

Adjuvant Chemoradiation for Localized Gastric Adenocarcinoma: An Institutional Experience

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Abstract

Background: Several studies have shown that surgery alone is not enough in the management of early gastric cancer with locoregional relapse in 40% to 60%. The frequency of relapses makes regional radiotherapy an attractive possibility for adjuvant therapy. The survival benefit of adjuvant chemoradiation over surgery alone was first established by the US Intergroup 0116 study.

Patients and methods: Between January 2010 and December 2014, 48 patients with localized gastric adenocarcinoma, managed at radiotherapy department of the national institut of oncology, they underwent adjuvant chemoradiation according the classical MacDonald regimen.

Results: This series consisted of non-metastatic patients, 68.8% (33) males with a mean age 51 years. 20.8% (10) of patients had relapses (all distant relapse). 22 (45.8%) patients died, only 8(16.6%) patients were lost to follow up. Almost all patients complete full course chemoradiation. The median follow-up duration was 25.4 (15.6-48) months. The 5 years OS and DFS was 40.8% and 49% respectively. Disease stage, operative procedure on primary tumor was an independent prognostic for both 5-year OS and DFS. The pN, surgical margin had a significant impact on OS.

Conclusion: Adjuvant chemo-radiation may be an effective and safe regimen for patients who have undergone gastrectomy with curative intent in locally advanced stomach cancer and did not receive preoperative chemotherapy.

Keywords: Postoperative chemoradiation; Resected gastric cancer; Adenocarcinoma

Background

Gastric cancer is the second leading cause of cancer related death among men and the fourth among women, and thus represents a significant global health concern [1]. The disease is commonly diagnosed at a locally advanced stage, and surgery remains the main treatment; The overall survival rate of patients who underwent surgery alone is about 45% at 5 years, that has undergone few changes over the last decades [2,3].

The curative treatment of gastric cancer requires surgical resection in less than 40% of cases [2,3]. Independent risk factors in the literature are tumor size (>4 cm), age (>70 years), proximal location, diffuse type of Lauren classification, tumor residue, Deep invasion (T3-T4), and the ratio of involved lymph nodes/total number (>20%) [4,5]. Locoregional recurrences on the tumor bed, on the anastomosis or in lymph nodes occur in 40% to 65% of the patients after resection with curative intent [6,7]. The frequency of this relapse makes regional radiotherapy an attractive possibility for adjuvant therapy [8].

Various chemotherapy regimens used to prevent relapse and improve the poor survival rates provide small but statistically significant clinical benefit [9,10]. Finally, the intergroup of gastrointestinal cancers (INT-0116) was the first to demonstrate in a phase III trial that concomitant radio-chemotherapy after complete gastric resection improves median relapse-free survival (30 vs 19 months, $p < 0.0001$) and overall survival (36 vs 27 months, $p < 0.01$) [11]. Following these results, postoperative radio-chemotherapy according to the Macdonald protocol became the new standard of care [11]. However, much concern remains regarding the toxicity of the regimen. 41% of patients had grade 3 digestive toxicity and 32% grade 4 [11]. The objective of our

retrospective study was to assess to impact of adjuvant chemoradiation of gastric adenocarcinoma on prognosis.

Materials and Methods

Between January 2010 and December 2014, we analyzed retrospectively the data of 48 patients with no metastatic and pathologically confirmed gastric adenocarcinoma staged according to the 6th edition of the American Joint Commission on Cancer (AJCC) 2010. All patients underwent adjuvant chemoradiation after surgery (gastrectomy with lymph node dissection depending on the location of the tumor). One patient underwent hemostatic gastrectomy which revealed gastric cancer, then lymph node dissection was not performed. R1 and R2 resections were only included if they were denied other treatment. Patients did not receive preoperative chemotherapy. The majority of patients (41 of 48) were treated using 5 cycles of 5FU/leucovorin chemotherapy every 28 days. Radiotherapy began with the second cycle (first, fourth, and fifth cycle using 5FU 425 mg/m² and folinic acid 20 mg/m² for 5 days; second cycle using 5FU 400 mg/m² and folinic acid 20 mg/m² for 4 days, and the third

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cycle using the same doses as the second but for 3 days). Seven patients received a capecitabine-based regimen at a dose of 750 mg/m² to 1000 mg/m² twice daily for 14 days, a cycle 28 days before radiotherapy and 2 cycles after. All patients were treated using a 3D conformal radiation technique. The CT simulation was performed in the supine position with arms above their head with slice thickness of 5 mm. The clinical target volume (CTV) included the operative bed, anastomosis with 2 cm of margin (gastrojejunal, oesophagojejunal) and nodal groups according to the tumor location. The planning target volume (PTV) consisted of the CTV with a 1 cm margin. The organs at risk were also delineated (kidneys, liver, heart, and spinal cord). A total radiation dose of 45 Gy was delivered in 25 fractions at 1.8 Gy per fraction, five days per week over five weeks. The treatment plan was approved by the radiation oncologist. One patient did not finish the radiotherapy course because of surgical complication (eventration), another one preferred to stop radiation therapy and he was lost of sight. The follow-up was scheduled every 3 months for the first 2 years and every 6 months after 2 years to detect recurrences and treatment complication. No routine endoscopy or CT scans (chest, abdomen, pelvis) were performed only if symptoms. The treatment related toxicities were assessed from patient's records.

The data was analyzed using SPSS version 20.0. Qualitative variables were presented as number and percentages. Quantitative variables were represented as average ± standard deviation for variables with normal distribution, and as median and interquartile range (IQR) for variables with skewed distributions. The survival rate was analyzed with the Kaplan-Meier method

Results

Between January 2010 and December 2014, 48 patients with locally advanced gastric cancer received adjuvant concomitant chemo radiation. The patients' characteristics are summarized in Table 1. The mean age was 51 ± 15 years with men represented more than two third of patients 68.8%. Only two patients 4.2% had a history of familial gastric cancer and one third of patients 33.4% with smoking history. Tumor was located in the upper third of stomach in 26 (54.2%) patients. Signet ring cells subtype pathology was present in 59% (28) of patients.

All patients underwent gastrectomy with lymph node dissection (Table 2); eight (16.7%) patients had positives margins (R1 or R2). Almost three third of patients 73% (35) underwent D1 or D1.5 Lymph node dissection. Stage II and III represented 44% and 56% respectively.

It was noted that 47% of patients experienced acute gastro-intestinal toxicities (vomiting, nausea, diarrhea, stomatitis, epigastralgia) whereas 33% of patients experienced acute hematological toxicities.

The median follow-up duration was 25.4 (15.6-48) months. Eighteen patients (39.5%) were alive and healthy, 22 (45.8%) patients were died. All patients 20.8% [10] with distant relapse were died. No local recurrence was reported. Only 8 (16.6%) patients were lost to follow up. We tried to contact these patients by phone and by sending correspondence letter without resulting from response. The 5 years OS (overall survival) and DFS (disease free survival) was 40.8% and 49% respectively (Figures 1 and 2). The univariate analysis (Tables 3 and 4) demonstrated that pN (p: 0.007 and p: 0.05) and the operative procedures on primary tumor (p: 0.04 and p: 0.01) had a significant impact on OS and DFS respectively. Whereas, the disease stage and the surgical margin were a significant factor for OS (p: 0.001, p: 0.002 respectively) (Figures 3 and 4). Also, the signet ring cells subtype pathology was a non-significant factor for OS (p: 0.08) but on the curve

| Items | | % (n) |
|--|---------------------------------|------------|
| Age of diagnostics | | 51 ± 15 |
| Gender | | |
| History | Male | 68.8% (33) |
| | female | 22.2% (11) |
| | smoking | 33.4% (16) |
| | Familial Gastric cancer history | 4.2% (2) |
| Mean duration of symptoms: 6 months | | |
| Tumor location | upper third (Antro-pyloric) | 54.2% (26) |
| | Lower third (Cardia-fundus) | 10.4% (5) |
| | Middle third | 25% (12) |
| | Entire stomach | 10.4% (5) |
| Pathology: Macroscopic | Ulcerating/budding | 62.5% (30) |
| | Ulcerating/infiltrating | 18.8% (9) |
| | Ulcerating | 10.4% (5) |
| | Budding | 6.3% (3) |
| | Infiltrating | 2.1% (1) |
| Microscopic | Adenocarcinoma | |
| | with signet ring cells | 59.3% (28) |
| | without signet ring cells | 4.6% (16) |
| Tumor grading | Well-differentiated | 6.3% (3) |
| | Moderately differentiated | 41.7% (20) |
| | Poorly differentiated | 16.7% (8) |
| | Undifferentiated | 14.5% (7) |
| | Not specified | 20.8% (10) |

Table 1: Clinical and pathological characteristics of patients.

patient without signet ring cells had better outcome (Figure 6). There was a negative correlation (r: -0.07) between the overall survival and the N ratio (the ratio of metastatic to examined lymph nodes) without reaching the threshold of significance (Figure 5).

The multivariate analysis confirmed that the disease stage as prognostic factor (p: 0.003 OR). The multivariate analysis was not performed for DFS because of the small number of events.

Discussion

Adjuvant CCR is a standard of care in gastric cancer patients, as this therapeutic modalities combination improved survival. We treated 48 patients, with locally advanced gastric cancer, by primary surgery followed by CCR. The median follow-up duration was 25.4 (15.6-48) months. The 5 years OS and DFS was 40.8% and 49% respectively. Disease stage was an independent prognostic factor either for OS or DFS. Although gastrectomy associated with lymph node dissection, depending on tumor location, is the main treatment of gastric cancer; control and survival rate at 5 years remains low, on the order of 20% to 30% in T3-T4 patients with positive lymph nodes [6,12]. In an attempt to prevent recurrence and increase the cure rate after surgery, multiple studies investigate the role of multimodal treatment approach [12]. Thus, the INT 0116 study published in 2001, was the pivotal randomized trial compared 2 arms: surgery associated or not to combined chemoradiation [11]: At 3 year PFS was 41% in the surgery arm alone and 50% in adjuvant CCR arm (p<0.001); 3 years OS was 41% in the surgery arm alone and 48% in adjuvant therapy arm (p=0.005) [11]. The update of the intergroup trial was confirmed the OS benefit at 10 years [13]. These results have been confirmed by other authors [12,14,15]. In our study, all patients received adjuvant CCR, the 5-year OS was 40.8% and 5 year DFS was 49%. These results are comparable to literature.

| Items | % (n) | |
|------------------------------------|----------------------------|-------------|
| Operative procedures Primary tumor | Total Gastrectomy | 41.7% (20) |
| | Subtotal Gastrectomy | 39.6% (19) |
| | Total extended Gastrectomy | 12.5% (6) |
| | Two-third Gastrectomy | 2.1% (1) |
| | Oesophagogastrectomy | 4.2% (2) |
| Lymph nodes dissection type | D0 | 14.6% (7) |
| | D1 | 39.5% (19) |
| | D1.5 | 35.4% (17) |
| | D2 | 8.3% (4) |
| | Not performed | 2% (1) |
| pT | pT2 | 4.2% (2) |
| | pT3 | 79% (38) |
| | pT4 | 16.6% (8) |
| Margins | R0 | 83.3% (40) |
| | R1 | 10.4% (5) |
| | R2 | 6.3% (3) |
| pN | N0 | 14.8% (7) |
| | N1 | 25.5% (12) |
| | N2 | 27.6% (13) |
| | N3a | 21.2% (10) |
| | N3b | 10.6% (5) |
| Stage | IIA | 17% (8) |
| | IIB | 27% (13) |
| | IIIA | 17% (8) |
| | IIIB | 31.9% (15) |
| | IIIC | 6.4% (3) |
| LVE | Positif | 54.3% (25) |
| | Negatif | 45.6% (21) |
| N Ratio | < 20% | 36.9% (17) |
| | >20% | 63% (29) |
| Chemotherapy (CMT) | CMT regimens | |
| | 5FU | 85.4% (41) |
| | Capecitabine | 14.5% (7) |
| | Number of cures | 4.64 ± 0.67 |

Table 2: Pathologic and therapeutic characteristics of patients.

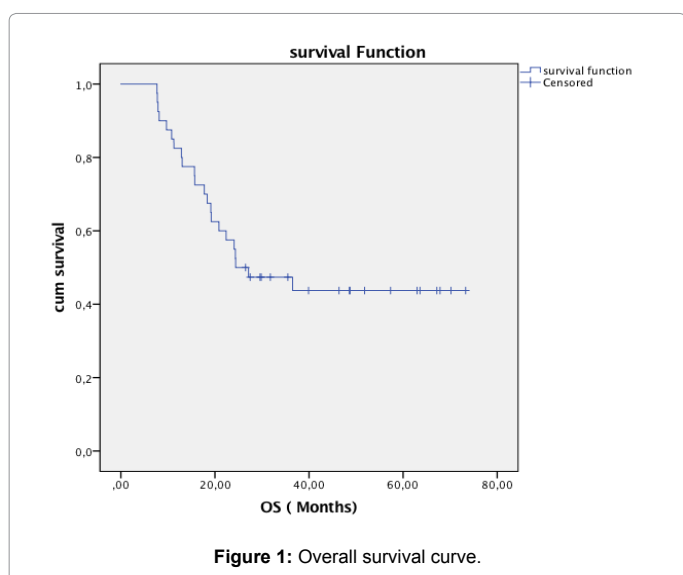


Figure 1: Overall survival curve.

Gastric cancer is mostly diagnosed at a locally advanced stage [1]. 56% of patients in this study were stage III (Figure 3). 95.8% of patients had T3-T4 tumor versus 69% in INT-0116 trial, even in several

retrospectives series more than 75% of patients was T3T4 [8,16-18]. In our study, 85% of patients had lymph nodes involvement as like in INT-0116 [11], similar results were cited in literature [8,12,16-18].

The number of involved lymph nodes has a significant impact on survival [19]. It has been demonstrated a correlation between the number of positive lymph node and the OS, which was lower if more than 16 nodes is involved [20] Thus a high N is an adverse factor [20]. Also, The N ratio was retained as an independent prognostic factor both in patients with D1 and D2 lymphadenectomy [21]. So, correlation of the two, the number of lymph node metastases and lymph node ratio, is

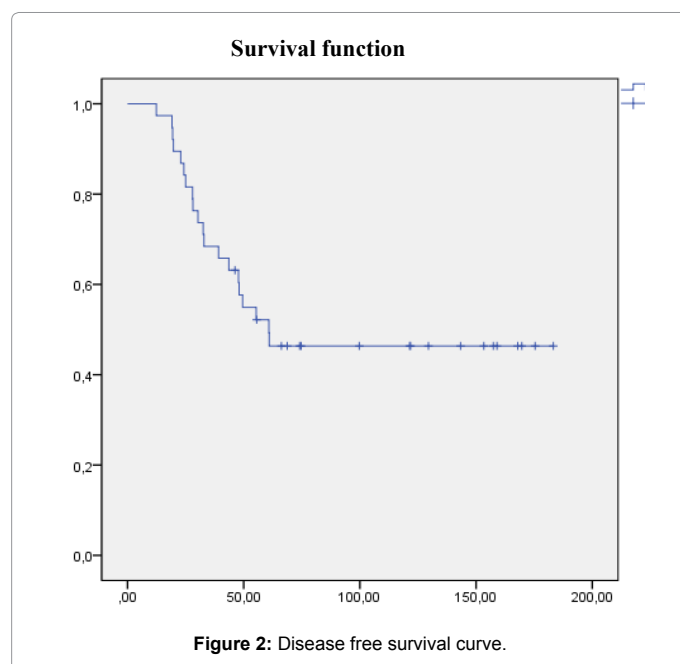


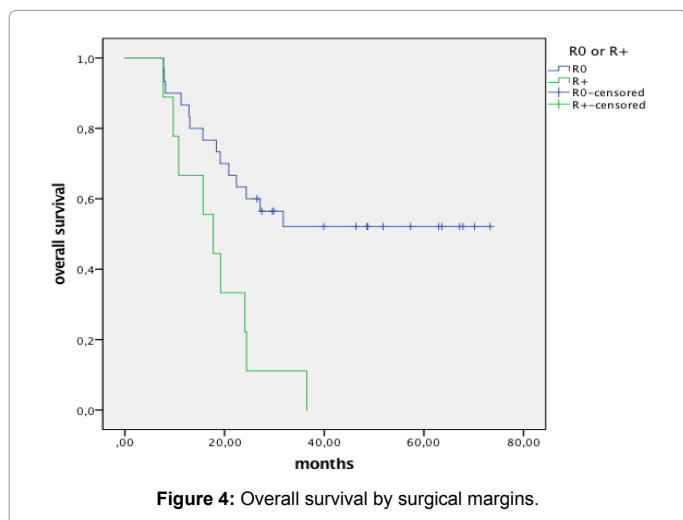
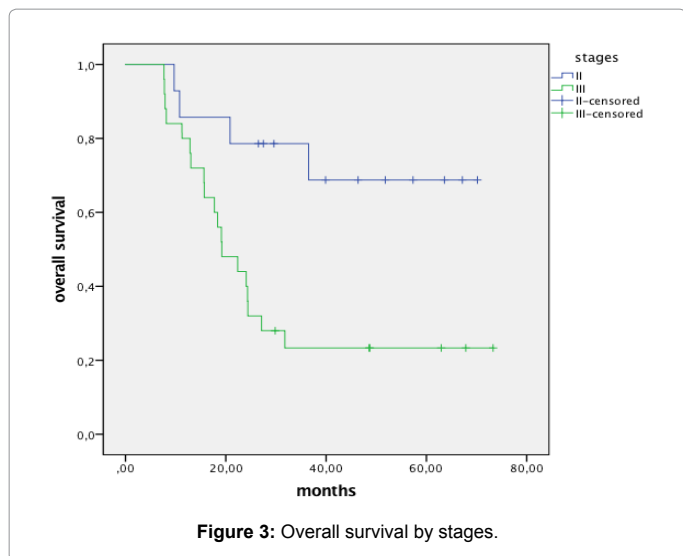
Figure 2: Disease free survival curve.

| | OS | | | DFS | | |
|---------------------------------------|------|------------|--------------|------|------------|-------------|
| | OR | 95%CI | p | OR | 95%CI | p |
| Tumor location | 1.09 | 0.49-2.42 | 0.82 | 1.07 | 0.42-2.68 | 0.88 |
| stage | 4.51 | 1.84-11.09 | 0.001 | 1.6 | 0.78-3.28 | 0.1 |
| Age | 0.99 | 0.95-1.03 | 0.72 | 0.98 | 0.94-1.03 | 0.53 |
| pN | 2.79 | 1.32-5.91 | 0.007 | 2.09 | 0.99-4.4 | 0.05 |
| Surgical margins | - | - | 0.002 | 5.00 | 0.92-26.9 | 0.06 |
| LN dissection type | 1.04 | 0.56-1.9 | 0.89 | 0.84 | 0.40-1.73 | 0.63 |
| N ratio | 0.66 | 0.06-6.74 | 0.72 | 4.13 | 0.30-56.15 | 0.3 |
| Pathology | - | - | 0.08 | | | |
| Operative procedures on primary tumor | 2.59 | 1.04-6.41 | 0.04 | 1.51 | -3.79 | 0.01 |
| CMT Regimen | 0.47 | 0.09-2.49 | 0.37 | 1.37 | 0.21-8.66 | 0.73 |
| Number Of CMT Cures | 1.28 | 0.55-2.96 | 0.56 | 1.04 | 0.39-2.76 | 0.93 |

Table 3: Univariate analysis for parameters influencing OS and DFS

| Gastrointestinal | Chemotherapy | Combined chemoradiation |
|------------------|--------------|-------------------------|
| Nausea/vomiting | 25 (52%) | 19 (39%) |
| Epigastralgia | 12 (25%) | 23 (47%) |
| Mucositis | 13 (27%) | 7 (14%) |
| Diarrhea | 21 (43%) | 23 (47%) |
| Hematological | | |
| Neutropenia | 27 (56%) | 16 (33%) |
| Anemia | 22 (45%) | 11 (22%) |

Table 4: Acute toxicities during chemoradiotherapy.

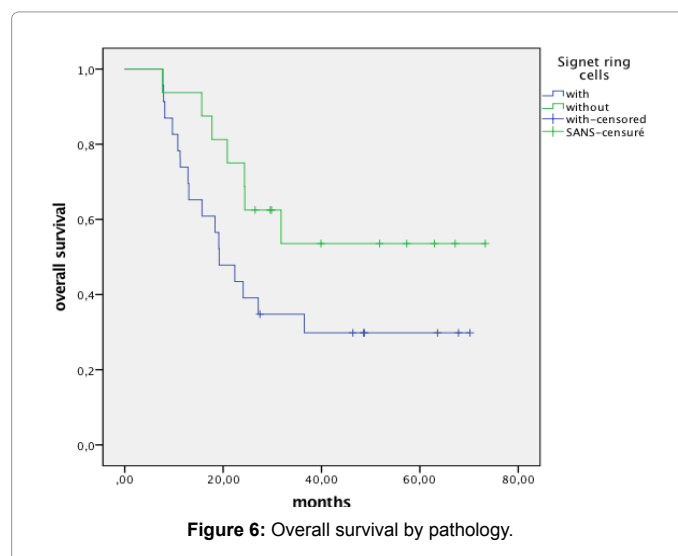
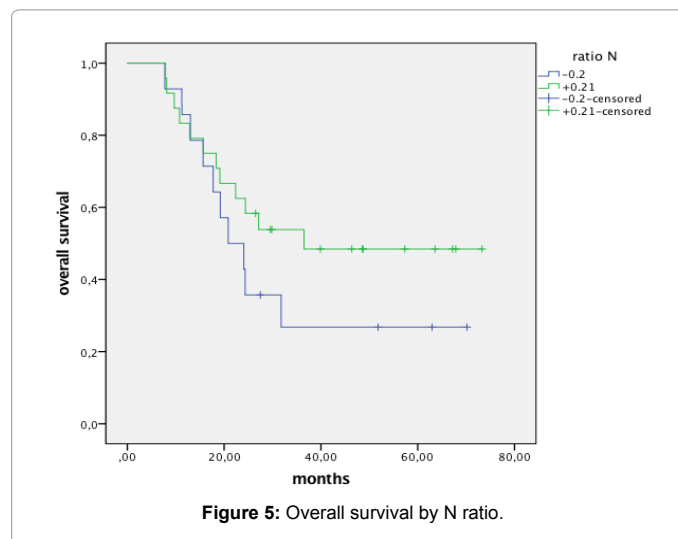


obvious [22]. In our study, the pN influenced the OS and the DFS, and there was a negative correlation between the OS and the N ratio without reaching the threshold of significance (Figure 5). The extent of lymph node dissection is controversial [12,19]. It has been suggested a survival benefit of the adjuvant chemoradiation therapy in D2-resected gastric cancer patients [12]. Four major randomized trials, investigated the extent of lymphadenectomy, show no survival advantage on outcome, even the postoperative mortality and morbidity among patients with D2 dissection is higher in patients from European descent [23-26]. In our study lymph node dissection extent showed no benefit neither in DFS nor in OS. Two controlled studies compared total gastrectomy to subtotal gastrectomy; There was no difference in mortality rate, and the 5-year OS was the same in both arms (48%) [27,28]. Unlike, in our study, there was a difference statistically significant in surgical procedure in 5-year OS ($p=0.04$). This can be explained that patients undergoing total gastrectomy probably reflects larger tumors and unfavorable proximal lesions that prompt such a procedure. A positive resection margin was shown to be an independent adverse factor for survival in several surgical series before the advent of adjuvant CRT regarding patients who have had a microscopically incomplete resection, a retrospective comparison of the Dutch D1D2 trial has suggested significant improvements in OS and local recurrence rates

with use of CRT after an R1 resection [29,30]. In our study, the surgical margin alter significantly outcome (Figure 4). In the INT-0116 study, only 181 (64%) completed treatment due to Grade 3-4 toxicities in 41% and 32% patients [11]. Similarly, other studies reported high toxicities grade 3-4 [31,32]. In our study the CCR was well tolerated thus almost all patient completed treatment. Also, others retrospectives series reported less grade 3-4 toxicities [33-35]. Maybe the use of conventional RT was the cause of relatively higher rates of toxicity in this study. The other risk factors (age, tumor size, tumor grade, LVE) known for their negative impact on survival were not found; though patient without signet ring cells subtype pathology had better outcome on the curve without reaching the threshold of significance (Figure 6). This can be explained by the small number of patients in our study. The main limitations of this study were the relatively small size, because of the majority of patients came from other structures, and the lack of reporting of data on toxicities grading associated with concomitant radio-chemotherapy.

Conclusion

The unfavorable prognosis of locally advanced stomach cancers justified numerous trials evaluating adjuvant treatments.



Chemoradiation was evaluated in a large controlled trial which showed a significant improvement in overall survival and recurrence-free survival after gastrectomy for localized stage cancers. Although our study has a low strength, this protocol is feasible in our institute with a fairly good tolerance, and without interruption of treatment.

Competing Interests

The authors declare that they have no competing interests.

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Ethics Approval and Consent to Participate

Not applicable

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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