International Research Journal of Oncology

3(4): 35-43, 2020; Article no.IRJO.65018

Adjuvant Radiotherapy for Gastric Cancer – Review

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Authors' contributions

This work was carried out in collaboration between both authors. Authors DSP and PN designed the review, performed literature search and summarization of articles. Author DSP wrote the first draft of the manuscript. Author PN read and revised the manuscript. Both authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Lomas Kumar Tomar, National University of Ireland, Ireland.
Reviewers:
(1) Jesse A. Stoff, Integrative Medicine of New York, USA.
(2) Momal Chand, Ascension St John Hospital, USA.
(3) Lenícia Cruz Soares, Universidade Federal De Pelotas, Brazil.
Complete Peer review History: http://www.sdiarticle4.com/review-history/65018

Review Article

Received 24 November 2020
Accepted 29 January 2021
Published 23 February 2021

ABSTRACT

Surgical excision forms the main treatment of gastric cancer. However, even after surgery, the median survival is limited to 12 to 20 months due to the high frequency of loco regional and/or metastatic recurrences. This led to clinical trials associating surgery with various forms of neoadjuvant or adjuvant treatments to improve tumour control and patient survival. The most common studied modalities are perioperative chemotherapy and adjuvant chemo-radiotherapy and both of these have shown improved survival. The aim of this review is to compile current knowledge about adjuvant radiotherapy in the management of gastric adenocarcinoma and to discuss the various techniques available and its toxicities.

Keywords: Gastric cancer; radiotherapy; adjuvant.

1. INTRODUCTION

Gastric cancer is the 5th most common cancer and the 2nd most common cause of cancer related deaths worldwide [1] In India it accounts for the 3rd most common cancer among men and 5th most common cancer among females [1]. Over the last decade the incidence as well as mortality of this tumour has increased significantly. Its incidence is different in various parts of the country being predominantly higher in eastern and southern parts of the country.

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One of the main cause of concern with gastric cancer is that majority of patients present in advanced stages (especially in countries in low-middle socio economic status) [2]. Prognosis of locally advanced gastric cancer is poor with a 5-year overall survival (OS) rate of 20-30% for surgery-only patients [3].

The treatment of gastric cancer is usually multimodality treatment with surgery, chemotherapy, radiotherapy and targeted therapy [4]. Surgical resection however remains the only treatment modality that is potentially curative for localized gastric cancer.

Total gastrectomy may not be necessary as long as free resection margins can be obtained with a subtotal resection. Distal tumours are usually treated by partial gastrectomy (if a 6 cm proximal clearance can be achieved). However, proximal tumours usually require total gastrectomy, because more limited resections tend to produce worse functional outcomes and may result in a higher rate of local recurrence [5].

There have been tremendous improvements in the technique and expertise of surgery, however, there is controversy about the extent of lymph node resection required. D1 resection includes removal of the perigastric nodes within 3 cm of the tumour. D2 resection is a more extensive dissection in which lymph nodes around the left gastric artery, hepatic artery, splenic hilum are removed along with splenectomy and distal pancreatectomy. D2 resection is more common in Japan, while the more limited D1 resection is more common in Western centers. Outcomes from Western centers performing more extensive D2 resections are worse than those obtained in Japan with greater postoperative morbidity and mortality (up to 10% perioperatively). These differences can be attributed to variation in surgical experience and also to the fact that patients in Japan are often younger and fitter implicating a difference in disease biology [6]. At least three randomized trials and a Cochrane review have not shown an advantage for more extensive lymph node resection. Most European and American guidelines, nevertheless, recommend D2 dissection for stage II and III gastric cancer. The guidelines also recommend that a minimum of 15 lymph nodes should be dissected and analyzed [7,8].

In patients with resectable disease, local and/or regional lymph node recurrence occurs in 54% of cases in second-look laparotomy [9]. Despite advancements in surgery there is presence of local as well as systemic failures which reinforces the concept of gastric cancer being a local presentation of a systemic condition that already presents as microscopic metastatic disease at the time of diagnosis [10]. With this concept a lot of studies have focused on the concept of neoadjuvant chemotherapy or perioperative chemotherapy before surgery [11]. This not only helps in down staging the tumour but also takes care of the micro metastatic disease.

Radiotherapy has always played a role in gastric cancer as adjuvant treatment. Multiple studies have been done regarding this for the last twenty years. However there is still controversy regarding its benefit in post-operative setting. There has been a lot of debate about the various indications of post-operative adjuvant radiotherapy and whether it is actually required or not. This aim of this review article is to go through the various trials of adjuvant radiotherapy in gastric cancer, understand the indications, techniques, toxicities. This review article is based on summarizing a literature search of various landmark trials of adjuvant radiotherapy in gastric cancer done over the last twenty years.

2. ROLE OF RADIOTHERAPY IN ADJUVANT SETTING –TRIALS

The benefit of adjuvant radiotherapy was initially highlighted in the study done by McDonald et al as part of INT 0116 study in 2001 [12]. Probably this is the most quoted study for adjuvant radiotherapy. A total of 556 patients with resected adenocarcinoma of the stomach or gastro-oesophageal junction were randomized to undergo observation or adjuvant chemo radiotherapy. Chemotherapy was given using 5 cycles of bolus 5-fluorouracil (5-FU) with leucovorin, and radiation therapy entailed delivery of a 45Gy dose to the tumour bed and regional lymph nodes, using opposed anterior and posterior fields concurrently with the second and third cycles of chemotherapy. The chemo radiotherapy arm showed an improved Overall Survival (OS) with a median of 36 months as compared with 27 months in those who were in the observation arm. The local failure rate (2% vs 8%) and regional failure rate (22% vs 39%) were lower following adjuvant chemo radiotherapy. They estimated that with radiation therapy there is a reduction in the risk of local relapse by nearly 10%, decreasing tumour spread to the

peritoneum, small omentum or large omentum, pancreas, and duodenum, as well as lymphatic or hematogenic dissemination, especially to the liver.

The rate of distant metastatic disease rates were similar between the two arms. Despite showing benefit of adjuvant chemo radiation the trial had many criticisms which hold true even today. One is the expected high toxicity both in terms of Gastrointestinal (GI) and hematological toxicity. The other is the limited extent of lymph node dissection performed in most patients enrolled. Although a full D2 lymph node dissection was recommended by the investigators, only 10% of enrolled patients underwent this procedure. D1 resection was done in 36% of patients while the remaining 54% of patients were treated with a D0 resection. Now the analysis revealed that adjuvant chemo radiotherapy might have compensated for suboptimal lymph node dissection. The 10 year follow up of the trial was published in 2012. Overall Survival (OS) and Relapse Free Survival (RFS) data continued to demonstrate benefit from postoperative chemo radiotherapy. Adjuvant chemo radiotherapy led to reduction in both overall relapse and loco regional relapse. Subset analyses showed robust treatment benefit in most subsets with the exception of patients with diffuse histology [13].

The other major landmark study was a randomized phase III trial called the ARTIST trial which evaluated the role of adjuvant chemo radiotherapy in patients with pathologic AJCC stage IB-IIIC [14]. The patients in this trial had undergone R0 resection with full D2 lymphadenectomy. In the investigational arm of the ARTIST trial, patients received 2 cycles of capecitabine and cisplatin (XP) prior to chemo radiotherapy which was given concurrent with capecitabine. This was followed by another 2 cycles of XP. The control group received treatment with XP only so as to find the benefit of addition of radiotherapy. The median follow-up was 5 years and there were no significant differences in Disease Free Survival (DFS) or Overall Survival (OS). However there was a trend toward improved DFS following the use of chemo radiotherapy. On further analysis statistically significant DFS benefit was seen for those patients with either node-positive disease or intestinal-type histology. So with this trial, the authors found that radiotherapy has a key role to play with the above two indications in particular. In ARTIST II trial the authors compared the efficacy of different chemotherapy regimens and chemo-radiotherapy. In the interim analysis of ARTIST II trial they found out that in curatively D2-resected, stage II/III, node-positive gastric cancer, adjuvant S1+oxaliplatin+Radiotherapy (SOXRT) as well as S1+oxaliplatin (SOX) were effective in prolonging DFS, when compared to S-1 monotherapy. S-1 is a novel oral fluoropyrimidine derivative, widely used for treating gastric, pancreatic, lung, head, neck and breast carcinomas [15].

The Dutch trial was a multicentric randomized trial comparing D1 and D2 lymph nodal dissection in gastric cancer. Among the 711 patients (380 D1, 331 D2) judged to have curable lesions, D2 patients had a higher operative mortality rate than D1 patients (10 vs 4%) and experienced more complications (43 vs 25%). They also needed longer postoperative stay in the hospital. Overall 5-year survival rates were similar in the D1 and D2 groups (45% for D1 and 47% for D2) [16].

In Asian countries, radical gastrectomy with D2 lymph node dissection has been considered as a standard treatment for advanced gastric cancer and this was applied earlier than Western countries. Few studies have shown the benefit of adjuvant chemotherapy alone. The ACTS-GC trial has reported better survival rates with S-1 monotherapy in Japan [17]. The CLASSIC trial has shown beneficial effect of the capecitabine plus oxaliplatin chemotherapy regimen (XELOX) in Korea [18].

2.1 Take Home Message

The results discussed in this section suggest that post-surgical adjuvant chemo radiotherapy should be offered in patients who have undergone curative surgical resection in the absence of neoadjuvant therapy or preoperative chemotherapy and in those with additional risk factors such as positive lymph nodes, particularly in the setting of D1 or D0 lymphadenectomy or intestinal histology. Adjuvant radiotherapy should be offered in all patients who undergo inadequate lymph node dissection.

There appears to be a wide variation among the guidelines according to various regions of the world. According to National Comprehensive Cancer Network (NCCN) guidelines for localized resectable gastric cancer the recommended treatment is gastrectomy with a D1 or a modified D2 lymph node dissection with a goal to examine minimum 15 lymph nodes [7]. They also

recommend that D2 dissection is to be done in large volume centers with expertise. European Society for Medical Oncology (ESMO) guidelines recommend that for ≥Stage IB gastric cancer who have undergone surgery without administration of preoperative chemotherapy (e.g. due to under staging before the initial decision for upfront surgery), postoperative chemo-radiotherapy (CRT) or adjuvant chemotherapy is recommended [8]. The Japanese however recommend use of perioperative chemotherapy with S-1 monotherapy or an oxaliplatin-based combination such as Capecitabine + Oxaliplatin (CapeOX) for adjuvant chemotherapy for stage III gastric cancer. In terms of surgery a D2 lymph node dissection is recommended.

3. ROLE OF ADJUVANT RADIOTHERAPY IN PATIENTS WHO HAVE RECEIVED NEOADJUVANT CHEMOTHERAPY – TRIALS

The benefits of neoadjuvant treatment are well known in various solid malignancies like breast cancer and rectal cancer. The rationale behind administration of neoadjuvant treatment is that it leads to down staging of the tumour for a more probable and curative R0 resection and also helps in targeting micro metastases. In the early 2000's few trials proved the benefit of perioperative chemotherapy when compared to surgery alone. The most famous trial which proved this was the Magic trial [19]. This trial included tumours of the stomach, gastroesophageal junction, and oesophagus, although the majority of tumours (74%) were located in the stomach. Patients who were randomized to perioperative chemotherapy and received 3 cycles of combination epirubicin, cisplatin, and 5-FU (ECF) prior to radical resection as well as 3 cycles of ECF in the postoperative adjuvant setting. Perioperative chemotherapy resulted in more primary tumour down staging, and it increased both OS and PFS. However, treatment completion was challenging for most patients, as only 42% of those enrolled were able to complete the full chemotherapy schedule. No patient had a pathologic complete response (pCR) at the time of surgery.

Then the next question arises is that is whether there is benefit of adjuvant chemo radiotherapy in the setting in which the patient receives pre-operative chemotherapy i.e. should the patient receive perioperative chemotherapy only or should radiotherapy be added in the adjuvant setting of such cases. For this CRITICS trial was done in which the aim was to compare perioperative chemotherapy with preoperative chemotherapy and postoperative chemo radiotherapy in patients with resectable gastric adenocarcinoma [20]. This was the first ever trial in which a head to head comparison of both these treatments was done. They enrolled 788 patients in the study. The surgery consisted of a radical resection of the primary tumour and at least a D1+ lymph node dissection. Chemotherapy consisted of three preoperative cycles given 3 weekly and three postoperative cycles of epirubicin, cisplatin or oxaliplatin and capecitabine given in various schedules. Chemo radiotherapy was given using a dose of 45 Gy in 25 fractions at 1.8 Gy per fraction, for 5 weeks, five daily fractions per week, and was combined with capecitabine and cisplatin. Postoperatively, 233 (59%) of 393 patients started chemotherapy and 245 (62%) of 395 started chemo radiotherapy. At a median follow-up of 61·4 months, median overall survival was 43 months in the chemotherapy group and 37 months in the chemo radiotherapy group (non-significant). The post-operative compliance was poor in both the groups as well. Due to the poor compliance seen in majority of post-operative arms, the CRITICS II trial is underway [21]. It has three arms (A) 4 cycles of docetaxel+oxaliplatin+capecitabine (DOC), (B) 2 cycles of DOC followed by chemo-radiotherapy (45Gy in combination with weekly paclitaxel and carboplatin) and (C) chemo radiotherapy.

4. TECHNIQUES OF RADIOTHERAPY AND TOXICITY

The techniques of radiotherapy have improved drastically over the past few decades. In the earlier trials like the Intergroup 0116 study conventional radiotherapy techniques were used which consisted of two Anterior-Posterior beams to a dose of 45 Gy in 25 fractions, however this led to more frequency of gastrointestinal toxicity (12). Grade 3–4 hematological toxicity rate was 54% and grade 3–4 gastrointestinal toxicity was 33%. As a result of which 17% of patients were unable to complete the planned irradiation due to significant toxicities. The patients had postoperative tumour bed irradiation, defined as the surgical anastomosis with proximal and distal margins of 2 cm including the lymph node areas. This was one of the major criticisms of this study. 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). Several dosimetric studies have shown that IMRT can lower the dose to organs at risk (liver and kidneys), suggesting the possibility of dose escalation [22,23].

The first evolution of radiation therapy in gastric cancer was 3D-CRT with direct planning. In a dosimetric study comparing 2D and 3D treatment plans, there was an advantage with 3D-CRT both in terms of target volume coverage and a reduction of the dose received by the kidneys [24]. The ARTIST trial was one of the major trials which used 3DCRT technique (14). In this study the main adverse reaction requiring a change of treatment was neutropenia. Grade 3–4 hematological toxicity in the CRT arm was 48% and the gastrointestinal toxicity rate was 17%. This trial was the first large-scale trial to demonstrate the feasibility of 3D-CRT after extensive D2 surgical lymph node dissection.

With the advent of IMRT it was found that it was advantageous with the fact that it led to decreased dosage to surrounding organs at risk. One retrospective study reported a decrease in the dose received by the liver and kidneys by comparing the treatments received by 57 patients in which 26 patients were treated using 3D-CRT and 31 with IMRT technique with a total dose of 45 Gy in both groups [25]. The rate of gastrointestinal toxicity was comparable in both groups, there were more treatment interruptions in the 3D-CRT arm as well as a higher elevation of serum creatinine (0.2 mg/dL increase in the 3D-CRT group) without showing any survival advantage. Similarly in another study by Stiekema et al compared dosimetric and clinical data from 87 patients, 31 treated with 2D radiation therapy with 2 anteroposterior beams, 25 with 3D-CRT, and 31 with IMRT [26] showed that IMRT decreased the dose received by the left kidney, which resulted in the statistically significant preservation of renal function.

In a systematic review and meta-analysis done by Fang Ren et al and published in 2019 studied 9 controlled clinical trials with a total of 516 patients comparing 3DCRT vs IMRT technique in gastric cancer. They found that 3 year OS, local control was better in the IMRT group with similar toxicity profile [27]. A study done by Ringash et al showed the advantages of IMRT plans both in terms of improved planning target volume coverage and sparing of critical organs at risk [28]. Organ motion should also be considered and a study evaluating the relevance of respiratory motion management showed that IMRT with the breath-hold technique could decrease organ movement and allow a dose escalation to 54Gy [29].

Li et al compared IMRT plans with single-/double-arc Volumetric Modulated Arc Therapy (VMAT) plans and found that double-arc VMAT showed improved tumour coverage and better kidney dose sparing than five-field (5F)-IMRT, and 5F-IMRT and Single Arc VMAT, whereas no advantage was observed regarding liver dose sparing [30]. Hu et al adopted beam angle and multicriteria optimization for IMRT and compared it with the VMAT technique, which showed similar target coverage and Organ at Risk (OAR) sparing [31]. These studies indicate that the dosimetric outcome of VMAT is not superior to that of the IMRT technique. However, VMAT has advantages in terms of efficiency of delivery with lesser monitor units and continuous delivery which enable a shorter treatment time when compared with IMRT technique.

4.1 Take Home Message

Wherever possible a patient should be offered IMRT/ VMAT based radiotherapy for post-operative adjuvant radiotherapy treatment in gastric cancer.

During the preparation of radiation therapy, the acquisition of the Computed Tomography (CT) scan images with slices of 3–5 mm thickness is necessary, with the patient in supine position and arms above the head. The injection of contrast enhancer facilitates the delineation of lymph nodes [32]. Variations in stomach filling and respiratory motion should be taken into consideration when designing optimal field arrangements. Clips placed during the dissection help in identification of tumour bed. The relative risk of nodal metastases at a specific location is dependent on the site of primary tumour and other factors which include depth of invasion into gastric wall. Nodal areas at risk include the perigastric, celiac, left gastric artery, splenic artery, splenic hilar, hepatic artery, porta hepatic, suprapyloric, subpyloric and pancreaticoduodenal lymph nodes. Coverage of nodal areas may be modified based in the clinical scenario and the risk of toxicity.

Accounting for tumour motion is a longstanding problem in the practice of radiation oncology. Respiratory motion leads to difficulties in position

reproducibility during imaging and also displaces the organs causing errors during radiation delivery. In radiotherapy planning for gastric tumours, organ motion was found to be an important factor, with mean of 17.5 mm craniocaudal displacement, 5.9 mm AP displacement and 2.7 mm right to left displacement. Inter-fraction motion was also significant. Some authors have recommended that organ motion be incorporated into the PTV for conformal or IMRT planning [33].

Radiotherapy contouring in cases of gastric cancer depends on the site and stage of the tumour. The Gross Tumour Volume (GTV) includes gross residual disease if any which is identified by CT imaging and surgical findings. Clinical Target Volume (CTV) includes remnant stomach, anastomosis (gastrojejunal, oesophagojejunal and duodenal stump) along with coverage of nodal groups according to the subsite of tumour. Planning Target Volume (PTV) is usually CTV + 1 cm margin. The dose prescribed is 45Gy in 25 fractions at 1.8Gy per fraction [34].

The lymph nodal volume is individualized according to the subsite of tumour i.e. GE-junction/Cardia (proximal), Corpus (middle) and antrum (distal) tumours. A representative axial section of tumor volume as well as few nodal lymph nodal stations are shown in Fig. 1.

- GE-junction/Cardia/proximal 1/3: Peri-oesophageal, perigastric, celiac and mediastinal.
- Corpus/middle 1/3: Perigastric, celiac,splenic, suprapancreatic, porta hepatis, pancreaticoduodenal.
- Antrum/distal 1/3: Perigastric, splenic, pancreaticoduodenal, porta hepatis, celiac, suprapancreatic. [35]

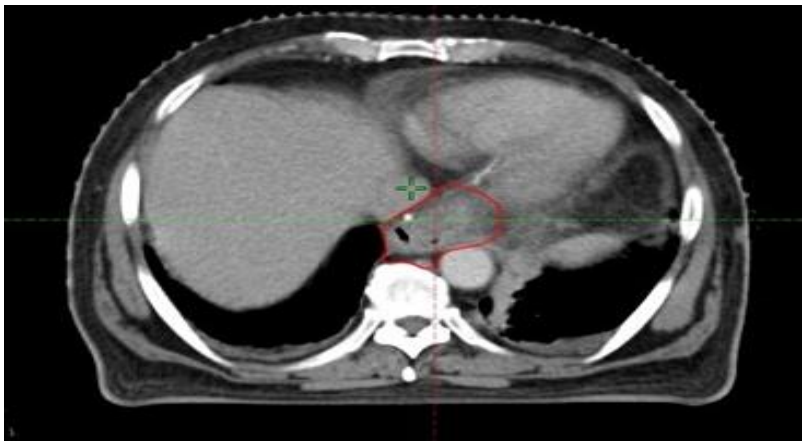

Fig. 1(a). Shows representative axial section showing remnant stomach (red)

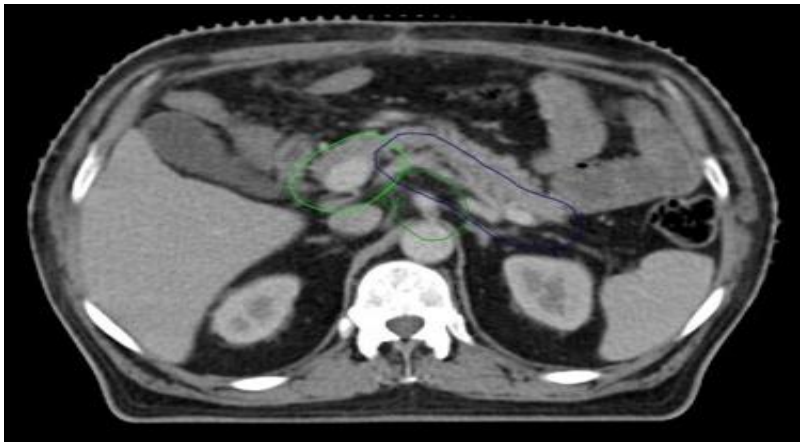

Fig. 1(b). Shows the representative axial section of lymph nodal stations - porta hepatic (light green), coeliac (dark green) and splenic (dark blue)

Treatment planning is essential to reduce the unnecessary radiotherapy dose to organs at risk like liver, kidneys, spinal cord, small bowel, heart and lungs. IMRT reduces the dose received by the organs at risk and optimizes the distribution of the dose to the target volume. This irradiation technique could allow dose escalation to at least 50.4 Gy. When available, patients should be treated with a breath hold technique in order to reduce respiratory motion. If not, an ITV based on a 4D CT scan should be added to the CTV. It seems important to note that in the 10-year follow-up update of patients in the INT 0116 trial, a larger number of second cancers was reported in the postoperative CRT group compared to the control arm but it remained non-significant.

5. CONCLUSION

In conclusion adjuvant radiotherapy in gastric cancer should be considered an important part of treatment especially in cases which have not received adequate neoadjuvant or pre-operative treatment or in those cases which have undergone inadequate surgery. When adjuvant radiotherapy is planned it should be preferably planned using IMRT technique so as to reduce doses to organ at risk and improve the tolerability of treatment.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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