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Neoadjuvant Chemotherapy in Local Advanced Gastric Cancer

Abdolhassan Talaiezadeh [1,*], Amir jafar Modirgolestan [2], Hodjatollah Shahbazian [3]

[1] Associate professor of surgery, surgical oncologist, Head of Cancer Research Center affiliated to Ahvaz University of Medical Sciences, Ahvaz, Iran.
[2] General surgery, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
[3] Assistant professor of radiotherapy and Oncology, Department of Radiotherapy and Oncology, Golestan Hospital, Cancer Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz. Iran.
Corresponding author: Abdolhassan Talaiezadeh, Associate professor of surgery, surgical oncologist, head of cancer research center affiliated to Ahvaz University of Medical Sciences, Ahvaz, Iran. Tel: +98-9161184922, E-mail: ah.talaiezadeh@ajums.ac.ir

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Background: Gastric cancer remains a major cause of cancer death in Iran despite a significant decreasing incidence in western countries. Surgery alone has not been effective for treatment of locoregional gastric cancer because of the low rate of curative resection and high incidence of local recurrence and distant metastases. Our aim was to determine the resectability of tumor after neoadjuvant chemotherapy.
Material and methods: Fourteen patients with clinical stage III gastric adenocarcinoma that initially seemed to be unresectable by laparoscopy were treated with three cycles of cisplatin 60 mg/m2, 5-Fluorouracil 750 mg/m2 and Epirubicin 50 mg/m2 three weeks before surgery.
Results: Thirteen patients were operable for surgery after neoadjuvant chemotherapy (Pvalue= 0.001), while one patient was not operable due to developing distal metastasis. Twelve (85.85%) patients were resectable with pathologic report of R 0 and, one (7.15%) patient was reported R1, (Pvalue= 0.001).
Result: A total number of 97 patients, with mediastinal involvement by primary masses, were contributed in this study. Biopsy was taken through the several ways. The numbers of 52(53.60%) "Lymphoma" and 45 (46.40%) cases with other pathologic results were dominantly detected with "tuberculosis". Two cases of lymphoma was found in two referred cases with MMs <10 years and the overall incidence of involvement was begun from first to fifth decades with the peak in third to fourth decades along with mostly anterior mediastinal locations.
Conclusion: This study shows that neoadjuvant chemotherapy improves operability and resectability of the tumor in patients with local advanced gastric adenocarcinoma.

Keywords: Gastric adenocarcinoma, Neoadjuvant chemotherapy, local advanced, Resectability

Background

Gastric cancer is one of the most common malignancies worldwide (1). In Iran, it is the most frequent malignancy and the leading cause of cancer–related mortality (2, 3, 4, 5). Surgery remains the only potentially curative therapeutic option, but five year survival for all patients is very poor, being approximately 10-15% (6). Surgery is an insufficient treatment for most patients in stage III and IV. Low curative resection rates and high failure rates are common in this group. On the other hand, chemotherapy alone has a minimal impact in long term survival. Nevertheless, combined preoperative chemotherapy followed by radical surgical resection has been recognized as an effective approach (7, 8).

Neoadjuvant therapy as chemotherapy, radiotherapy or targeted therapy is a new modality in cancer treatment. The main objective of this modality of treatment is change a radical & mutilating surgery to a conserving procedure to save shape and action of that organ. For example changing a radical mastectomy to a preserving breast in breast cancer or replace a sphincter saving procedure in rectal cancer instead of abdominoperineal resection and permanent colostomy. The second aim of neoadjuvant therapy is evaluation of response to adjuvant therapy before removal of tumor by surgery.

In the last decade, neoadjuvant chemotherapy has been used to decrease the tumor burden before resection and to improve the prognosis of late stage, but in resectable gastric cancer (6). A preoperative chemotherapy regimen would have advantages over postoperative chemotherapy alone, including "increasing the likelihood of curative resection by down staging the tumor, eliminating micrometastases, rapidly improving tumor-related symptoms and determining whether the tumor is sensitive to chemotherapy (8).

We evaluated the effects of neoadjuvant chemotherapy on operability, resectability, complications and down staging in patients with local advanced gastric cancer.

Materials and Method

It was an interventional clinical trial as a pilot study that was performed between 2006 and 2009 at Ahvaz Jundishapur University hospitals (Ahvaz, Iran). The treatment methods for this study were approved by the ethics committee of our university, and written informed consent was obtained from each of the patients before he/she was included in this study.

The patients were clinically diagnosed based on fiberoptic gastroduodenal endoscopy and biopsy After diagnosis of gastric adenocarcinoma, ab-

dominopelvic CT scan, chest X-Ray, complete blood count, liver function test and biochemistry tests were performed. All patients underwent diagnostic laparoscopy for determining tumor size and shape, liver and other organs metastasis, adhesion of stomach to adjacent organs, peritoneal seeding and ascites. For patients without ascites, 1000cc of normal salin solution was injected into the abdomen and was aspirated. Cytological examination for ascitic fluid or lavage fluid was done. Patients with intraabdominal seeding & distant metastasis excluded.

From July 2006 to March 2009, 32 patients were enrolled in our study, 18 of whom with stage IV, peritoneal seeding and malignant ascites cytology of ascites or lavage fluid, were excluded. Finally our study consisted of 14 patients with clinical stage III gastric adenocarcinoma.

The patients received three cycles of chemotherapy with cisplatin 60 mg/m2, 5FU 750 mg/m2 and Epirubicin 50 mg/m2 preoperatively. Surgery was scheduled to take place within three to four weeks after completion of the preoperative chemotherapy cycles. Then the patients were evaluated for resectability (Ro: resected tumor with negative microscopic margin, R1: resected tumor with positive microscopic margin, R2: resected tumor with remain gross tumoral margin). Then patients received three cycles of chemotherapy postoperatively. The statistical significance was evaluated with X2 test and fisher test. All data were analyzed using SPSS, version 16.0 (Chicago, IL, USA).

Results

Fourteen patients with clinical stage III gastric adenocarcinoma were enrolled in this study. Thirteen patients were operable for surgery after neoadjuvant chemotherapy which was statistically significant (p value= 0.001), while one patient was not operable in account of developing abdominal metastasis. The group comprised 9 (64.2%) men and 5 (35.8%) women, 4 (28.5%) of whom aged between 40 to 60 years and 10 (71.5%) aged above 60 years.

Five patients had severe adhesion of the stomach to adjacent organs in diagnostic laparoscopy performed before neoadjuvant chemotherapy that adhesion had been significantly decreased after chemotherapy. In this study, 12 (85.85%) patients were resectable with pathologic report of R0 and, one (7.15%) patient was reported R1, which was statistically significant (p-value: 0.001). There was not palpable mass in gastric wall during surgery of one patient which may due to down staging after neoadjuvant chemotherapy. One patient had upstaging after neoadjuvant chemotherapy.

Evaluating of postoperative complications reflected 6 (37.5%) patients without complications, 2(12.5%) patients presented with wound infection and one (6.25%) patient developed wound dehiscence. None of the patients presented with leakage of anastomosis.

Discussion

The surgical removal of gastric cancer is a standard treatment approach if the cancer has not spread too far. However, many patients present with advanced disease (Stage II IA, IIIB, and IV) that are unresectable. Surgery is an inadequate and insufficient treatment for patients with advanced gastric cancer, because locoregional and distant failures have been reported with a high frequency. Neoadjuvant chemotherapy has recently received extensive attention as an attempt to increase the rate of complete tumor resection (7). In a survey by Kelsen et al, patients received FAMTX (Methotroxate, Doxorubicin, 5FU) before surgery and cysplatin and 5FU after surgery. Eighty nine percent of the patients were operable, 61% had resectable tumor and mean survival was 15 months (9). In a study by Cascinu et al, 82 patients with advanced unresectable gastric cancer were treated with a Platinol® and anthracycline-based regimen followed by surgery. The response rate was 49%; 7% experienced a complete response. In 4 of the 6 clinical complete responses, there was also a pathologic complete response. Thirty-seven of the 40 responders underwent surgery. With a median follow-up of 4 years, the median survival for the entire group was 17 months but only 12 months for the inoperable patients. The researchers reported that 68% of the resected patients were alive and 65% were disease -free (10). A study involving 42 patients who received chemotherapy (2-4 cycles) prior to surgery showed, survival was improved in patients who responded to chemotherapy and subsequently underwent surgery (11).

As with any sequencing of therapies, there are potential disadvantages to using neoadjuvant chemotherapy. The most important potential disadvantage is the selection of the appropriate patient. It is possible that patients who do not require such intense and risky treatment would be included in the neoadjuvant group based on clinical staging of their disease. It is also possible that patients who are potentially curable by appropriate surgery would have progression of their disease while receiving induction treatment and thus be harmed. Preoperative treatment also has the disadvantage of obscuring the true pathologic stage, thus making it very difficult to assess the benefit of therapy in a clinical trial setting accurately. Finally, when an exceptional response occurs to induction therapy, there is the risk that less aggressive surgery will be performed, thus compromising the patient's outcome. These are certainly important potential concerns and must be factored into any evaluation of neoadjuvant treatment. In the case of gastric cancer, however, the challenge of the disease clearly justifies such an aggressive approach (12). Dolores Gallardo-Rinco´n and others showed that cisplatin, etoposide, leucovorin, and 5-fluorouracil combination is active in advanced gastric cancer and the toxicity level is acceptable. This treatment permitted a 17.5% resection rate in previously unresectable

tumors (13). Nacagava et al showed that neoadjuvant chemotherapy in patients with advanced adenocarcinoma of the stomach and positive cytology of ascites fluid does not have significant effect on survival (14). We also excluded patients with positive cytology of ascites fluid.

Schumacher and colleagues stress that on the basis of an accurate staging, neoadjuvant chemotherapy in a highly selected patient set with gastric adenocarcinoma appears to result in short term and long term survival benefit for a subgroup of patients compared with historic data (15). A study from the Siewert's institution shows that the rate of tumor cell micro involvement is markedly lower in patients who are treated with preoperative chemotherapy compared with patients who are primarily resected (16). In a survey by Dugo and others, 3-year-survival of patients with advanced gastric cancer who underwent neoadjuvant chemotherapy before D2 surgery, was compared to patients who underwent surgery without neoadjuvant chemotherapy.

Results showed that there is a significant statistical relation between tumor regression by neoadjuvant therapy and 3-year-survival. They also showed that patients who had got down staging would benefit from reoperation (17).

In a study by Crookes and associates, fifty nine patients received intraperitoneal neoadjuvant chemotherapy followed by postoperative intraperitoneal infusion using 5- fluoro-2' deoxyuridine and cisplatin. Seventy one percent of these patients were R0 with mortality rate of 5% and mean survival of 4 years (18). Such therapy has a potential local effect on peritoneal surfaces, but considerable drug is absorbed through the portal circulation with potential hepatic efficacy.

Swisher and colleagues found that only those patients achieving complete response had a survival advantage (19). Nakata and colleagues observed that changes in tumor marker levels during induction chemotherapy correlated with response and improved survival (20). Recently adding radiotherapy to neoadjuvant chemotherapy is promising (21).

However, in our study, of the 32 patients with gastric adenocarcinoma, neoadjuvant chemotherapy was initially planned for 14 p atients who had clinical stage III. Of these 14 patients, 13 patients were operable after neoadjuvant chemotherapy that was statistically significant who seemed to be unresectable by CT scan findings and laparoscopy (P value=0.001). Eighty five percent of the patients had (R0) resection.

We didn't have significant down staging in our patients that may be due to few numbers of patients enrolled in our study. We also had one upstaging by liver metastasis.

Conclusion

In conclusion, this study shows that neoadjuvant chemotherapy improves operability and resectability of the tumor in patients with local advanced gastric adenocarcinoma. However, we didn't find significant up or down staging which may be due to low number of patients participated in our study. There was not significant increasing in the rate of postoperative complications.

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