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Gastric cancer

Rak żołądka

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S u m m a r y

Gastric cancer stall remains a common and highly fatal disease. Despite potentially curative resection of stomach cancer, majority of patients die of disease relapse. Randomized study in the Western world failed to show improvement in survival with extended lymph node dissection (D2 lymphadenectomy). The high recuurence rate makes gastric cancer a disease difficult to cure by surgery alone. In order to improve the survival different perioperative modalities are assessed. Results from the randomized phase III MAGIC trial and French FFCD trial support the idea of preoperative chemotherapy. Neoadjuvant 5-fluorouracil/cisplatin based chemotherapy is now a standard of care in many European countries for locally advanced gastric cancer. Neoadjuvant chamoradiation still remains experimental. As against neoadjuvant chemoradiation, adjuvant chemoradiation is considered to be a standard therapy in the USA and some European countries. Trastuzumab is recommended in patients diagnosed with metastatic cancer of the stomach and of gastro-esophageal junction who did not earlier receive anti-cancer therapy due to disseminated disease and whose tumor cells show HER2 overexpression.

Key words: gastric cancer, perioperative treatment, chemotherapy, radiotherapy, molecularly targeted therapy

S t r e s z c z e n i e

Wyniki leczenia raka żołądka są niezadowalające. Zwiększenie zakresu limfadenektomii nie prowadzi do poprawy wyników. Poprawy wyników leczenia poszukuje się w leczeniu okołooperacyjnym, tj. kojarzeniu leczenia chirurgicznego z radioterapią, chemioterapią lub chemioradioterapią. Ze względu na znaczną toksyczność leczenia, jak również brak dobrze przeprowadzonych badań III fazy, przedoperacyjna chemioradioterapia raka żołądka nadal pozostaje metodą eksperymentalną, natomiast przedoperacyjna chemioterapia na podstawie badań MAGIC i FFCD rekomendowana jest jako standard postępowania w Wielkiej Brytanii i większości pozostałych krajów europejskich. W odróżnieniu od przedoperacyjnej chemioradioterapii, uzupełniająca chemioradioterapia uznawana jest za standard postępowania w Stanach Zjednoczonych Ameryki i niektórych krajach europejskich. W leczeniu rozsianej choroby nowotworowej trastuzumab w skojarzeniu z chemioterapią stanowi nową opcję terapeutyczna u chorych, u których stwierdzono w komórkach guza nadekspresję HER2.

Słowa kluczowe: rak żołądka, leczenie okołooperacyjne, chemioterapia, radioterapia, terapia molekularnie ukierunkowana

Although most countries around the world report decreased incidence of gastric cancer (i.e. tumors located distally to the gastroesophageal junction), the disease continues to pose a significant epidemiological problem in Poland. Gastric cancer incidence and mortality rates in Poland among both men and women remain at similar levels (in 2007, standardized incidence and mortality ratios in men were 12.8/100,000 and 13.11/100,000, respectively, and in women 4.87/100,000 and 4.87/100,000, respectively), which makes the incidence and mortality ratio oscillate around 1, and in the population of women it is exactly equal to 1(1). This indicates ineffectiveness of treatment and poor prognosis for patients with this disease. Five-year survival rates are highly unsatisfactory.

In Poland, the relative 5-year survival rates in male and female populations are 14.9% and 18.2%, respectively, and 16.1% for both populations combined (2). These results are worse than in other European countries. The mean 5-year survival in women and men estimated for patients diagnosed between 2000 and 2002 in Europe based on the EUROCARE-4 study is 23.4% (1).

The reasons behind poor treatment results include: a high postoperative local or nodal recurrence rate of 30-87%, a high postoperative metastasis rate of 20-66%, limited effectiveness of earlier treatments, limited knowledge of molecular biology of gastric cancer. The WHO classification distinguishes the following types of gastric cancer: a high-, moderate-, and low-grade adenocarcinoma with its two subtypes: tubular and papillary, mucinous carcinoma, squamous carcinoma; adenosquamous carcinoma, poorly differentiated carcinoma, mucocellular carcinoma and nondifferentiated carcinoma.

The most recent staging classification of gastric cancer (7th edition) published by the International Union Against Cancer has introduced changes to the T and N descriptors (3).

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ*: intraepithelial tumor without invasion of the lamina propria
T1 Tumor invades lamina propria, muscularis mucosae or submucosa
T1a Tumor invades lamina propria or muscularis mucosae
T1b Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
T4 Tumor invades serosa (visceral peritoneum) or adjacent structures
T4a Tumor invades serosa (visceral peritoneum)
T4b Tumor invades adjacent structures

Regional Lymph Nodes (N)

NX Regional lymph node(s) cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1-2 regional lymph nodes
N2 Metastasis in 3-6 regional lymph nodes
N3 Metastasis in seven or more regional lymph nodes
N3a Metastasis in 7-15 regional lymph nodes
N3b Metastasis in 16 or more regional lymph nodes

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis

Histologic Grade (G)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Anatomic stage/Prognostic groups

Stage	Primary Tumor (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
	T1	N1	M0
IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
IIIB	T4b	N0, N1	M0
	T4a	N2	M0
	T3	N3	M0
IIIC	T4a	N3	M0
	T4b	N2,N3	M0
IV	Any	Any N	M1

The main treatment for gastric cancer patients remains to be surgery, the extent of which depends on the clinical stage and location of the disease. Depending on tumor location, total or subtotal gastrectomy is performed. D2 lymphadenectomy (removal of D1 lymph nodes: located along the lesser and greater gastric curvatures plus the celiac-axis, the common hepatic artery, the splenic artery, the splenic hilum, the left hepatic artery) and a minimum of 25 lymph nodes in the sample is the established standard of treatment.

Theoretically, improvement in gastric cancer treatment results should be sought via improving surgical treatment results or using adjuvant or neoadjuvant treatment. Unfortunately, increasing the extent of lymphadenectomy from D1 to D2 does not result in an increased 5-year survival rate in operated patients. **Moreover, D2 lymphadenectomy is associated with a higher rate of complications and postoperative deaths.** Therefore, seeking the options for improving treatment results in perioperative treatments seems to be rational.

Neoadjuvant treatment in gastric cancer

Studies on neoadjuvant treatment include both radiotherapy and chemotherapy, as well as both of these methods combined – chemoradiotherapy.

Neoadjuvant radiotherapy

A randomized study evaluating the effectiveness of neoadjuvant radiotherapy in comparison with surgical treatment alone by Zhang et al. showed a 10% increase in 5-year survival rate in the group receiving preoperative radiotherapy in comparison with the group who underwent surgical treatment only. The 5-year survival rates were 30 and 20%, respectively (4). Moreover,

the group receiving radiotherapy showed a decrease in local recurrence rate.

In a randomized study by Skoropad et al., a group of 152 patients underwent surgical treatment preceded by 20 Gy radiotherapy or surgical treatment alone. After a 20-year follow-up the authors did not detect any difference in survival between the two study groups (5).

Neoadjuvant chemotherapy

The first results of randomized studies on the role of neoadjuvant chemotherapy have been discouraging. A Dutch study comparing survival rates between two groups of patients who either received 4 preoperative courses of FAMTX chemotherapy (5-fluorouracil, doxorubicin and methotrexate) or were treated with surgery alone found increased median survival (30 months) among patients who underwent only a surgical procedure, compared to the group of patients receiving combined therapy (18 months) (6). Moreover, the resectability rates were similar in both study groups. What is noteworthy is that the study was performed in a small patient population (59 patients). A Japanese study evaluating the effectiveness of neoadjuvant chemotherapy with the UFT (tegafur + uracil) regimen revealed a beneficial effect of chemotherapy on improving survival, but only in patients with stage II and stage III disease (7). Based on a result analysis of 4 studies, Wu et al. revealed a lack of effect of neoadjuvant chemotherapy on survival (8).

The first randomized clinical study that proved the effectiveness of preoperative chemotherapy in patients with gastric cancer was the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) study comparing perioperative treatment (3 courses of preoperative ECF (epirubicin, 5-FU, cisplatin) chemotherapy and 3 courses of postoperative chemotherapy with the same regimen) in combination with surgery with surgical treatment alone. The group of patients receiving preoperative chemotherapy showed a 13% increase in overall 5-year survival. The 5-year survival rates in the group receiving combination treatment and in the group treated only surgically were 36 and 23%, respectively (9). The MAGIC study has been criticized for inadequate patient qualification for neoadjuvant treatment. Neither the peritoneal fluid cytology nor the endoscopic ultrasound (EUS) was routinely performed.

Another randomized study on the role of preoperative chemotherapy, albeit published only in the form of a summary, is the Fédération Francophone de la Cancérologie Digestive (FFCD) study (10). This study randomized patients to receive either surgical treatment preceded by chemotherapy with cisplatin and 5-fluorouracil or surgical treatment as the sole treatment method. The group of patients receiving combination therapy was found to have a higher proportion of R0 resections than the group treated with surgery only. This proportion in the two groups was 84% and 73%, respectively. **Also, the overall 5-year survival rate was higher in the group receiving combination treatment.** The 5-year survival rates in the two groups were 38 and 24%, respectively.

Due to significant treatment toxicity, as well as a lack of well-conducted phase III studies, neoadjuvant chemoradiotherapy in gastric cancer patients remains an experimental method, however, based on the results of MAGIC and FFCD studies, preoperative chemotherapy is recommended as a standard procedure in the UK and in most of the other European countries (11).

Adjuvant radiotherapy

Adjuvant radiotherapy in gastric cancer patients includes the use of intraoperative radiotherapy (IORT) and teleradiotherapy.

IORT allows:

- improvement of the therapeutic index
- reduction of the irradiated area
- protection of normal radiation-sensitive structures
- an increase in therapeutic dose

As far as adjuvant therapy in gastric cancer is concerned, IORT causes a decrease in the risk of local recurrences by approximately 50%, however, there is no effect on patient survival. Moreover, IORT is associated with a high rate of vascular toxicity (3-12%).

A study by Hallisey et al. evaluating three treatment methods; surgery, surgery in combination with postoperative chemotherapy, and surgery in combination with postoperative radiotherapy did not show superiority of any of these methods in improving survival, nonetheless adjuvant radiotherapy showed an over two-fold decrease in the local recurrence rate in comparison with surgery alone (12).

Adjuvant chemotherapy

Studies on the role of adjuvant chemotherapy have yielded contradictory results. Two extremes can be observed. One extreme comprises Asian, mainly Japanese, papers documenting a beneficial effect of chemotherapy on survival, and the other extreme comprises western papers indicating that chemotherapy has marginal or no effect on improving survival. These discrepancies may be explained both with a different biology of the gastric cancer, and generally lower clinical stage of the disease in the Asian population as well as different gastric cancer classifications, causing qualification to treatment among patients who according to other classifications (WHO, American) do not require such treatment (early disease). Moreover, randomization of patients in Japanese studies raises significant doubts. In the 1970s, patients randomized to receive adjuvant therapy had undergone either a radical or palliative procedure. For example, Fujimoto et al. who evaluated the role of adjuvant 5-fluorouracil used in combination with FT-207, a 5-fluorouracil analog, included 22 patients who had undergone a palliative procedure into the group of 107 patients who had undergone a radical procedure (13). Median survival values were compared

with the control group i.e. patients who had undergone surgery only. Also, an addition of another chemotherapy agent of similar effects to the chemotherapy regimen raises serious doubts. An increased median survival was observed only in the group operated radically who received combination treatment. A study by Nakajima et al. presented a similar problem with the inclusion of patients undergoing palliative procedures (14). The patients received either surgical or combination treatment, with mitomycin C monotherapy as adjuvant treatment. That study did not show any difference in survival between the two groups. In another study published 9 years later, Nakajima et al. demonstrated that adjuvant chemotherapy with uracil and tegafur increases median survival in the group with stage $T_2N_{1-2}M_0$ disease (15). Sakuramoto et al. demonstrated a 10% increase in 3-year survival rate in the group receiving adjuvant S-1 therapy in comparison to patients treated with surgery alone. The 3-year survival rates in the two groups were 80.1% and 70.1%, respectively (16). It is noteworthy, however, that due to the complex pharmacokinetics and pharmacodynamics of this drug (it is composed of 3 elements) its effectiveness in a non-Asian population may be different. Thus, a similar study needs to be conducted in a non-Asian population before definite conclusions can be drawn.

Contrary to the Asian authors, most western authors deny any effects of chemotherapy on survival.

Adjuvant chemoradiotherapy

Macdonald et al. reports that the use of adjuvant chemoradiotherapy increased the median survival by 9 months. Median survival in patients treated with surgery only and in those receiving combination treatment was 27 and 36 months, respectively. Also, an increase in 3-year survival rate from 31 to 48% was observed in the group receiving combination treatment (17). However, that study was criticized due to significant toxicity rates, with 3 deaths, grade 3 toxicity in 41% patients and grade 4 toxicity in 32% patients. Moreover, the majority of patients underwent either D0 (54% patients) or D1 (36% patients) lymphadenectomy, with D2 lymphadenectomy performed only in 10% patients. Thus, it can be stated that the role of adjuvant chemoradiotherapy in D2 lymphadenectomy patients is not clear and that the observed increase in survival in the combination treatment group is a result of compensating for suboptimal surgical treatment. A paper by Dikken et al. confirms the doubts as to the role of adjuvant chemoradiotherapy in D2 lymphadenectomy patients (18). The authors show that adjuvant chemoradiotherapy significantly reduces the local recurrence rate in patients who underwent D1 lymphadenectomy in comparison with those who underwent surgery only (5 *vs.* 17%, $P = 0.0015$), however, no statistically significant difference was found between D2 lymphadenectomy in combination with adjuvant chemoradiotherapy in comparison with surgery alone (local recurrence rates were 2 and 8%, respectively).

Despite these limitations, adjuvant chemoradiotherapy is considered the standard treatment in the USA and in some European countries.

Indications for adjuvant chemoradiotherapy in gastric cancer are:

- infiltration of the entire wall of the stomach (pT3, pT4),
- lymph node ratio ≥ 0.2 (20%) (the number of positive metastatic lymph nodes to the number of examined lymph nodes),
- high-grade disease (G3),
- tumor cell emboli present in blood vessels,
- nerve trunk infiltration,
- adipose tissue infiltration.

Palliative treatment

Until recently, gastric cancer was considered to be a tumor of low chemosensitivity, causing scepticism, to say the least, towards the usefulness of chemotherapy in the treatment of this disease. Currently, chemotherapy is the routine palliative treatment in gastric cancer. **The development of palliative chemotherapy in gastric cancer can be divided into several stages:**

1) **a period of monotherapy (mainly with fluorouracil or mitomycin),** which allowed only a partial response to treatment without apparent effect on survival,

2) **a period of polychemotherapy with non-cisplatin-based regimens (e.g. the FAM regimen, involving fluorouracil, doxorubicin, and mitomycin),** helping to achieve even complete regressions without clear effects on survival. This period saw the introduction of the FAMTX regimen based on fluorouracil, doxorubicin, calcium folate, and high-dose methotrexate. In comparison to FAM, the FAMTX regimen provided a higher response rate (41 vs. 9%) and an increased median survival (42 weeks vs. 29 weeks). Due to these better treatment results, the FAMTX regimen came to be perceived as the golden standard in gastric cancer chemotherapy in the early 1990s. The necessity to monitor serum methotrexate levels, which was an obstacle for many oncology centers, proved to be a drawback in the use of this regimen.

3) **a period of polychemotherapy with cisplatin-based regimens** with a documented potential for improved survival. In the USA, a 2-agent FUP regimen (cisplatin and fluorouracil) was used and in Europe, a 4-agent PELF regimen (cisplatin, epirubicin, fluorouracil, calcium folate) or a 3-agent EAP regimen (cisplatin, etoposide, doxorubicin) was used. These chemotherapy regimens provided response rates of 37-72% and median survival of 4-7 months. What needs to be emphasized, is that despite its significant effectiveness the EAP regimen was characterized by a high toxicity, especially towards bone marrow. The introduction of the ECF regimen, which became the next golden standard in gastric cancer therapy in Europe after FAMTX, was a significant breakthrough in palliative cisplatin-based chemo-

therapy of this disease. This new regimen, introduced in the Royal Marsden Hospital, UK, was based on Lokich's (1981) idea regarding continual exposure of colorectal cancer cells to fluorouracil. The ECF regimen is based on continuous multiple-week infusions of fluorouracil and the administration of cisplatin and epirubicin. In comparison to FAMTX, the ECF regimen was characterized by a higher response rate (45 *vs*. 21%), increased median time to progression (7.4 months *vs.* 3.4 months) and increased median overall survival (8.9 months *vs.* 5.7 months).

4) **the current period of new drug development, including target therapy**. New agents used in gastric cancer chemotherapy include: docetaxel, oxaliplatin, irinothecan, capecitabine, and S-1. A study comparing DCF regimen (docetaxel, cisplatin, and fluorouracil) to the already mentioned FUP regimen (cisplatin, fluorouracil) showed DCF to provide a higher response rate (39% vs. 23%), an increased median time to progression (5.2 months *vs*. 3.7 months), and an increased median overall survival (10.2 months *vs*. 8.5 months).

Capecitabine has clinical effectiveness similar to that of fluorouracil, with fewer side effects, what is more, capecitabine is administered orally. This may constitute a useful alternative to fluorouracil for some patients with advanced gastric cancer. The drug changes into its active form, fluorouracil, only after being absorbed by cells in the division phase. An enzyme thymidine phosphorylase, catalising the final conversion of capecitabine to fluorouracil is expressed to a greater extent in rapidly dividing cancer cells than in the surrounding healthy tissue. The effectiveness of capecitabine in gastric cancer chemotherapy was proven in two studies ML17032 and REAL2 (in combination with oxaliplatin).

S-1 is a novel oral agent containing 3 pharmacological components: tegafur, a prodrug of 5-fluorouracil, gimeracil, an inhibitor of the enzyme dihydropyrimidine dehydrogenase (DPD), and oteracil (potassium oxonate), an agent reducing gastrointestinal side effects. The SPIRITS trial comparing a 2-agent regimen (S-1 plus cisplatin) with S-1 monotherapy showed an increased median survival in patients receiving the 2-agent regimen in comparison to monotherapy (13 months *vs*. 11 months). Also, the median progression-free survival was significantly greater in the group treated with S-1 plus cisplatin versus the other group (6 months *vs*. 4 months).

Palliative chemotherapy increases survival. Although the results of the most recent phase III studies indicate the effectiveness of docetaxel, oxaliplatin and capecitabine, the median overall survival rates remain highly unsatisfactory. Gastric cancer belongs to the type of neoplasm with overexpression of many factors taking part in signal transduction, which creates an opportunity for the evaluation and possible use of novel molecularly targeted drugs. For example, overexpression of HER2 can be found in approximately 22% gastric cancer patients. Adequate HER2 assessment plays an important role in disease course prognosis and in selecting the right treatment. Currently, there are two main HER2 assessment methods: immunohistochemistry (IHC) assessing overexpression of HER2 receptor, or the number of receptor molecules on cell surface, and fluorescent in situ hybridization (FISH), helping to determine the number of gene copies responsible for creating and function of a HER2 receptor (there are 2 copies of that gene in a normal cell, whereas in a neoplastic cell there may be much more). The IHC staining scale includes 4 degrees: 0 (negative for HER2 overexpression), 1+ (negative for HER2 overexpression), 2+ (inconclusive HER2 overexpression), and 3+ (positive for HER2 overexpression). Generally, the result of FISH staining is determined as positive when the ratio of the number of copies of the HER2 gene in a neoplastic cell to the number of copies of chromosome 17 is greater or equal 2. HER2 overexpression is found mainly in intestinal-type tumors. Also, it is more frequently associated with cancers of the gastro-esophageal junction, than of the body of the stomach. Prognosis in patients with HER2-positive tumors is poorer than that in patients with HER2-negative tumors, however, paradoxically, HER2 overexpression allows the use of molecularly targeted treatment (target therapy). **Trastuzumab is the first biological drug (targeted therapy) that has shown benefits in the form of increased median overall survival.** In the ToGA study, presented at the ASCO conference in the USA in 2009, patients who received chemotherapy (fluorouracil or capecitabine and cisplatin) in combination with trastuzumab achieved increased median overall survival in comparison to the group receiving chemotherapy only (13.5 months vs. 11.1 months). In the subgroup with HER2 overexpression at IHC2+/FISH+ or IHC3+ treated with chemotherapy and trastuzumab or chemotherapy alone, the median survival was 16 and 11.8 months, respectively. Thus, trastuzumab in combination with chemotherapy is a new therapeutic option in the patients with advanced gastric cancer with HER2 overexpression (19). In the complete paper, published in 2010 the median survival in patients receiving chemotherapy plus trastuzumab and those receiving chemotherapy alone was 13.8 months and 11.1 months, respectively (20).

Trastuzumab is recommended in patients diagnosed with metastatic cancer of the stomach and of the gastro-esophageal junction who did not earlier receive anti-cancer therapy due to disseminated disease and whose tumor cells show HER2 overexpression score of IHC 2+ confirmed with FISH+ results or a score of IHC 3+.

Therefore, the degree of HER-2 protein expression or the amplification of its gene must be assessed in patients with gastric cancer, as well as tumors of the gastro-esophageal junction, and in the case of overexpression of this protein or gene amplification, the use of trastuzumab with cisplatin-based and fluoropyrimidine-based chemotherapy is recommended.

BIBLIOGRAPHY

1. Didkowska J, Wojciechowska U, Zatoński W: Nowotwory złośliwe w Polsce 2007 roku. Centrum Onkologii-Instytut im. M. Skłodowskiej-Curie w Warszawie. Warszawa 2009 r.
2. Wojciechowska U, Didkowska J, Zatoński W: Wskaźniki przeżyć chorych na nowotwory złośliwe w Polsce w latach 2000-2002. Centrum Onkologii-Instytut im. Marii Skłodowskiej-Curie. Warszawa 2009.
3. Sobin L, Gospodarowicz M, Wittekind C: UICC TNM Klasyfikacja nowotworów złośliwych. Wyd. 7. Via Medica 2010; 58-61.
4. Zhang ZX, Gu XZ, Yin WB et al.: Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of adenocarcinoma of gastric cardia (AGC) – report on 370 patients. Int J Radiat Oncol Biol Phys 1998; 42: 929-934.
5. Skoropad V, Berdov B, Zagrebin V: Concentrated preoperative radiotherapy for resectable gastric cancer: 20-years follow-up of a randomized trial. J Surg Oncol 2002; 80: 72-78.
6. Hartgrink HH, van de Velde CJ, Putter H et al.: Neo-adjuvant chemotherapy for operable gastric cancer: long term results of the Dutch randomised FAMTX trial. Eur J Surg Oncol 2004; 30: 643-649.
7. Nio Y, Koike M, Omori H et al.: A randomized consent design trial of neoadjuvant chemotherapy with tegafur plus uracil (UFT) for gastric cancer – a single institute study. Anticancer Res 2004; 24: 1879-1887.
8. Wu AW, Xu GW, Wang HY et al.: Neoadjuvant chemotherapy versus none for respectable gastric cancer. Cochrane Database Syst Rev 2007; (4): CD005047.
9. Cunningham D, Allum WH, Stenning SP et al.: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 335: 11-20.
10. Boige V, Pignon J, Saint-Aubert B et al.: Final results of a randomized trial comparing preoperative 5-fluorouracil (F)/cisplatin (P) to surgery alone in adenocarcinoma of the stomach and lower esophagus (ASLE): FNLCC ACCORD07-FFCD 9703 trial. J Clin Oncol 2007; 25: 4510.
11. Okines A. Verheij M, Allum W et al.: Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 (Suppl. 5): 50-54.
12. Hallisey MT, Dunn JA, Ward LC et al.: The second British Stomach Cancer Group Trial of adjuvant radiotherapy or chemotherapy in respectable gastric cancer: five-year follow-up. Lancet 1994; 343: 1309-1312.
13. Fujimoto S, Akao T, Itoh B et al.: Protracted oral chemotherapy with fluorinated pyrimidines as an adjuvant to surgical treatment for stomach cancer. Ann Surg 1977; 185: 462-466.
14. Nakajima T, Fukami A, Ohashi I et al.: Long-term follow-up study of gastric cancer patients treated with surgery and adjuvant chemotherapy with mitomycin C. Int J Clin Pharmacol Biopharm 1978; 16: 209-216.
15. Nakajima T, Kinoshita T, Nashimoto A et al.: Randomized controlled trial of adjuvant uracil-tegafur versus surgery alone for serosa-negative, locally advanced gastric cancer. Br J Surg 2007; 94: 1468-1476.
16. Sakuramoto S, Sasako M, Yamaguchi T et al.: Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007; 357: 1810-1820.
17. Macdonald JS., Smalley SR., Benedetti J et al.: Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001; 345: 725-730.
18. Dikken JL, Jansen EPM, Cats A et al.: Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer. J Clin Oncol 2010; 28: 2430-2436.
19. Van Cutsem E, Kang Y, Chung L et al.: Efficacy results from the ToGA trial: a phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer. J Clin Oncol 2009;27 (June suppl.), No 18S, abstract LBA 4509.
20. Bang YJ, VanCutsem E, Feyereislova A et al.: Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomized controlled trial. Lancet 2010; 376 (9742): 687-697.

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