

# Comparison of International Guidelines on the Accompanying Therapy for Advanced Gastric Cancer: Reasons for the Differences

Katrin Bauer, Marcel Schroeder<sup>1</sup>, Franz Porzsolt<sup>2</sup>, and Doris Henne-Bruns<sup>1</sup>

*Department for General, Visceral, Vascular, Thoracic and Pediatric Surgery of the Kempten Clinic, Kempten,*

*<sup>1</sup>Department for General and Visceral Surgery of the Ulm University Clinic, Ulm,*

*<sup>2</sup>Working Group "Healthcare Research" at the Department for General and Visceral Surgery of the Ulm University Clinic, Ulm, Germany*

The purpose of this study was to determine if international guidelines differ in their recommendations concerning additive therapy for advanced, but potentially curable, gastric cancer. A systematic search of the English and German literature was conducted in the databases Medline, Cochrane Database, Embase, and PubMed. The search terms used were 'guidelines gastric cancer,' 'guidelines stomach cancer,' and 'Leitlinien Magenkarzinom.' Six different guidelines published after January 1, 2010, in which the tumors were classified according to the seventh edition of the TNM system (2010), were identified. Although the examined guidelines were based on the same study results, their recommendations concerning accompanying therapy for gastric cancer differ considerably. While perioperative chemotherapy is recommended in Germany, Great Britain, and large parts of Europe, postoperative adjuvant radiochemotherapy or perioperative chemotherapy is recommended in the USA and Canada. In Japan, postoperative adjuvant chemotherapy is recommended. The results of identical studies were interpreted differently in different countries. Since considerable effort is required for each country to separately test relevant studies for their validity and suitability, an international cooperation could simplify the creation of a common basis for guidelines and contribute to improved comparability of international guidelines.

**Key Words:** Guidelines; Gastric cancer; Lower esophageal cancer; Cancer of the esophagogastric junction; Perioperative therapy

## Introduction

### 1. Gastric cancer

Tumors of the upper gastrointestinal tract are among the most common malignancies. Approximately 700,000 people die annually of gastric cancer worldwide.<sup>1</sup>

Fifteen years ago, the 5-year survival rate for advanced gastric

cancer was approximately 25% in Europe.<sup>2</sup> The current prognosis for 5-year survival is 25% to 30% if perioperative, preoperative, and postoperative (radio-) chemotherapy protocols are administered.

### 2. The importance of guidelines

Between 400,000 and 1 million controlled studies are carried out internationally each year. This large volume of studies complicated the extraction of the necessary information for any study/research. Guidelines are designed to facilitate medical decision-making within the framework of efficient patient treatment and are fundamental components of quality assurance and management. They must include external scientific knowledge to be able to serve as reliable bases for physician and patient decision-making. This requires systematic research and evaluation of the literature on the different indications. The methodical quality of the studies on

Correspondence to: **Katrin Bauer**

Department for General, Visceral, Vascular, Thoracic and Pediatric Surgery of the Kempten Clinic, Westendstrasse 9, 87439 Kempten, Germany

Tel: +49-831-9606074, Fax: +49-831-83294

E-mail: [katrin\\_joerg@gmx.de](mailto:katrin_joerg@gmx.de)

Received February 12, 2015

Revised March 17, 2015

Accepted March 17, 2015

© This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

which guidelines are based is referred to as the ‘level of evidence,’ as shown in Table 1.<sup>3-5</sup>

After analyzing the evidence, concrete guideline recommendations are derived from the literature and assigned graduated recommendations. Potential conflicts of interest must be disclosed. Guidelines should be regularly revised and the duration of their validity provided.<sup>5</sup>

Since the beginning of the 1990s, specialist organizations in different countries have developed guideline programs to ensure and improve the provision of healthcare. The USA, Canada, New Zealand, and Scotland were among the first countries to develop guidelines. In Germany, guidelines have been developed since 1993.

### 3. Purpose of this study

The purpose of this study was to determine if international

**Table 1. Levels of evidence according to the methodical quality of studies**

Level	Methodical quality of study
1a	Systematic reviews of randomized controlled trials
1b	Individual randomized controlled trials
1c	All-or-none randomized controlled trials
2a	Systematic reviews of cohort studies
2b	Individual cohort study or low-quality randomized controlled trial
2c	Outcomes research
3a	Systematic review of case-control studies
3b	Individual case-control study
4	Case series
5	Expert opinion

**Table 2. Results of systematic literature search**

Country	Organization	Title	Year
Germany <sup>6</sup>	German Society for Digestive and Metabolic Diseases e.V. (DGVS)	S3 Guideline Gastric Cancer Diagnosis and Therapy of Adenocarcinomas of the Stomach and Esophagogastric Junction	2011
Great Britain (UK) <sup>7</sup>	Department of Surgery, Royal Marsden National Health Service Foundation Trust, London, UK	Guidelines for the Management of Esophageal and Gastric Cancer	2011
Europe <sup>8</sup>	European Society for Medical Oncology	Gastric Cancer: European Society for Medical Oncology Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	2013
USA <sup>9</sup>	National Comprehensive Cancer Network	Gastric Cancer	2014
Canada <sup>10</sup>	Alberta Health Services	Gastric Cancer	2013
Japan <sup>11</sup>	Japanese Gastric Cancer Association	Japanese Gastric Cancer Treatment Guidelines	2010

DGVS = Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten.

guidelines differ in their recommendations for an accompanying therapy for advanced, but potentially curable, gastric cancer.

## Materials and Methods

For the selection of the guidelines we made some inclusion criteria to choose them. The guidelines must be available in English or German and based on scientific literature. To guarantee that the content and time interval of the guidelines were comparable, only guidelines published after January 1, 2010, with tumor classification according to the seventh edition of the TNM system (2010) were included.

The systematic literature search was conducted with Ovid. The databases Medline, Cochrane Database, Embase, and PubMed were examined. The search terms used were ‘guidelines gastric cancer,’ ‘guidelines stomach cancer,’ and ‘Leitlinien Magenkarzinom.’ The following websites, medical institutions, and specialist societies were also evaluated: [www.leitlinien.de](http://www.leitlinien.de), [www.AWMF.org](http://www.AWMF.org), [www.g-i-n.net](http://www.g-i-n.net), and [www.guideline.gov](http://www.guideline.gov).

Using this method, we identified six different guidelines (Table 2).<sup>6-11</sup>

## Results

The results of an examination of the therapeutic recommendations from the assessed guidelines are shown below.

The German S3 guidelines recommend operating on all potentially resectable tumors (T1~T4). Category T1 tumors should only be treated operatively. Perioperative chemotherapy can be administered for T2 tumors. Perioperative chemotherapy should be admin-

istered for localized uT3 or resectable uT4a gastric cancer and adenocarcinomas of the esophagogastric junction. Adenocarcinomas of the esophagogastric junction require a perioperative chemotherapy or a perioperative radiochemotherapy. A D2 lymphadenectomy is the standard surgical therapy with curative intention.

The British guidelines of the Department of Surgery, Royal Marsden National Health Service Foundation Trust recommend surgical treatment for resectable gastric cancers. Perioperative chemotherapy is the standard accompanying therapy. Postoperative adjuvant radiochemotherapy can be administered if no preoperative chemotherapy was administered or if surgical tumor reduction was insufficient. A D2 lymphadenectomy is standard surgical therapy with curative intention.

The guidelines of the European Society for Medical Oncology (ESMO) recommend surgical resection for T1b to T3 tumors. A D2 lymphadenectomy is standard for surgical therapy with curative intention. Perioperative chemotherapy is recommended for tumor stages >T1N0.

The American guidelines of the National Comprehensive Cancer Network (NCCN) recommend surgical treatment for all resectable gastric cancers of stages T1 to T4 without metastases in other organs. Regardless of the presence of lymph node metastases, perioperative chemotherapy or postoperative adjuvant radiochemotherapy should be administered for localized gastric cancers. Preoperative radiochemotherapy is recommended for carcinomas of the esophagogastric junction. However, postoperative adjuvant chemotherapy is only recommended for patients who underwent D2 lymphadenectomy, which is the standard surgical treatment with curative intention.

The Canadian guidelines of the Alberta Health Services also recommend surgical removal of all resectable gastric cancers without metastases in other organs. T1 tumors without lymph node metastases require only surgical resection. T2 tumors without lymph node metastases and T1 tumors with lymph node metastases to one or two local lymph nodes should receive postoperative adjuvant radiochemotherapy in addition to surgical resection. All other operable gastric cancers without metastases in other organs should be treated with postoperative adjuvant radiochemotherapy or perioperative chemotherapy. D1 lymphadenectomy is the standard surgical treatment with curative intention.

The Japanese guidelines of the Japanese Gastric Cancer Association (JGCA) recommend surgical treatment of all resectable gastric cancers without metastases in other organs. T1 and T2 tumors without lymph node metastases and T1 tumors with metastasis in

one or two local lymph nodes require no accompanying therapy. Advanced stage T3 and T4 tumors require postoperative adjuvant chemotherapy following tumor resection. D1 lymphadenectomy should be performed for T1 tumors without lymph node metastases. A modified D2 lymphadenectomy is the standard procedure for more extensive gastric tumors resected with curative intention.

Table 3 provides an overview of the recommendations of different guidelines for accompanying therapy for advanced gastric cancers.

Due to the inhomogeneity of therapy guidelines, we examined the scientific data on which the various guidelines are based by evaluating the literature.

## 1. Literature on which the German guidelines are based

Recommendations for perioperative chemotherapy for advanced gastric cancer were based on three studies. When the commission created this guideline in 2010, only the British MAGIC study was available in its entirety. This study was considered a pioneer in perioperative chemotherapy. Cunningham et al.<sup>12</sup> reported an improvement of 12.5% in the 5-year survival rate.

Their results were confirmed in the French ACCORD study.<sup>13</sup> A third study from Germany (EORTC) also verified a benefit in patients receiving perioperative chemotherapy.<sup>14</sup>

Only abstracts of the two latter studies were available at the time the guidelines were created, resulting in an evidence level of Ib (no meta-analyses).

The 66 guideline experts did not reach an unanimous decision. Fifty percent voted for a level B recommendation due to the identified weaknesses in the cited studies. The MAGIC and ACCORD studies were criticized, above all, for their lack of surgical and pathological quality controls and the fact that only about 50% of the patients in the perioperative-chemotherapy group were able to complete the study according to the protocol. The prematurely terminated EORTC study was criticized for having inadequate power.

Based on GebSKI et al.'s meta-analysis<sup>15</sup> in 2007, preoperative radiochemotherapy for carcinomas of the esophagogastric junction is recommended as an alternative to perioperative chemotherapy alone.

In contrast, preoperative radiochemotherapy for the treatment of gastric cancer was explicitly rejected in the German S3 guidelines. Due to the small number of cases and absence of a control group, there are no valid data for this kind of accompanying therapy. The adverse effects of preoperative radiochemotherapy also contribute to deterioration in the patient's health status.<sup>16,17</sup>

**Table 3. Recommendations for adjuvant therapy for gastric cancer in different national guidelines**

	Germany	UK	ESMO	USA	Canada	Japan
Perioperative therapy						
Chemotherapy	T3 NO/ <sup>†</sup> T4a NO/ <sup>†§</sup>	Rec* <sup>§</sup>	Rec* <sup>§</sup>	T2 NO/ <sup>†</sup> , T3 NO/ <sup>†</sup> T4 NO/ <sup>††</sup>	T1 N2/3 T2 N <sup>†</sup> T3 NO/ <sup>†</sup> T4 NO/ <sup>†§</sup>	Not rec*
Radiochemotherapy	Only AEG <sup>†</sup> tumors <sup>§</sup>	Not rec*	Not rec*	Only AEG <sup>†</sup> tumors <sup>§</sup>	Not rec*	Not rec*
Adjuvant therapy						
Chemotherapy	Not rec*	Not rec*	Not rec*	Only after D2 lymphad-ectomy <sup>§</sup>	Not rec*	T1 N2/3 T2 N <sup>†</sup> T3 N0/ <sup>†</sup> T4 NO/ <sup>†§</sup>
Radiochemotherapy	Not rec*	Not rec*	Not rec*	T1 N <sup>†</sup> (T2 N0) T2 N <sup>†</sup> T3 N0/ <sup>†</sup> T4 N0/ <sup>†‡</sup>	T1 N1 T2 N0 T1 N2/3 T2 N <sup>†</sup> T3 N0/ <sup>†</sup> T4 N0/ <sup>†§</sup>	Not rec*

\*Rec: recommended.

<sup>†</sup>AEG: Adenocarcinomas of the Esophagogastric Junction.

<sup>§</sup>Preoperative phase: three 3-week cycles of epirubicin (50 mg/m<sup>2</sup>) and cisplatin (60 mg/m<sup>2</sup>) administered intravenously (IV) on day one plus continuous IV infusion of 5-fluorouracil (5-FU, 200 mg/m<sup>2</sup>/d) over 21 days.

Operative phase: Surgical resection with oncologic principles.

Postoperative phase: As described above in the pre-operative phase.

<sup>§</sup>Five 4-week cycles where of leucovorin (20 mg/m<sup>2</sup> IV) followed by daily administration of 5-FU (425 mg/m<sup>2</sup> IV) on the first five consecutive days of cycles 1, 4, and 5. During cycles 2 and 3, radiotherapy is administered on weekdays in 25 fractions (180 cGy per fraction). Leucovorin (20 mg/m<sup>2</sup> IV) followed by 5-FU (400 mg/m<sup>2</sup> IV) are administered daily on the first four and last three days of radiotherapy.

<sup>§</sup>The guidelines do not provide concrete recommendations for chemo- and/or radiotherapy, but describe the regimens of different studies:

- MAGIC study<sup>12</sup>: Chemotherapy was administered for three cycles preoperatively and three cycles postoperatively. Each 3-week cycle consisted of epirubicin (50 mg/m<sup>2</sup> body surface area) by intravenous bolus and cisplatin (60 mg/m<sup>2</sup> IV) with hydration on day 1 and 5-FU (200 mg/m<sup>2</sup>) daily for 21 days by continuous IV infusion with the use of a double-lumen Hickman catheter and a portable infusion pump.
- ACCORD study<sup>13</sup>: chemotherapy comprises two or three preoperative cycles of 5-FU (800 mg/m<sup>2</sup>/d) as continuous IV infusion for 5 consecutive days (days 1-5) and cisplatin (100 mg/m<sup>2</sup>) as a 1-hour infusion every 28 days. Three to four postoperative cycles may be applied, in cases of good tolerance and no evidence of progressive disease after preoperative chemotherapy, for a total of six cycles.

<sup>§</sup>S-1 (an oral fluoropyrimidine) is started within 6 weeks post-surgery after sufficient recovery from the intervention. A 6-week cycle consisting of 4 weeks of daily oral administration of S-1 (80 mg/m<sup>2</sup>) followed by 2 weeks of rest is repeated during the first year after surgery.

<sup>†</sup>ECF (epirubicin, cisplatin, and 5-FU): epirubicin (50 mg/m<sup>2</sup> IV) and cisplatin (60 mg/m<sup>2</sup> IV) on day 1 and 5-FU (200 mg/m<sup>2</sup>) by continuous IV infusion over 24 hours on days 1-21. Three 21-day cycles were applied preoperatively and three cycles postoperatively.

Or

Fluorouracil and cisplatin: 5-FU (800 mg/m<sup>2</sup>) by continuous IV infusion over 24 hours daily on days 1~5 and cisplatin (75-80 mg/m<sup>2</sup> IV) on day 1. Two to three 28-day cycles preoperatively and three to four cycles postoperatively, for a total of 6 cycles.

<sup>†</sup>1 cycle before and 2 cycles after chemoradiation

Capecitabine (750~1,000 mg/m<sup>2</sup>) by oral administration twice daily (per os BID) on days 1~14

Cycled every 28 days

or

1 cycle before and 2 cycles after chemoradiation

Leucovorin (400 mg/m<sup>2</sup> IV) on days 1 and 15 OR days 1, 2, 15, and 16

Fluorouracil (400 mg/m<sup>2</sup> IV push) on days 1 and 15 OR days 1, 2, 15, and 16

Fluorouracil (600 mg/m<sup>2</sup>) by continuous IV infusion over 22 hours daily on days 1, 2, 15, and 16

Cycled every 28 days

<sup>§</sup>capecitabine and oxaliplatin:

Capecitabine (1,000 mg/m<sup>2</sup> per os BID) on days 1~14

Oxaliplatin (130 mg/m<sup>2</sup> IV) on day 1

Cycled every 21 days for 8 cycles

or

Capecitabine and cisplatin:

Capecitabine (1,000 mg/m<sup>2</sup> per os BID) on days 1~14

Cisplatin (60 mg/m<sup>2</sup> IV) on day 1

Cycled every 21 days for 6 cycles

With radiation

5-FU (200~250 mg/m<sup>2</sup>) by continuous IV infusion over 24 hours on days 1~5 or 1~7

Weekly for 5 weeks.

With radiation

Capecitabine (625~825 mg/m<sup>2</sup> per os BID) on days 1~5 or 1~7

Weekly for 5 weeks

<sup>†</sup>Paclitaxel and carboplatin:

Paclitaxel (50 mg/m<sup>2</sup> IV) on day 1

Carboplatin under the curve (AUC) 2 IV on day 1

Weekly for 5 weeks

Cisplatin and 5-FU:

Cisplatin (75~100 mg/m<sup>2</sup> IV) on days 1 and 29

5-FU (750~1,000 mg/m<sup>2</sup>) by continuous IV infusion over 24 hours on days 1~4 and 29~32

35-day cycle

Cisplatin (15 mg/m<sup>2</sup> IV) daily on days 1~5

5-FU (800 mg/m<sup>2</sup>) by continuous IV infusion over 24 hours on days 1~5

Cycled every 21 days for 2 cycles

Oxaliplatin and 5-FU:

Oxaliplatin (85 mg/m<sup>2</sup> IV) on day 1

Leucovorin (400 mg/m<sup>2</sup>) on day 1

5-FU (400 mg/m<sup>2</sup> IV push) on day 1

5-FU (800 mg/m<sup>2</sup>) by continuous IV infusion over 24 hours on days 1 and 2

Cycled every 14 days for 3 cycles with radiation and 3 cycles after radiation.

In addition, evidence supporting the administration of postoperative adjuvant chemotherapy is insufficient, even if a marginal survival advantage was demonstrated in a meta-analysis of patients receiving postoperative treatment.<sup>18–22</sup>

There is no standard for postoperative adjuvant radiochemotherapy following R0-resection and sufficient lymphadenectomy. Studies conducted to clarify this indication showed a certain survival advantage for patients treated with postoperative radiochemotherapy,<sup>23,24</sup> but a D2 lymphadenectomy was performed in only a few patients, and no definitive statement can be made while maintaining a high surgical standard.

Both postoperative adjuvant procedures could be considered for patients at high risk of recurrence and who received no preoperative therapy.

## 2. Literature on which the British guidelines are based

The British guideline also based its recommendations for perioperative chemotherapy on the MAGIC study<sup>12</sup> and the abstract of the ACCORD study.<sup>13</sup> The two studies claimed a survival advantage of 12.5% and 14%, respectively.

Meta-analyses, particularly from Asian countries,<sup>18,25,26</sup> were able to demonstrate a certain survival advantage after administration of postoperative adjuvant chemotherapy. However, postoperative adjuvant chemotherapy is not a standard approach following stomach resection with curative intention and should only be used in patients at high risk of recurrence who did not receive preoperative chemotherapy.

Postoperative adjuvant radiochemotherapy has been used, especially in the USA, following the publication of the Intergroup 0116 Trial study.<sup>23</sup> However, this should only be considered for patients at high risk of recurrence and no preoperative therapy. The patients of the UK are not comparable with the patients of the intergroup-study because of the great differences to make the lymphadenectomy.

## 3. Literature on which the European Society for Medical Oncology guidelines are based

These guidelines also cite the MAGIC<sup>12</sup> and ACCORD<sup>13</sup> studies conducted in patients receiving perioperative chemotherapy. Perioperative chemotherapy has become the standard therapy for gastric cancer in large parts of Europe and Great Britain.

It remains unclear whether postoperative adjuvant chemotherapy or radiochemotherapy provides better therapeutic success. The results of the CRITICS study<sup>27</sup> should clarify this question. In contrast

to the USA,<sup>28</sup> there are no clear recommendations for postoperative adjuvant radiochemotherapy in Europe because the surgical quality in Europe is higher and the dangers of toxic side effects are taken more seriously.

According to a current meta-analysis, only a very small benefit is derived from postoperative adjuvant chemotherapy in Europe compared to Asian countries,<sup>29,30</sup> even though Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) Group's meta-analysis<sup>19</sup> demonstrated a marginal survival benefit of 6.8%.

The ESMO does not discuss preoperative radiochemotherapy.

## 4. Literature on which the American guidelines are based

The recommendations for postoperative adjuvant radiochemotherapy are based on a phase 3 study by Macdonald et al.<sup>23</sup> in 2001, which showed a significant median overall survival of patients receiving postoperative adjuvant radiochemotherapy following surgery. The high number of grade 3 and 4 toxicities was attributed to the administration of currently outdated chemotherapeutic regimes. The recommendations apply particularly to patients undergoing D0 or D1 lymphadenectomies, because the number of patients who underwent D2 lymphadenectomies is too small to provide sufficient power to confirm an advantage in this group. In a follow-up study, the same patients were observed over a period of 10 years. Survival rates remained the same, confirming the results of the study by Macdonald et al.<sup>23</sup> The number of patients who experienced late toxic effects did not increase.<sup>28</sup>

One possible alternative to postoperative adjuvant radiochemotherapy is perioperative chemotherapy.<sup>12,13</sup> The authors, however, critically mention that neither the MAGIC nor ACCORD study has sufficient power to evaluate the role of pre- or postoperative adjuvant treatment because D2 lymphadenectomies were not routinely performed.

The authors only recommend postoperative adjuvant chemotherapy for patients who underwent a D2 lymphadenectomy.<sup>31,32</sup> In general, they see a greater benefit of postoperative adjuvant chemotherapy in Asian patients.<sup>31,33</sup>

Recommendations for preoperative radiochemotherapy for carcinomas of the esophagogastric junction are based on the studies by van Hagen et al.,<sup>34</sup> Rivera et al.,<sup>35</sup> and Stahl et al.<sup>36</sup> Perioperative chemotherapy is considered a worse alternative.<sup>12,13</sup>

## 5. Literature on which the Canadian guidelines are based

Depending on the tumor size, the Canadian guidelines recom-

**Table 4. Literature (first author) used as the basis for recommended adjuvant therapies for gastric cancers in the six guidelines**

Variable	Germany	UK	ESMO	USA	Canada	Japan
Perioperative/neo-adjuvant therapy						
Chemotherapy	Cunningham (MAGIC) <sup>12</sup> Ychou (ACCORD) <sup>13</sup>	Cunningham (MAGIC) <sup>12</sup> Ychou (ACCORD) <sup>13</sup>	Cunningham (MAGIC) <sup>12</sup> Ychou (ACCORD) <sup>13</sup>	Cunningham (MAGIC) <sup>12</sup> Ychou (ACCORD) <sup>13</sup>	Cunningham (MAGIC) <sup>12</sup> Ychou (ACCORD) <sup>13</sup>	Cunningham (MAGIC) <sup>12</sup>
Radiochemotherapy	Ajani (RTOG 9904) <sup>17</sup> Safran <sup>16</sup>			Ajani (RTOG 9904) <sup>17</sup> Stahl <sup>36</sup> Rivera <sup>35</sup> Van Hagen <sup>34</sup>		Ajani (RTOG 9904) <sup>17</sup>
Adjuvant therapy						
Chemotherapy	Janunger <sup>18</sup> Paoletti <sup>19</sup> Hermans <sup>20</sup> Earle <sup>21</sup> Mari <sup>22</sup>	Janunger <sup>18</sup> Lui <sup>26</sup> Gianni <sup>25</sup>	Bang, Noh (CLASSIC) <sup>31,30</sup> Sasako <sup>29</sup>	Bang, Noh (CLASSIC) <sup>31,30</sup> Sakuramoto (ACTS-GC3) <sup>33</sup>		Sakuramoto (ACTS-GC3) <sup>33</sup>
Radiochemotherapy	Macdonald, Smalley (Intergroup 0116) <sup>23,28</sup>	Macdonald, Smalley (Intergroup 0116) <sup>23,28</sup>	Macdonald, Smalley (Intergroup 0116) <sup>23,28</sup> Lee (Artist) <sup>32</sup>	Macdonald, Smalley (Intergroup 0116) <sup>23,28</sup>	Macdonald, Smalley (Intergroup 0116) <sup>23,28</sup>	Macdonald, Smalley (Intergroup 0116) <sup>23,28</sup>

ESMO = European Society for Medical Oncology.

mend either perioperative chemotherapy or postoperative adjuvant radiochemotherapy. The 5-year survival rate increased from 26% with surgery alone to 40% with postoperative adjuvant radiochemotherapy.<sup>23</sup> Perioperative chemotherapy increased the 5-year survival rate to 36.3% compared with the 23% after surgery alone,<sup>12</sup> or to 38% compared with the 24% after surgery alone.<sup>13</sup>

No other accompanying therapies are mentioned in the Canadian guidelines.

## 6. Literature on which the Japanese guidelines are based

Recommendations for postoperative adjuvant chemotherapy are based on the ACTS-GC3 study, in which the patients treated with postoperative adjuvant therapy after tumor resection had a 3-year survival rate of 80.1% compared to the 70.1% in patients treated with surgery alone.<sup>33</sup>

Preoperative radiochemotherapy should not be administered except in clinical studies. Although the results of a phase 2 study, in which no vital cells were found in 20% to 30% of patients following preoperative radiochemotherapy, sound promising, they have not been confirmed in randomized studies.<sup>17</sup>

In contrast to the USA, D2 lymphadenectomies are performed routinely and the standard of surgery is high in Japan; hence, there was no evidence for the effectiveness of postoperative adjuvant radiochemotherapy.<sup>23,28</sup> Perioperative chemotherapy has become an established practice in Europe since the publication of the MAGIC

study.<sup>12</sup> There has been no effect observed in Japan, but perioperative chemotherapy remains an option for patients with poor prognosis and high risk of recurrence.

Table 4 shows the most important studies on which recommendations for or against the investigated therapies are based in the six discussed guidelines.

## Discussion

The guidelines examined in this paper were published within the past 5 years, and expert groups had access to comparable sources when developing the guidelines. Therefore, we would expect nearly identical therapy recommendations. A comparison of the guidelines reveals distinct differences. For advanced stages of gastric cancer, there are differing recommendations for perioperative chemotherapy, postoperative adjuvant chemotherapy, perioperative radiochemotherapy, or postoperative adjuvant radiochemotherapy in the individual countries. Recommendations for or against a therapy are based on the same scientific publications.

For example, the Intergroup 0116 study by Macdonald et al.<sup>23</sup> published in 2001 was cited in all six guidelines (Table 4), but recommendations for postoperative adjuvant radiochemotherapy based on this study can only be found in the American and Canadian guidelines. These two countries rated the effect of radiochemotherapy higher than its toxicity and the absence of D2

lymphadenectomy. Guideline experts from the other four countries came to a contrary assessment. A comparison of the German S3 guidelines with the British, American, and Scottish guidelines for the diagnosis and treatment of advanced gastric cancer was recently conducted by Moehler et al.<sup>37</sup> Regarding the recommendations for perioperative or postoperative adjuvant therapy, they concluded that perioperative chemotherapy has become an established practice in Europe. In the USA, postoperative adjuvant radiochemotherapy is favored, with perioperative chemotherapy considered an alternative therapy.<sup>36</sup>

Consensus in guideline committees substantially depends on the interpretation of the studies on which the guidelines are based. A reliable interpretation depends on a high degree of validity of these clinical studies. The validity of perioperative chemotherapy studies (MAGIC, ACCORD, and EORTC) was already judged by our group to be limited due to several grave shortcomings.<sup>37</sup> Nevertheless, the British MAGIC study was cited in all guidelines examined and, with the exception of Japan, all national guidelines recommended perioperative chemotherapy based on this study. Due to its limited validity, the endpoints of morbidity, mortality, patient satisfaction, and quality of life could hardly be evaluated.

Discrepancies between the guidelines resulted from different interpretations of the same studies. We assume that the decisions were actually based on different value judgments that are influenced not only by scientific evidence, but also by other factors such as public and political opinion, and financial and structural realities. For example, distal cancers are more prevalent in Japan and Korea, and D2 gastrectomy is more easily performed due to the higher volume and greater availability of experienced surgeons, as well as the patients' body habitus.

Treatment of advanced gastric cancer is, therefore, not internationally comparable.

Every country, regardless of size, expends great effort to develop its own guidelines. In the future, an international cooperation should be established to create guidelines.<sup>38,39</sup> Each country could contribute to each of the following five steps to provide an international guideline basis. This basis for guidelines would allow each nation to individually evaluate the available scientific evidence, but reduce the huge effort required by each country in the absence of international cooperation.

Countries expend great efforts to collect the questions to be answered in most guidelines, identify relevant literature to answer these questions, and critically evaluate the validity of each publication containing concrete statements supporting a guideline. There

**Table 5. Five steps required to produce a basis for international guidelines**

Number	Step
1	Collection of questions to be answered in the guidelines
2	Identification of relevant literature to answer these questions
3	Critical evaluation of each publication with concrete statements supporting a guideline
4	Presentation of accepted studies as valid and relevant for the guidelines by an international committee
5	Designation of questions in the guidelines that are answered by valid and relevant results of clinical studies

is no need to conduct a time-consuming evaluation of a study's validity if it does not concretely provide a recommendation supporting the guideline. If scientific evidence claims to be internationally valid, an international committee should be able to present acceptable studies as valid and formative, eventually creating a basis for international guidelines. These studies would be able to answer some of the initially posed questions. Services not represented in the international guidelines but included in the catalogue of national guidelines would depend on the prosperity and expectations of a country's citizens. Table 5 summarizes the five steps required to create the basis for international guidelines.

Although many of the same study results are used to produce the different guidelines, the rational recommendations for accompanying therapy for advanced gastric cancer vary among countries, sometimes considerably. This is due to discrepancy in the interpretation of the same study results by different countries.

As a great deal of effort is required for each country to separately evaluate the validity and suitability of relevant studies for inclusion in guidelines, international cooperation for the creation of a common basis for guidelines could facilitate their development and contribute to greater comparability.

## References

1. World Cancer Research Fund International (WCI). Cancer frequency by country, source: GLOBOCAN 2008 database (version 1.2) [Internet]. London: WCI; [accessed 2014 Feb 14]. Available from: <http://www.wcrf.org>.
2. Verdecchia A, Francisci S, Brenner H, Gatta G, Micheli A, Mangone L, et al; EURO-CARE-4 Working Group. Recent cancer survival in Europe: a 2000-02 period analysis of EURO-CARE-4 data. *Lancet Oncol* 2007;8:784-796.

3. Qaseem A, Forland F, Macbeth F, Ollenschläger G, Phillips S, van der Wees P; Board of Trustees of the Guidelines International Network. Guidelines International Network: toward international standards for clinical practice guidelines. *Ann Intern Med* 2012;156:525-531.
4. Australian Government National Health and Medical Research Council (NHMRC). How to review the evidence: systematic identification and review of the scientific literature [Internet]. Canberra: NHMRC; [accessed 2015 Feb 11]. Available from: <http://www.nhmrc.gov.au/publications/synopses/cp65syn.htm/>.
5. Lelgemann M, Ollenschläger G. Evidence based guidelines and clinical pathways: complementation or contradiction? *Internist (Berl)* 2006;47:690, 692-697.
6. AWMF, Deutsche Krebsgesellschaft, Deutsche Krebshilfe. S3-Leitlinie "Diagnostik und Therapie der Adenokarzinome des Magens und ösophagogastralen Übergangs" [Internet]. [accessed 2012 Feb 1]. Available from: [http://www.awmf.org/uploads/tx\\_szleitlinien/032-009l\\_S3\\_Magenkarzinom\\_Diagnostik\\_Therapie\\_Adenokarzinome\\_Magen\\_ösophagogastralen\\_Übergang\\_2012-02\\_01.pdf/](http://www.awmf.org/uploads/tx_szleitlinien/032-009l_S3_Magenkarzinom_Diagnostik_Therapie_Adenokarzinome_Magen_ösophagogastralen_Übergang_2012-02_01.pdf/).
7. Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R; Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the British Society of Gastroenterology and the British Association of Surgical Oncology. Guidelines for the management of oesophageal and gastric cancer. *Gut* 2011;60:1449-472.
8. Okines A, Verheij M, Allum W, Cunningham D, Cervantes A; ESMO Guidelines Working Group. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21 Suppl 5:v50-v54.
9. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology (NCCN guidelines), gastric cancer (including cancer in the proximal 5 cm of the stomach) [Internet]. Fort Washington: NCCN; [accessed 2015 Feb 10]. Available from: [http://www.nccn.org/professionals/physician\\_gls/pdf/gastric.pdf/](http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf/).
10. Alberta Health Services. Gastric cancer, clinical practice guideline GI-008 [Internet]. Edmonton (AB): Alberta Health Services; [accessed 2015 Feb 9]. Available from: <http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-gi008-gastric.pdf>.
11. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011;14:113-123.
12. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11-20.
13. Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011;29:1715-1721.
14. Schuhmacher C, Gretschel S, Lordick F, Reichardt P, Hohenberger W, Eisenberger CF, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. *J Clin Oncol* 2010;28:5210-5218.
15. Gebski V, Burmeister B, Smithers BM, Foo K, Zalberg J, Simes J; Australasian Gastro-Intestinal Trials Group. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol* 2007;8:226-234.
16. Safran H, Wanebo HJ, Hesketh PJ, Akerman P, Janitti D, Cioffi W, et al. Paclitaxel and concurrent radiation for gastric cancer. *Int J Radiat Oncol Biol Phys* 2000;46:889-894.
17. Ajani JA, Winter K, Okawara GS, Donohue JH, Pisters PW, Crane CH, et al. Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): quality of combined modality therapy and pathologic response. *J Clin Oncol* 2006;24:3953-3958.
18. Janunger KG, Hafström L, Glimelius B. Chemotherapy in gastric cancer: a review and updated meta-analysis. *Eur J Surg* 2002;168:597-608.
19. GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. *JAMA* 2010;303:1729-1737.
20. Hermans J, Bonenkamp JJ, Boon MC, Bunt AM, Ohyama S, Sasako M, et al. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. *J Clin Oncol* 1993;11:1441-1447.
21. Earle CC, Maroun JA. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials. *Eur J Cancer* 1999;35:1059-1064.



22. Mari E, Floriani I, Tinazzi A, Buda A, Belfiglio M, Valentini M, et al. Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomised trials. A study of the GISCAD (Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente). *Ann Oncol* 2000;11:837-843.
23. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, 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.
24. Valentini V, Cellini F, Minsky BD, Mattiucci GC, Balducci M, D'Agostino G, et al. Survival after radiotherapy in gastric cancer: systematic review and meta-analysis. *Radiother Oncol* 2009;92:176-183.
25. Gianni L, Panzini I, Tassinari D, Mianulli AM, Desiderio F, Ravaioli A. Meta-analyses of randomized trials of adjuvant chemotherapy in gastric cancer. *Ann Oncol* 2001;12:1178-1180.
26. Liu TS, Wang Y, Chen SY, Sun YH. An updated meta-analysis of adjuvant chemotherapy after curative resection for gastric cancer. *Eur J Surg Oncol* 2008;34:1208-1216.
27. Dikken JL, van Sandick JW, Maurits Swellengrebel HA, Lind PA, Putter H, Jansen EP, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). *BMC Cancer* 2011;11:329.
28. Smalley SR, Benedetti JK, Haller DG, Hundahl SA, Estes NC, Ajani JA, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol* 2012;30:2327-2333.
29. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *J Clin Oncol* 2011;29:4387-4393.
30. Noh SH, Park SR, Yang HK, Chung HC, Chung IJ, Lee, KH, et al. Adjuvant capecitabine and oxaliplatin (XELOX) for gastric cancer after D2 gastrectomy: final results from the CLASSIC trial. *Ann Oncol* 2013;24:iv14
31. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, et al; CLASSIC trial investigators. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet* 2012;379:315-321.
32. Lee J, Lim do H, Kim S, Park SH, Park JO, Park YS, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. *J Clin Oncol* 2012;30:268-273.
33. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al; ACTS-GC Group. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007;357:1810-1820. Erratum in: *N Engl J Med* 2008;358:1977.
34. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al; CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-2084.
35. Rivera F, Galán M, Tabernero J, Cervantes A, Vega-Villegas ME, Gallego J, et al; Spanish Cooperative Group for Digestive Tumor Therapy. Phase II trial of preoperative irinotecan-cisplatin followed by concurrent irinotecan-cisplatin and radiotherapy for resectable locally advanced gastric and esophago-gastric junction adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2009;75:1430-1436.
36. Stahl M, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol* 2009;27:851-856.
37. Moehler M, Baltin CT, Ebert M, Fischbach W, Gockel I, Grenacher L, et al. International comparison of the German evidence-based S3-guidelines on the diagnosis and multimodal treatment of early and locally advanced gastric cancer, including adenocarcinoma of the lower esophagus. *Gastric Cancer* 2014 [Epub].
38. Bauer K, Porzolt F, Henne-Bruns D. Can perioperative chemotherapy for advanced gastric cancer be recommended on the basis of current research? A critical analysis. *J Gastric Cancer* 2014;14:39-46.
39. Ollenschläger G, Marshall C, Qureshi S, Rosenbrand K, Burgers J, Mäkelä M, et al; Board of Trustees 2002, Guidelines International Network (G-I-N). Improving the quality of health care: using international collaboration to inform guideline programmes by founding the Guidelines International Network (G-I-N). *Qual Saf Health Care* 2004;13:455-460.