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Original Article

Results of Adjuvant Chemoradiotherapy in Operated Gastric Cancer Patients at a Tertiary Cancer Center in Kashmir

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Abstract

Background: Gastric cancer (GC) is the second most common cancer among men and the third most among females in Asia and worldwide. The prognosis of GC remains poor despite the improvement in interventions during the last years.

Materials and Methods: The study was a nonrandomized retrospective analysis. 52 patients with gastric adenocarcinoma treated with combined surgery and chemoradiotherapy with available clinical data were eventually included in this study. During the follow-up period, any suspected relapse was confirmed by biopsy, if possible. The site and date of the first relapse were recorded. The patients were evaluated for treatment-related toxicity, local recurrences, and distant metastases.

Results: The median age of patients was 60 years (34-80), and the male/female ratio was 4.2 (42 males and 10 females). 25 (48.1%) patients had disease in distal stomach. In terms of gastrointestinal complications, nausea and diarrhea were the most common toxicity, and the most common hematological toxicity was Grade 3 leukopenia with few patients having cardiac toxicity in the form of bradycardia. Within a median follow-up of 12 months (range 6-40 months), out of 52 patients, 1 patient died of treatment-related toxicity, 36 out of 51 patients (70.6%) developed relapse at the end of the study and 29.4% patients were disease free at the end of study. 1 year disease free survival (DFS) and 2 years DFS was 45.09% and 19.60%, respectively. The median time to recurrence from surgery was 12 months (95% confidence interval: 8.118-15.112). Of these patients, 5 (13.9%) patients developed a local recurrence, 22 (61.1%) patients developed distant metastases and 9 (25%). patients developed both local and systemic metastasis.

Conclusion: Our results with McDonald's protocol in our analysis were not encouraging possibly due to a small patient cohort, higher stage at presentation, aggressive histological variant and probably nonavailability of conformal radiotherapy techniques. With continued progress in improving radiotherapy techniques, developing more effective systemic regimens, and identifying biomarkers of treatment response, the role of adjuvant chemoradiotherapy will likely become better defined.

Key words: Chemoradiotherapy, Gastric cancer, Recurrence, Surgery

INTRODUCTION

Cancer is one of the most dreaded diseases in the world and recognized as the second killer disease in humans.[1] It is predicted that by 2020, up to 70% of the 20 million new cases annually will occur in the developing countries[2] and over 10 million people will die annually by the year 2020 due to cancer.[1,3,4] There are approximately 2-2.5 million cases of cancer in India at any given point of time, with around 7-9 lakh new cases being detected each year and nearly half of these cases die each year[5] and the burden is going to be double in 2026.[6]

Gastric cancer (GC) is an important social and health problem worldwide, with nearly one million new patients diagnosed annually,[7] representing 24% of all malignancies on a global scale.[7] It remains a significant cause of worldwide cancer-related mortality, resulting in an

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estimated 7 lakh deaths and ranking as the second leading cause of cancer-related deaths.[8]

Worldwide GC is the second most common cancer among men and third most among females.[7] In India, it is the 5th most common cancer among males and 7th most common cancer among females.[9] Kashmir valley is a high prevalence zone for GC.[10,11] The incidence of GC in Kashmir has been reported to exceed all cancers by about 40%, and there is three to fourfold increased incidence compared to various metropolitan cancer registries across India.[10,11] Dietary factors are implicated as a main reason for the high incidence of this cancer. Consumption of high salt content food (including salted tea), and infection with *Helicobacter pylori* bacteria may be possible reasons for high incidence of this cancer in this population.[11]

The symptoms and signs of the GC are often reported late when the disease is already in advanced stages with developed and developing countries reporting a 5 years survival of around 30% and 20% respectively.[12] The prognosis of GC remains poor despite improvements in diagnostic and therapeutic modalities over the last few years.[13,14] Complete tumor removal with sufficient resection margin plus extended lymph node dissection are considered to be important determinants of loco-regional disease control and improved survival. Although surgery remains the mainstay of potentially curative treatment for early stage GC, it is curative in <40% of cases[15] and the long-term survival even in patients with complete resection and negative surgical margins is guarded.[13,14] In patients with deep invasion of the gastric wall or regional lymph node metastases the relapse and death rates from recurrent GC exceed 70-80%. Loco-regional recurrences in the tumor bed, anastomotic site or regional lymph nodes occur in 40% to 65% of patients after curative-intent resection;[16] the frequency of this relapse makes regional radiotherapy an attractive possibility for adjuvant therapy.

Positive results with radiotherapy and/or chemotherapy in patients with locally advanced or unresectable gastric adenocarcinoma were reported by several studies,[17-19] but the benefits of radiotherapy in adjuvant setting after a curative gastric resection was controversial until the U.S. Intergroup study (INT-0116) which demonstrated that combined chemo-radiation following complete gastric resection improved median relapse-free survival (30 vs. 19 months, $P < 0.0001$) and overall survival (OS) (36 vs. 27 months, $P = 0.01$).[20] An updated report of this trial has confirmed that this benefit is still maintained in the long term.[21] These results have changed the standard of care in many countries following potentially curative resection of GC from observation alone to adjuvant combined chemoradiotherapy.

The aim of this study was to analyze the possible benefit of postoperative adjuvant chemoradiotherapy after curative resection in GC patients, to assess relapse rate and disease-free survival (DFS), incidence and patterns of relapse and toxicity profile.

MATERIALS AND METHODS

The present study was a nonrandomized retrospective analysis. The medical records of patients treated with postoperative chemotherapy and radiotherapy for histologically confirmed adenocarcinoma of the stomach between January 2011 and August 2014 were reviewed and 52 patients were taken for analysis. All patients had a complete preoperative clinical and laboratory staging that included a detailed clinical examination and blood measurements including carcinoembryonic antigen levels, a computed tomography (CT) scan of the thorax, abdomen and pelvis, upper GI endoscopy and a gastric biopsy. A complete GC resection with curative intent was performed (total or subtotal gastrectomy). Patients were staged according to the tumor, node, metastasis (TNM) AJCC cancer staging system. All patients had recovered sufficiently from their surgery before adjuvant therapy and had adequate major organ function assessment at the commencement of treatment (including cardiac, hepatic, renal and bone marrow function). Patients with metastatic disease were excluded from the analysis. Also excluded from the study were patients whose detailed clinical data could not be found or was remotely informative. Patients received combined adjuvant chemoradiotherapy if they had at least one of the following criteria: (a) Serosal invasion, (b) extension to adjacent organs, (c) metastases to the regional lymph nodes and (d) positive surgical margins. Chemotherapy was administered on an outpatient basis. All patients had received a 5-day cycle of bolus 5-fluorouracil at 425 mg/m^2 and leucovorin at 20 mg/m^2 followed 4 weeks later by radiotherapy concomitant with the administration of fluorouracil on the first 4 and the last 3 days of radiotherapy. 4 weeks after completion of radiotherapy, two more 5-day cycles of chemotherapy had been administered with a 4-week interval. External beam radiotherapy was delivered by a Cobalt^{60} unit (due to non-availability of linear accelerator and conformal radiotherapy facilities at our center). Two parallel-opposed (antero-posterior and postero-anterior) radiation portals were used. Both the fields were treated on each treatment session. Oral barium contrast was given to the patients during the simulation procedure for better target volume delineation. The tumor bed, the anastomotic site, the stump, and the loco-regional lymph nodes were treated. Antiemetics were administered orally 1 h before irradiation. The treatment was given for 5 days a week for 5 weeks.

The daily radiation dose ranged from 1.8 to 2.0 Gy and the median total radiation dose was 45 Gy. All patients were followed up in an outpatient basis, after the end of radiotherapy, every 3 months for the first 2 years, every 6 months for the 3rd and 4th year and annually thereafter. Their evaluation included a physical examination, blood count and biochemical analyses. A chest radiograph, CT scans of the pelvis and abdomen was done every 6 months for the first 2 years and endoscopic examination was performed once a year. Bone scans were obtained on indication. Patients were evaluated for treatment-related toxicity, local recurrences, and distant metastases. The treatment-related toxicity was graded according to world health organization classification.[22]

During the follow-up period, any suspected relapse was confirmed by biopsy, if possible. Typical nodules in liver or lung with imaging studies and typical lesions in the radioisotope bone scan were accepted as relapse without histological confirmation. The site and date of the first relapse were recorded. The site of relapse was classified as follows: The relapse was coded as locoregional if the tumor was detected within the radiation fields (including surgical anastomosis, remnant stomach or gastric bed) and regional lymph nodes; and distant metastasis was defined as lymph node recurrence outside the radiation field, peritoneal seeding, liver metastasis, or metastasis of other extra-abdominal sites.

Statistical Analysis

DFS was defined as the time from completion of surgery to the last date the patient was known to be disease-free. The Kaplan-Meier product limit method[23] was used to estimate survival rates. To assess the importance of potential prognostic factors, univariate and multivariate analyses using log-rank test and Cox's proportional hazards regression model was used. A $P < 0.05$ was considered significant. All analyses were performed using SPSS for Windows 10.0 software.

RESULTS

A total of 52 patients with gastric adenocarcinoma treated with combined surgery and chemoradiotherapy with available clinical data were eventually included in this study. The median age of patients was 60 years (range 34-80) and the male/female ratio was 4.2 (42 males and 10 females). 25 (48.1%) patients had disease in distal stomach. A distal gastrectomy was performed in 22 patients (42.3%) while 13 patients (25%) underwent a subtotal gastrectomy. 47 (90.4%) patients underwent D1 lymphadenectomy. 29 (55.8%) patients had disease beyond serosa and 49 (94.2%) patients had palpable regional lymph nodes intraoperatively. 25 (48.1%) patients had intestinal type and 27 (51.9%) patients had diffuse type of adenocarcinoma according to Lauren classification.[24] Tumor size (the largest diameter defined in millimeters, measured in a pathological specimen) ranged from 25 mm to 90 mm (mean 51.2 mm; median 57.5 mm). According to tumor histology, there were 5 (9.6%) well differentiated tumors, 23 (44.2%) moderately differentiated tumors, and 24 (46.2%) poorly differentiated tumors. 41 (78.8%) patients had T3 disease. The mean number of resected lymph nodes was 13.26 (1-37). The mean nodal ratio (i.e. the number of dissected metastatic lymph nodes divided by the total number of removed nodes) was 0.397. Over 42% patients exhibited a nodal ratio ≥0.4. 43 (82.7%) had positive LNs, while in 9 (17.3%) patients no LN infiltration was detected. 41 (78.8%) patients had R0 resection. According to the TNM staging system, 21 patients were Stage II, 13 Stage IIIA, 14 patients were Stage IIIB, and 1 patient was Stage IIIC. The median interval between surgery and start of chemoradiation was 40 days (21-98 days). The main patient characteristics and tumor characteristics are presented in Tables 1 and 2.

Table 1: Patient characteristics

Characteristics	Number of patients (%)
Age (years)	
Median	60
Range	34-80
Male sex	42 (80.8)
Location of primary tumor	
Proximal	12 (23.1)
Body	15 (28.8)
Distal	25 (48.1)
Interval between surgery and the start of treatment (days)	
Median	40
Range	21-98
Type of operation	
Total gastrectomy	10 (19.2)
Subtotal gastrectomy	13 (25)
Proximal gastrectomy	7 (13.5)
Distal gastrectomy	22 (42.3)
Lymph node dissection	
D1	47 (90.4)
D2	5 (9.6)
Lauren classification	
Intestinal	25 (48.1)
Diffuse	27 (51.9)
Stage	
1A	1 (1.9)
IB	2 (3.8)
IIA	9 (17.3)
IIB	12 (23.1)
IIIA	13 (25)
IIIB	14 (26.9)
IIIC	1 (1.9)
Margin status	
R0	41 (78.8)
R1	11 (21.2)

Toxicity

In terms of gastrointestinal complications, nausea was the most common toxicity and 7 patients (13.5%) experienced nausea graded as 3 or higher. Diarrhea graded as 3 or higher occurred in 6 patients (11.5%). The most common hematological toxicity was Grade 3 leukopenia seen in 9 (17.3%) patients. 6 (11.5%) patients had cardiac toxicity in the form of bradycardia. One (1.92%) patient died due to this treatment-related toxicity (bradycardia) (Table 3).

Survival and Relapse

Within a median follow-up of 12 months (range 6-40 months), out of 52 patients, 1 patient had died of treatment-related toxicity, 36 out of 51 patients (70.6%) had developed relapse at end of study and 29.4% patients were disease free at the end of study. 1 year DFS and 2 years DFS was 45.09% and 19.60%, respectively. The median time to recurrence from surgery was 12 months (95% confidence interval: 8.118-15.112) (Figure 1). Of these patients, 5 (13.9%) patients developed a locoregional recurrence, 22 (61.1%) patients developed distant metastases, and 9 (25%) patients developed both local and systemic metastasis. The most common site of metastasis was the liver (23 patients). Peritoneal carcinomatosis with ascites, bone metastasis, splenic metastasis, anterior abdominal wall metastasis, and nonregional nodal metastasis (right axillary node, supraclavicular node, inguinal node) metastases were also reported (Table 4).

Prognostic Factors for Recurrence

To evaluate the prognostic factors of recurrence, variable clinicopathological factors - sex, age, type of surgery, location of tumor, histological type (WHO classification, grade, Lauren type), invasion to more than the serosa, number of involved lymph nodes, TNM stage, grade, lymphovascular invasion (LVI), perineural invasion (PNI), and margin status were analyzed; but sex, age, type of operation, location of tumor, histological type, number of involved lymph node, grade, PNI, and margin were unrelated to recurrence rate and median DFS. The TNM stage and the invasion to more than the serosa, LVI +ve

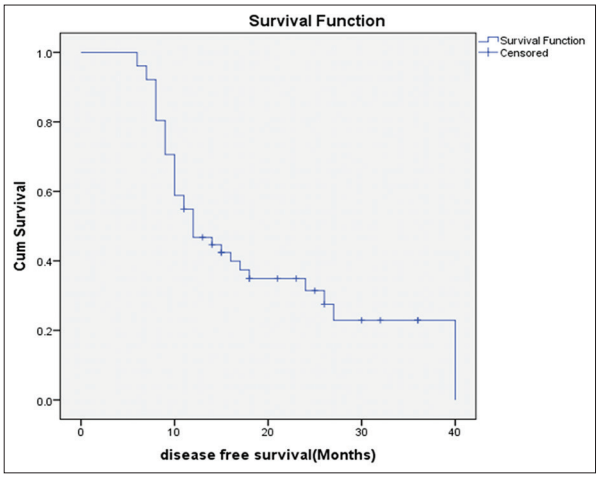

Figure 1: Disease free survival (months)

Table 2: Tumor characteristics

Characteristics	Number of patients (*n*) (%)
Tumor size (mm)	
Median	57.5
Range	25-90
T-stage	
T1	1 (1.9)
T2	8 (15.4)
T3	41 (78.8)
T4	2 (3.8)
N-stage	
N0	9 (17.3)
N1	13 (25)
N2	16 (30.8)
N3	14 (26.9)
Nodal ratio	
<0.4	30 (57.7)
≥0.4	22 (42.3)
Stage	
I	3 (5.7)
II	21 (40.4)
III	28 (53.8)
IV	0
Grade	
1	5 (9.6)
2	23 (44.2)
3	24 (46.2)
LVI	
+ve	27 (51.9)
−ve	25 (48.1)
PNI	
+ve	33 (63.5)
−ve	19 (36.5)

PNI: Perineural invasion, LVI: Lymphovascular invasion

Table 3: Major toxic effects of chemoradiotherapy

Type of toxic effect	Number of patients (%)
Nausea	7 (13.5)
Diarrhoea	6 (11.5)
Leucopenia	9 (17.3)
Neutropenia	9 (17.3)
Thrombocytopenia	4 (7.6)
Bradycardia	6 (11.5)

Table 4: The recurrent sites of 36 patients

Recurrent sites	Number of patients (%)
Locoregional	5 (13.9)
Systemic	22 (61.1)
Both	9 (25)
Liver	23 (63.8)
Peritoneal metastasis	2 (5.5)
Bone metastasis	1 (2.8)
Splenic metastasis	1 (2.8)
Anterior abdominal wall metastasis	2 (5.5)
Non regional nodal metastasis (axillary, supraclavicular, inguinal)	3 (8.3)

and Stage 3 versus Stage 1 and 2 were found to be risk factors for relapse rate and DFS (Figures 2-4).

DISCUSSION

The prognosis of patients with locally advanced GC who undergo surgery alone is poor, with 5 years OS of around 20-30% in node-positive disease.[25,26] The high recurrence rates even after curative resection makes it important to consider postoperative adjuvant therapy for patients with GC.[27,28] Several studies such as GITSG, 1982; Moertel *et al.*, 1984; Allum *et al.*, 1989; Regine and Mohiuddin, 1992[17-19,29] show positive effects of radiotherapy and/or chemotherapy in patients with locally advanced or unresectable gastric adenocarcinoma, but the benefit of adjuvant treatment after curative resection remains controversial. Intergroup trial[20] showed that adjuvant chemoradiotherapy reduced recurrences and increased survival of patients with gastric adenocarcinoma. Undoubtedly, a renewed interest in GC treatment arose after the US Intergroup trial (0116), which demonstrated a clear survival advantage of adjuvant chemoradiotherapy and strongly supported the integration of this treatment as part of standard care for patients who have undergone curative resection for high-risk adenocarcinoma of the stomach and gastroesophageal junction.[20] U.S. Intergroup study (INT-0116) was the first to demonstrate that combined chemo-radiation following complete gastric resection improves median relapse-free survival (30 vs. 19 months, $P < 0.0001$) and OS (36 vs. 27 months, $P = 0.01$).[20] The 3 years survival rates were 41% and 50%, respectively ($P = 0.005$). Following these results, post-operative adjuvant chemo-radiation as per the INT-0116 trial, -called "Macdonald regimen," became the new standard of care. An updated report of this trial has confirmed that this benefit is still maintained at the long term.[21] No adjuvant regimen has definitively supplanted fluorouracil-based chemoradiotherapy. However, this result does not apply to all cases of resected gastric adenocarcinoma because most of the patients (approximately 90%) in this study had undergone limited (D0 or D1) lymph node dissection, which might be associated with increased risk of residual positive nodes. The study reported that 19% of the patients in the chemoradiotherapy arm had relapsed locally, whereas 29% had relapsed in the control arm, and the sites of relapse were mainly lokoregional. This result may suggest the possibility of inadequate local control with limited (D0 or D1) lymph node dissection.[20]

Comparison of patient profile, tumor characteristics as well as treatment results, in terms of toxicity and efficacy were carried out between the INT-0116 trial and the current analysis. Although number of patients in both groups were not comparable (556 vs. 52), the patient populations in both studies were very similar, with a median age of 60 years

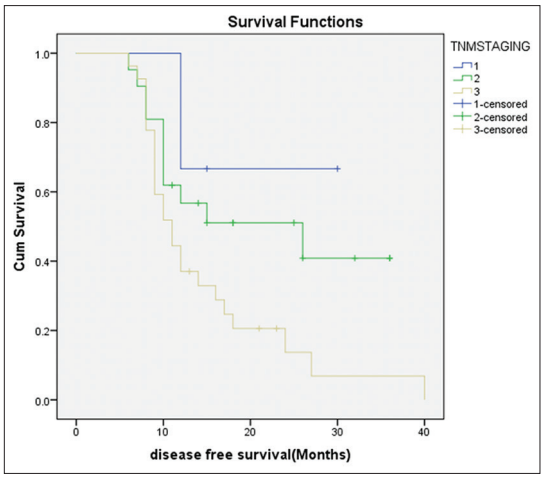

Figure 2: Disease free survival according to tumor, node, metastasis stage

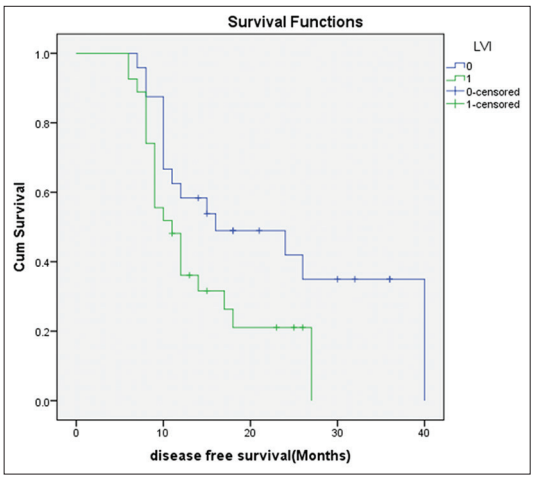

Figure 3: Disease free survival according to lymphavascular invasion (lymphovascular invasion +)

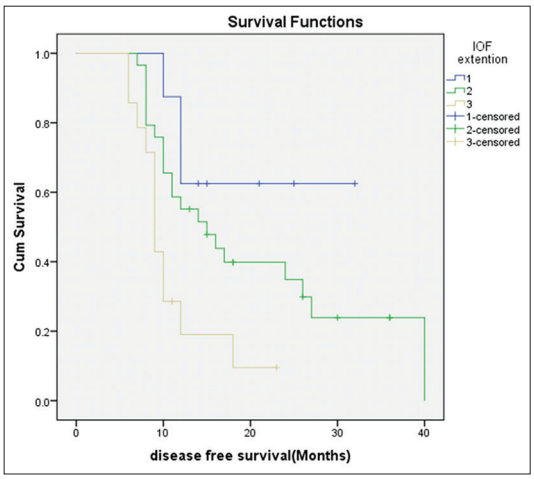

Figure 4: Disease free survival according to IOF extension

with male preponderance (72% and 80.8%). Similarly, type of lymphadenectomy was D1 in approximately 90% of patients in both studies. In both studies most tumors were classified as T3-4 and/or N+ although in the current one there was slightly higher proportion of T3-4 tumors (82.6% vs. 68%). There were certain differences between two studies like high percentage of diffuse histology in our study population compared to INT-0116 trial (51.9% vs. 30.23%) and bad prognostic features like LVI (51.9%), PNI (63.5%) which were not mentioned in reference study. Multivariate analysis showed that tumor invasion beyond serosa or lymph node metastasis is risk factors for total recurrence. That is, patients with T3, T4 and/or lymph node metastasis could be candidates for adjuvant radiotherapy or chemoradiotherapy.[30] The relapse rate in our study is high (70.6% vs. 43%) and DFS is low (12 vs. 36 months) compared to INT-0116 trial probably because of very less number of patients in our study; short median follow-up (1 vs. 5 years); high proportion of T3/T4 tumors; diffuse histology and lymphovascular invasion which are known bad prognostic and independent risk factors for local recurrence in GC. The toxicity pattern was also very similar, with most toxicities being hematological and gastrointestinal with comparable rates of severe (Grade ≥3) toxicities and toxicity-related treatment discontinuations. Hughes, 2004[31] reported almost similar relapse rates (68%) as our study as all parameters were comparable to ours like number of patients (45), T3/T4 (85%) and node positivity (82.7%) and toxicity profile.

Some results report that not only the pN stage but also the number of resected lymph nodes inversely correlates with lower survival rates.[32,33] Marchet *et al*.[32] reported a correlation between the resection of 16 or less lymph nodes and the lower 5 years OS rate in comparison with patients where 16 or more lymph nodes were resected. Wydmanski[34] reported that a nodal ratio of <0.6 correlated with a better prognosis; the 5 years OS in a group of patients with a nodal ratio <0.6 was 45% compared with 19% in cases where the nodal ratio was >0.6. In this study, not only the pN stage but also the number of dissected metastatic lymph nodes divided by the total number of removed nodes (defined as a nodal ratio) was correlated with a decrease in DFS and relapse rate. It appears that the nodal ratio is a more precise prognostic factor than the absolute number of dissected metastatic lymph nodes. Another prognostic factor is tumor size.[32,33] Together with growth of tumor volume, the risk of distant metastases and locoregional recurrence is increased as seen in our study. After the publication of the INT0116 study, a change in everyday practice has been made and more patients received fluorouracil-based chemotherapy in addition to radiotherapy.[35]

Our results with McDonald's protocol in our analysis were not encouraging possibly due to a small patient cohort, higher stage at presentation, aggressive histological variant and probably nonavailability of conformal radiotherapy techniques.

One possible way to improve the efficacy of INT-0116 in our setting might be to integrate newer chemotherapy agents, such as the taxanes, oxaliplatin and oral fluoropyrimidines, in the treatment. Another promising way would be to combine chemotherapy with biological agents like trastuzumab, which has been shown to improve substantially the results of chemotherapy in advanced GC with overexpression of HER2.[36] A second approach to enhance the efficacy of INT-0116 chemotherapy would be to modify the timing of its delivery, like in the "MAGIC" trial.[37] Based on the current data from the decades of studies on adjuvant therapy for GC and particularly from the updated data from the "ARTIST" trial,[38] the benefit of adjuvant chemoradiotherapy appears to outweigh the risks in patients with node-positive disease and intestinal-type histology, so these pathologic factors should be taken into account when considering adjuvant therapy in fit patients after gastric resection.

With the introduction of more advanced radiotherapy techniques, including the use of CT simulator and a more conformal delivery of radiotherapy, the potential for toxicity from abdominal radiotherapy has decreased and the precision of radiotherapy delivery has improved the accuracy of delineating areas at risk in the abdomen for patients receiving adjuvant radiotherapy for GC while minimizing the volume of normal tissue irradiated.

"The chemoradiotherapy after induction chemotherapy of cancer in the stomach" trial is currently investigating perioperative treatment with epirubicin, cisplatin, and capecitabine chemotherapy alone versus epirubicin, cisplatin, and capecitabine chemotherapy followed by concurrent chemoradiotherapy with cisplatin and capecitabine in patients with GC after D1 or greater resection.[39] The results of these, and other, large randomized trials will continue to lead us further along the path of refining our management of GC and further defining the role of radiotherapy in this disease.

CONCLUSION

With continued progress in improving radiotherapy techniques, developing more effective systemic regimens, and identifying biomarkers of treatment response, the role of adjuvant chemoradiotherapy will likely become better defined.

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