Review Article

Radiotherapy in gastric cancer: does it still play a significant role?

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Contributions: (I) Conception and design: I Angelicone; (II) Administrative support: MF Osti; (III) Provision of study materials or patients: M Rotondi, G Facondo; (IV) Collection and assembly of data: F de Giacomo; (V) Data analysis and interpretation: A Priore; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Surgery is the mainstay of treatment, but often insufficient or unsuitable, for patients with nonmetastatic gastric cancer, that will experience local and distance recurrence. The integration of systemic and locoregional therapy has demonstrated superior survival outcomes, so chemotherapy and radiotherapy are becoming progressively approved as the better multidisciplinary treatment for locally advanced gastric cancer (LAGC), described as gastric cancer or esophagogastric junction (EGJ) cancer. The role of radiotherapy in the treatment of this tumor is still controversial and there is not unanimity on which method is the best. Compared to surgery alone, neoadjuvant chemoradiotherapy (NACRT) improve survival outcomes in patients affected by EGJ cancer, and further studies could be done to establish whether there are effective benefits also in gastric cancer. Postoperative chemoradiotherapy is recommended for patients treated with gastrectomy with lymph node dissection (LND) less than D2. Patients with LAGC could take advantage from preoperative and postoperative radiotherapy, especially in combination with chemotherapy.

Keywords: Gastric cancer; radiotherapy; chemoradiotherapy; neoadjuvant; adjuvant

Received: 01 August 2022; Accepted: 13 March 2023; Published online: 12 April 2023.
doi: 10.21037/dmr-22-55
View this article at: https://dx.doi.org/10.21037/dmr-22-55

Introduction

Over the past 50 years, gastric cancer (GC) recorded a global decrease in mortality and incidence, even though in 2020 over one million of new cases and 769,000 deaths have been registered. Incidence rates are high in the East of Asia and Europe and low in the North of America and Europe (comparable to Africa) (1). Median age of diagnosis is 69 years and male/female ratio is 1.5 to 1 (2).

Histologically, 90% of GC are adenocarcinoma and the others are gastrointestinal stromal tumor (GIST), carcinoid, small-cell, MALT lymphoma, sarcoma, leiomyosarcoma and undifferentiated (2). Although GC is often described as a single entity, adenocarcinoma also involves the esophagogastric junction (EGJ) and lesions classified as Siewert type III are considered gastric cancers, so they should be treated as these (3).

Only a small percentage of GC is diagnosed as early gastric cancer because of atypical symptoms and lack of screening systems, so more than half of patients are diagnosed with a locally advanced disease at presentation (4), with a suboptimal prognosis that is also due to its aggressive biological behavior in general. Locally advanced gastric cancer (LAGC) is usually described as a GC or EGJ cancer (EGJC) staged with the tumor-node-metastasis (TNM) staging system as cT2 to cT4, with or without confirmed nodal involvement (any N) and without distant metastasis (M0) (5,6).

In general, surgery is the mainstay of treatment for non-metastatic GC. Although complete surgical resection offers the greatest chance of healing, it is often inadequate or unsuitable for patients with LAGC. Local and distant recurrence will occur in this type of patients within 1 year of radical surgery alone and their 5-year survival rate is less

than 50% (7,8).

The integration of systemic and locoregional therapy has demonstrated more disease control and less local recurrence, so multidisciplinary treatment strategies that include chemotherapy (CT) and radiotherapy (RT) are becoming progressively approved as the best treatments for GC.

The most famous study shifting the role of RT from traditional palliative to adjuvant therapy for GC was published in 2001 by Macdonald *et al.* (the INT0116 study) (9).

Following this, many studies have been conducted to investigate the survival benefit also of neoadjuvant RT in combination with CT for patients with GC.

However, the weak points of these trials were the relatively small number and heterogeneity of the selected patients, so the results obtained were inconclusive and/or conflicting.

Therefore, the role of RT in GC is still controversial and there is no unanimity on which method is the best.

Preoperative radiotherapy: neoadjuvant chemoradiotherapy (NACRT) *vs.* surgery alone

The main advantage of preoperative RT in the management of GC is downstaging of disease in patients with LAGC, who become candidates for surgery. Furthermore, according to some studies, preoperative RT plays a role in the reduction of residual microscopic disease after surgery and viable cell dissemination (10,11).

The main studies available that evaluate NACRT in the LAGC are mostly related to the EGJC.

Multimodal treatment for LAGC has been introduced because radical surgery alone did not offer adequate survival rate. In particular, NACRT or perioperative CT is recommended for EGJC (12-15).

The phase III CROSS trial (16) demonstrated that, compared to surgery alone, NACRT achieve a satisfactory pathological complete response (pCR) rate and improve R0 resection rate (92% *vs.* 69%, P<0.001) and overall survival [OS; hazard ratio (HR): 0.65; 95% confidence interval (CI): 0.49–0.87] of patients with lower esophageal and EGJ cancer. Furthermore, the latest published results of the CROSS trial (17) demonstrated that the survival benefits offered by NACRT gone on over 10 years in the long-term follow-up. Specifically, NACRT reduced the risk of death from esophageal cancer (EC) or EGJC (HR: 0.60; 95% CI: 0.46–0.80), with an absolute 10-year OS benefit of 13% (38% *vs.* 25%). The rate of major adverse events related to NACRT was adequate (6% leukopenia and 5% anorexia) and in-hospital mortality was similar in the two groups. In conclusion, preoperative chemoradiotherapy improve survival and it was well tolerated.

In the study of Ronellenfitsch *et al.* (18) younger patients have higher survival benefits.

Preoperative radiotherapy: NACRT *vs.* NACT

As suggested by the last NCCN guidelines (19), NACRT and NACT are two possible treatment options for LAGC, but it is unclear whether preoperative chemoradiotherapy is superior to preoperative CT alone in terms of survival.

The German POET trial was the first randomized controlled phase III study to compare induction CT (arm A) with induction chemoradiotherapy (arm B) followed by surgery in patients with EGJC. Based on an interim analysis published in 2009 (20), the primary end-point, i.e., the 3-year survival rate, was not met, but there was a trend for improvement by adding RT to preoperative CT (from 27.7% to 47.4%; HR: 0.67; log-rank P=0.07). The long-term results after a median follow-up of 10 years (21) suggest a survival benefit for NACRT compared with NACT: OS at 3- and 5-year was 26.1% and 24.4% in arm A and 46.7% and 39.5% in arm B (HR: 0.65; 95% CI: 0.42–1.01; P value 0.055 in favor of the NACRT group). Local progression-free survival (PFS) after tumor resection was significantly improved by induction chemoradiotherapy (HR: 0.37; 95% CI: 0.16–0.85).

The randomized phase III trial TOPGEAR (22) compared perioperative CT (3 preoperative and 3 postoperative cycles) with induction CT (2 preoperative cycles) followed by chemoradiotherapy and surgery in patients with GC or EGJC (Siewert types II and III). Interim results demonstrate that NACRT is safe and feasible and it can be delivered without a significant increase in treatment toxicity or surgical morbidity.

A randomized, open label, single-center phase II trial (NCT02301481) (23) compared safety and effectiveness of these two therapeutic strategies for patients with LAGC. The NACRT group had a significantly better major pathological response than the NACT group (37.9% *vs.* 17.9%, P=0.019). The postoperative complications between the two populations were not significantly different. Five-year OS rate was 50.1% (for NACT) and 61.9% (for NACRT); median PFS was 37.3 and 63.4 months, respectively.

On the contrary, the phase III NEO-AEGIS trial (24) and a Swedish trial (25) suggest that NACRT do not offer greater benefits in terms of survival outcomes than NACT, although NACRT is associated with a higher complete histological response and R0 resection rate and with a lower frequency of positive lymph nodes.

Postoperative RT

Gastrectomy with D2 lymph node dissection (LND) is the standard care for localized GC. However, in stages II-III survival outcomes are not encouraging with surgery alone, and this is linked to the loco-regional recurrence (LRR) (26,27).

Postoperative chemoradiotherapy (CRT) or adjuvant CT is recommended for stage ≥ IB subjected to surgery without preoperative chemotherapy (e.g., due to downstaging before the decision for upfront surgery) (28). Perioperative and adjuvant treatments have been established as standard of care to increase the survival on the basis of randomized trials and meta-analyses (29). NCCN recommend adjuvant CRT plus CT for patients with T3–4 or lymph-node metastases and LND < D2 and suggest CT alone for those who have undergone a D2 LND and for patients with R1 (microscopic residual) or R2 (macroscopic residual) resection (30).

The INT-0116 trial (9) was the first study that shows the excellent results of adjuvant CRT: compared to surgery alone it significantly improved survival in patients with GC stage IB–IV (M0) who hadn't received preoperative treatment (40% *vs.* 28% at 5 years). Moreover, there was also a decrease in local failure in the CRT group (19% *vs.* 29%). The median follow-up of more than 10 years confirms that survival remained significant in patients treated with adjuvant CRT (31).

A retrospective analysis by Park *et al.* (32) compared outcomes of surgery alone (D1–2 dissection) to postoperative CRT. The results showed that postoperative CRT was associated with lower recurrence rates after D1 LND, with same recurrence rates between the two groups after D2 LND.

Two other trials analyzing adjuvant NACRT of localized GC conclude that after D2 gastrectomy, compared with CT alone, postoperative RT has no additional benefit.

CRITICS study (33) compares perioperative CT (arm A) with preoperative CT followed by postoperative CRT (arm B). This phase III trial showed no major survival benefits for patients in arm B. Peritoneal metastasis in GC is associated with a poor prognosis and it was occurred less often in arm A and this might explain why arm A had better outcomes. In the trial of Lee *et al.* (34) analyzed postoperative CRT compared to adjuvant CT alone in completely resected GC with D2 LND. According to published results, postoperative CRT did not reduce recurrence rates after D2 in patients with radical surgery. Unlike the primary endpoint the study shows improved disease-free survival (DFS) was observed in a subgroup of postoperative CRT arm with positive lymph node (3-year DFS: 78% *vs.* 72%).

The phase III ARTIST-2 trial (35) has not shown a significant advantage of DFS for the addition of RT to postoperative CT (3-year DFS: 72.8% *vs.* 74.3%).

Conclusions

Patients with LAGC may benefit from chemoradiotherapy in both the form of neoadjuvant and adjuvant treatments. Compared to surgery alone, NACRT is the modality of choice for EGJC in terms of survival outcomes and allows for higher radical resection rates, with a satisfactory toxicity profile, but more research could be done to see if the benefit seen in EGJC could translate into benefit in GC.

Postoperative CRT is recommended for patients with T3–4 or lymph-node metastases and LND < D2 and CT alone for those who have undergone a D2 LND and for patients with R1 (microscopic residual) or R2 (macroscopic residual) resection.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Paolo Mercantini) for the series "Multidisciplinary Treatment in Gastrointestinal Cancer" published in *Digestive Medicine Research*. The article has undergone external peer review.

Peer Review File: Available at https://dmr.amegroups.com/article/view/10.21037/dmr-22-55/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dmr.amegroups.com/article/view/10.21037/dmr-22-55/coif). The series "Multidisciplinary Treatment in Gastrointestinal

Cancer" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/dmr-22-55
Cite this article as: Angelicone I, de Giacomo F, Priore A, Rotondi M, Facondo G, Osti MF. Radiotherapy in gastric cancer: does it still play a significant role? Dig Med Res 2023;6:25.