

Neoadjuvant treatment of gastric adenocarcinoma: why our attitude is reserved

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Background. The US inter group study INT 0116 in 2001 and UK NCRI MAGIC Trial in 2005 with better results of combined treatment of gastric cancer provoked a discussion which continues until now. We have experience in neoadjuvant treatment of gastric cancer since 1980, and our attitude towards it is reserved.

Materials and methods. We present the data collected in our three studies. The first one was a randomized study of patients with stage III gastric cancer performed in 1980–1990. The results of neoadjuvant chemotherapy and surgery were compared with those of surgery alone. The second was a randomised study of patients with stage III gastric cancer, performed in 1996–1999 to assess the value of neoadjuvant chemotherapy. In our third study we analysed patients after radical surgical treatment in 1987–1996.

Results. The period of recurrence and three-year survival was longer in the neoadjuvant chemotherapy group, while the 5-year survival showed no statistically significant difference in our first study.

In our second study, the median survival of patients in the neoadjuvant chemotherapy group was 49.5 months and in group II (without chemotherapy) 50.5 months. The difference was not statistically significant ($p > 0.05$).

In our third study we analysed patients after radical surgical treatment in 1987–1996. Stage III gastric cancer patients received adjuvant chemotherapy – Mayo clinic regimen 5 FU/LV. The median survival was 43.2 months.

Conclusions. The value of adjuvant treatment in the early stages of gastric cancer after R0 D2 surgery is disputable. Neoadjuvant chemotherapy should be used to achieve R0 surgery when resectability is impossible without it.

Key words: gastric adenocarcinoma, neoadjuvant treatment, perioperative treatment

INTRODUCTION

Gastric cancer is a dangerous and serpentine disease that causes serious problems in modern oncology. It is one of the most common malignancies diagnosed all over the world, with mortality of 12% and making up to 10% of all cancer cases. The number of gastric cancer cases has been decreasing in Lithuania: the morbidity has decreased about 30% during the last 20 years. Nearly 1000 new cases of gastric cancer are diagnosed every year in Lithuania. There were 3200 patients with gastric cancer at the end of 2004, but the results of their treatment are not sufficient (1,2).

There are discussions about the value of perioperative treatment of gastric cancer during the last years. The US intergroup study INT 0116 in 2001 and UK NCRI MAGIC Trial in 2005 with the better results of combined treatment of gastric cancer provoked the discussion. The total survival in the American study

was 12 months, and in the British study it was 4 months in favour of the combined treatment (3–6). Our attitude toward the neoadjuvant chemotherapy in treating gastric cancer is reserved, and we evaluated our results very carefully before we reached this conclusion (7–10).

We suppose that neoadjuvant treatment of gastric cancer should not be used in the early stages of cancer when optimal surgery could be performed. Gastric cancer and gastroesophageal junction and lower oesophageal cancer should be separated, and the results of the treatment should be assessed separately.

MATERIALS AND METHODS

We present our three studies to stand our position concerning reserved attitude towards neoadjuvant chemotherapy.

Our first study, a randomized study of patients with stage III gastric cancer, was performed in 1980–1990. The patients were divided into 4 groups:

Group I – preoperative chemotherapy + surgery. Regimen consisted of 5-fluorouracil (5-FU) 12 mg/kg IV every second day till total dose of 3.0–3.5 g; cyclophosphan 0.2 g IV every

second day till total dose of 1.0 g; natulan 50 mg *per os* every day till total dose of 0.5 g. There were 70 patients in this group.

Group II – control group – surgery alone, 70 patients.

Group III – surgery + chemotherapy with the same regimen: 5-fluorouracil (5-FU) 12 mg/kg IV every second day till total dose of 3.0–3.5 g; cyclophosphan 0.2 g IV every second day till total dose of 1.0 g; natulan 50 mg *per os* every day till total dose of 0.5 g. 31 patients were in this group.

Group IV – surgery + chemotherapy with the regimen of 5-FU 0.5 g IV every second day till the total dose of 5.0 g. There were 50 patients.

Patients of groups III and IV were not randomized, so the results of their treatment are only of informative character (7).

Our second study – a randomized study of patients with stage III gastric cancer – was carried out in 1996–1999 to assess the value of neoadjuvant chemotherapy. 30 patients were randomized into two groups when stage III gastric cancer was diagnosed preoperatively. Laparoscopy was used for the accuracy of staging. Group I patients received neoadjuvant chemotherapy. All the patients of both groups underwent D2 radical surgical resection and received standard adjuvant chemotherapy. Regimen for neoadjuvant chemotherapy was 5-FU 600 mg/m² IV and leucovorin 30 mg/m² IV day 1–5. Surgery was performed in 10–12 days (8–10).

The third study was not a randomized one to evaluate the results of surgical gastric cancer treatment in 1987–1996. The study included 831 patients (1, 2, 9).

RESULTS

All the patients in the first study of 1980–1990 had stage III gastric cancer. There were 37% of postoperative complications in the first group of patients with neoadjuvant chemotherapy, and mortality rate was 10%. The postoperative morbidity rate in the second control-group of patients was the same, 37%, and mortality constituted 8.5%. The patients of groups III and IV were selected after surgery, so mortality was not evaluated, and morbidity was 29% and 26%, respectively. Morphological evaluation revealed that suboptimal surgery was 72% in groups I and II (group III – 53%, group IV – 57%).

The period of recurrence – disease-free survival – was 19 ± 2 months in group I, 10 ± 1 months in group II, 9 ± 1 months in group III, and 14 ± 2 months in group IV. The difference is statistically significant ($p < 0.05$) (Fig. 1).

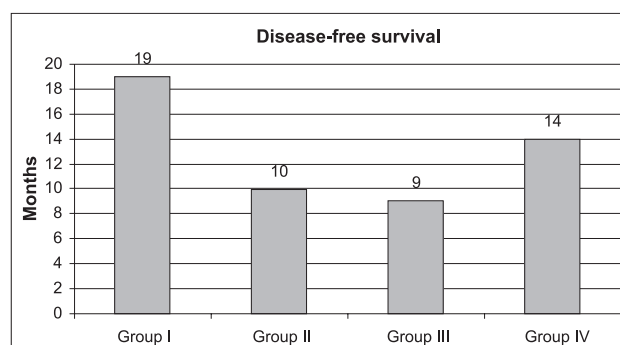


Fig. 1

Three-year survival was 44% in group I, 32% in group II, 45% in group III, and 31% in group IV. The difference is statistically significant ($p < 0.05$).

Five-year survival was 33% in group I, 32% in group II, 33% in group III, and 25% in group IV. The difference is not statistically significant ($p > 0.05$) (Fig. 2).

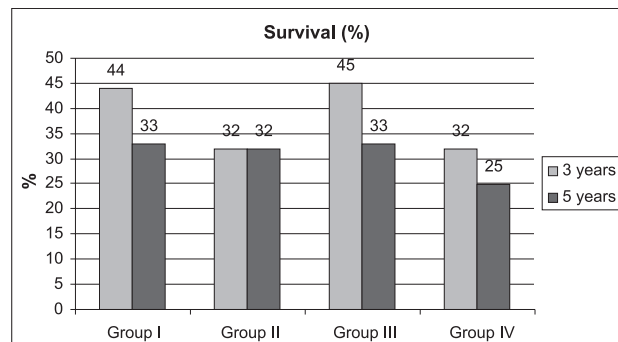


Fig. 2

The second study of 1996–1999 was a randomized study of patients with stage III gastric cancer to assess the value of neoadjuvant chemotherapy. 30 patients were randomized into two groups of 15 patients each, when stage III gastric cancer was diagnosed preoperatively. 128 laparoscopies were performed during the period 1995–1998 for the accuracy of staging gastric cancer, after stage III gastric cancer had been diagnosed by all other methods. 34 patients were randomized into two groups. 19 patients received preoperative chemotherapy, 15 patients underwent surgery. 4 patients were cancelled from group I, as stage II (2 patients) and stage IV (2 patients) was diagnosed postoperatively.

The median age of patients was 65.4 years in group I and 56.5 years in group II. Postoperative morbidity was similar in both groups, 20% and 15%, correspondingly. The most common complications were postoperative pneumonia and wound infection.

Patients in both groups received standard adjuvant chemotherapy postoperatively: three courses of 5-FU 425 mg/m² IV and leucovorin 20 mg/m² IV day 1–5. The median survival was analysed considering the subgroup of stage III: IIIA and IIIB, as the prognosis of stage IIIB was worse (Fig. 3).

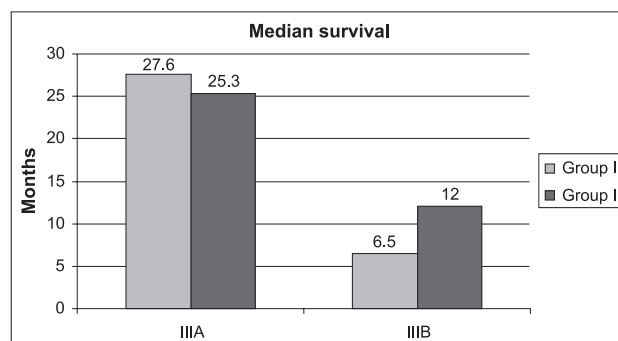


Fig. 3

Two patients in group I, both had stage IIIA gastric cancer, and three patients in group II (IIIA – 2, IIIB – 1) were alive on the last day of the study. The median survival of the patients was

49.5 months in group I and 50.5 months in group II. The difference is not statistically significant ($p > 0.05$).

In our third study we analysed patients after radical surgical treatment in 1987–1996. Patients with stage III gastric cancer received adjuvant chemotherapy – Mayo clinic regimen 5 FU / LV. The morbidity rate was 25%, mortality rate 5%. 5 year survival was 35%. The median survival was 43.2 months.

DISCUSSION

The US intergroup study INT 0116 and UK NCRI MAGIC Trial randomized studies revealed that combination of perioperative chemotherapy and/or chemo radiation with surgical treatment of gastric cancer improves the results of treatment (3–6). Similar results were achieved in our randomized study in 1980–1990; recurrence in the group with preoperative chemotherapy was 10 months later than in the control group. 3-year survival was longer in the first group, 44% vs. 32%, but 5-year survival was the same – 33% vs. 32%. When we compare the results of the treatment of patients who received adjuvant chemotherapy with 5 FU, cyclophosphane and natulane with those of the first group, we make the conclusion that they are similar. Only in 28% of cases surgery was optimal in both groups. We suppose that better treatment results in the group of combined treatment were observed because of chemotherapy when not enough radical surgery was performed (1, 2, 7).

This observation initiated our second study to compare neoadjuvant chemotherapy + surgery + adjuvant chemotherapy with surgery + adjuvant chemotherapy. Only patients with stage III gastric cancer were included into this study. Laparoscopy was used for more accurate staging parallel with other instrumental investigation methods. The interim analysis revealed the same median survival – 49.5 months vs. 50.5 months. The difference is not statistically significant ($p > 0.05$), so this study was discontinued (8–10).

Analysis of standard treatment results (R0 radical resection + adjuvant chemotherapy) revealed 5-year survival of 35% of patients. The median survival was 43.2 months (1).

We have come to the conclusion that the results of treatment of patients with stage III gastric cancer are better in the combined treatment groups, when it is not possible to perform radical resection. When R0 radical resection is performed, neoadjuvant chemotherapy has no influence for survival.

MAGIC study revealed better 3- and 5-year survival in the group with preoperative chemotherapy, 50% vs. 41% and 36% vs. 23% as well as 4 months longer median survival. SWOG 9008/INT 0116 study revealed median survival of patients with combined treatment 35 months vs. 27 months in the surgical group (3–6). Both studies included patients with stage I and II gastric cancer, however, the treatment results were worse than those in our studies where patients with stage III gastric cancer were treated by R0 surgery and adjuvant chemotherapy. We suppose that lower median survival was influenced by the patients with gastroesophageal junction and lower oesophageal cancer. The treatment results of patients with gastroesophageal junction and lower oesophageal cancer are worse compared with other localisation of gastric cancer.

Experts at the 7th international gastrointestinal cancer congress in Barcelona in 2005 drew the conclusion that the treat-

ment results of gastric cancer are not sufficient, and perioperative treatment can improve them (4). We suggest that indications for perioperative treatment should be narrowed. In the early stages of gastric cancer with T1, T2, N0, M0 the value of adjuvant treatment is disputable, and radical R0 resection with D2 type lymphonodectomy is sufficient. Neoadjuvant chemotherapy should be used to achieve down staging and to perform R0 radical resection. Postoperative chemo radiation should be used in such cases when resection is not radical or metastases in lymph nodes exceed 7. We also propose to perform randomized studies and to separate patients with gastric cancer and those with gastroesophageal junction and lower oesophageal cancer.

CONCLUSIONS

1. The value of adjuvant treatment in the early stages of gastric cancer after R0 D2 surgery is disputable.
2. Neoadjuvant chemotherapy should be used to achieve R0 surgery when respectability is impossible without it.
3. Postoperative chemo radiation should be used in the case of suboptimal surgery (R1, R2, and D0) or in the case of optimal R0 surgery with many metastases in the lymph nodes.
4. Patients with early stages of gastric cancer and patients with gastroesophageal junction and lower oesophageal cancer should not be included into prospective studies.

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SKRANDŽIO ADENOKARCINOMOS NEOAJUVANTINIS GYDYMAS – KODĖL MŪSŲ POŽIŪRIS REZERVUOTAS

S a n t r a u k a

Ižanga. INT 0116 2001 m. JAV ir NCRI MAGIC Trial 2005 m. Jungtinės Karalystės studijos pateikė geresnius skrandžio vėžio kombinuoto gydymo rezultatus. Tai sukėlė optimizmo bangą gydant operabilų skrandžio vėžį. Mūsų neoadjuvantinio skrandžio vėžio gydymo patirtis siekia 1980 metus. Deja, mūsų rezultatai nėra tokie optimistiški ir požiūris į perioperacinį skrandžio vėžio gydymą išlieka gana rezervuotas. Ši nuomonė pagrįsta mūsų atliktų tyrimų duomenimis.

Metodologija. Pateikiame trijų mūsų atliktų studijų rezultatus. Pirma – randomizuota studija, atlikta 1980–1990 metais. Buvo tirti pacientai, sergantys III stadijos skrandžio vėžiu ir palygintas gydymas neoadjuvantine chemoterapija ir vien tik operacija. Antros mūsų studijos, atliktos 1996–1999 m., tikslas buvo įvertinti neoadjuvantinės chemoterapijos reikšmę gydant III stadijos skrandžio vėžį. Trečioje studijoje buvo analizuoti radikalaus chirurginio skrandžio vėžio gydymo rezultatai 1987–1996 metais.

Rezultatai. Visi pirmos studijos pacientai sirgo III stadijos skrandžio vėžiu. Pacientai buvo suskirstyti į 4 grupes: I – neoadjuvantinė chemoterapija + operacija, II – tik operacija, III ir IV – operacija bei skirtingo režimo chemoterapija. Neoadjuvantinės chemoterapijos grupėje pooperacinių komplikacijų skaičius – 37%, mirtingumas – 10%. Antroje, chirurginėje, grupėje komplikacijų skaičius tas pats – 37%,

mirtingumas – 8,5%. Laikas iki atkryčio pirmoje grupėje – 19 ± 2 mėn., antroje – 10 ± 1 mėn., trečioje – 9 ± 1 mėn. ir ketvirtoje – 14 ± 2 mėn. ($p < 0,05$). Trejus metus išgyveno 44% I grupės, 32% II, 45% III ir 31% IV grupės pacientų. Skirtumas statistiškai patikimas ($p < 0,05$). Penkerius metus išgyveno 33% I grupės, 32% II, 33% III ir 25% IV grupės pacientų ($p > 0,05$).

1996–1999 m. tirtos dvi ligonių, sirgusių III skrandžio vėžio stadija, grupės. Atsitiktinės atrankos būdu 30 ligonių suskirstyta atitinkamai po 15 į tiriamąją ir kontrolinę grupes. 1995–1998 m. ligoniams buvo atliktos 128 laparoskopijos siekiant prieš operaciją nustatyti skrandžio vėžio stadiją. 19 pacientų skirta priešoperacinė chemoterapija, 15 – tik chirurginis gydymas. Iš 19 ligonių, gavusių priešoperacinę chemoterapiją, tiriamojame grupėje liko 15, nes 2 ligoniams po operacijos diagnozuota II, 2 – IV stadija. Vidutinis tiriamosios grupės ligonių amžius – 65,4 metų, kontrolinės – 56,5. Pooperacinių komplikacijų skaičius abiejose grupėse buvo panašus: I – 20%, II – 15%. Siūlių nelaikymo ar mirties atvejų abiejose grupėse nebuvo. Tiriamosios grupės ligoniai vidutiniškai išgyveno 49,5 mėn., kontrolinės grupės – 50,5 mėnesio. Skirtumas statistiškai nereikšmingas ($p > 0,05$).

Trečia studija apėmė 1987–1996 m. Jos metu ligoniai gydyti radikaliai. III stadijos skrandžio vėžiu sergantiems pacientams po operacijos skirta adjuvantinė chemoterapija 5-Fu/LV Mayo klinikos režimu. Pooperacinės komplikacijos stebėtos 25% operuotų pacientų, pooperacinis mirštamumas – 5%. Penkerius metus išgyveno 35% šios grupės pacientų. Vidutinė gyvenimo trukmė – 43,2 mėnesio.

Įvertinus mūsų darbo rezultatus peršasi išvada, kad neoadjuvantinė chemoterapija efektyvi tuomet, kai operacija nėra pakankamai radikali.

Išvados. Atlikus R0, D2 rezekciją ligoniams, sergantiems ankstyvų stadijų skrandžio vėžiu, papildomo gydymo nauda abejotina. Neoadjuvantinė chemoterapija turėtų būti taikoma abejojant operacijos radikalumu. Pooperacinis chemospindulinis gydymas taikytinas pacientams po suboptimalios rezekcijos (R1, R2, D0) ar po optimalios operacijos radus daug metastazinių limfmazgių. Į prospektyvinius tyrimus netikslinga įtraukti ankstyvomis ir vėlyvomis skrandžio vėžio stadijomis, taip pat kardioezofaginės dalies ir stemplės apatinio trečdžio navikais sergančius pacientus.

Raktažodžiai: adenokarcinoma, neoadjuvantinis gydymas, priešoperacinis gydymas