postoperative CRT (45 Gy with concurrent capecitabine) followed by two cycles of XP [12,13]. Radiation therapy was delivered using two antero-posterior beams. The 3-year disease-free survival rate was 74% in the XP arm versus 78% in the XP-CRT-XP arm (p = 0.09) [12,14]. However, a post hoc analysis including the 396 patients with pathological lymph node involvement showed a benefit of CRT in this population with a 3-year disease-free survival rate of 72% in the XP arm versus 78% in the XP-CRT-XP (p = 0.04) [12,14].

Several dosimetric studies have shown that IMRT can lower the dose to organs at risk (liver and kidneys), suggesting the possibility of dose escalation [15,16]. In a retrospective study, a dose of 50.4 Gy delivered by IMRT was compared to a dose of 45 Gy by 3D-CRT treatment in 24 patients in combination with concurrent chemotherapy [17]. A similar safety profile was observed in this small series. A prospective phase II study including 110 patients assessed a 50.4 Gy (28 fractions of 1.8 Gy) IMRT with concurrent FOLFOX [18]. The tolerance was acceptable [18]. Its efficacy was not compared to the same treatment at a dose of 45 Gy. However, there is no clinical study comparing prospectively a dose escalation to the standard treatment of 45 Gy.

Neoadjuvant radiation therapy trials for unresectable locally advanced gastric cancer using doses of 50.4 Gy resulted in significant tumor responses [19,20]. One study reported 42% of pathological complete responses, still 4% of patients had grade 5 toxicity