

WJG 20th Anniversary Special Issues (8): Gastric cancer**Adjuvant chemotherapy for gastric cancer: Current evidence and future challenges**

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Abstract

Gastric cancer still represents one of the major causes of cancer mortality worldwide. Patients survival is mainly related to stage, with a high proportion of patients with metastatic disease at presentation. Thus, the cure rate largely depend upon surgical resection. Despite the additional, albeit small, benefit of adjuvant chemotherapy has been clearly demonstrated, no general consensus has been reached on the best treatment option. Moreover, the narrow therapeutic index of adjuvant chemotherapy (*i.e.*, limited survival benefit with considerable toxicity) requires a careful assessment of expected risks and benefits for individual patients. Treatment choices vary widely based on the different geographic areas, with chemotherapy alone more often preferred in Europe or Asia and chemoradiotherapy in the United States. In the present review we discuss

the current evidence and future challenges regarding adjuvant chemotherapy in curatively resected gastric cancer with particular emphasis on the recently completed landmark studies and meta-analyses. The most recent patient-level meta-analysis demonstrated the benefit of adjuvant chemotherapy over curative surgery; the same Authors also showed that disease-free survival may be used as a surrogate end-point for overall survival. We finally discuss future research issues such as the need of economic evaluations, development of prognostic or predictive biomarkers, and the unmet clinical need of trials comparing perioperative chemotherapy with adjuvant treatment.

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Key words: Gastric cancer; Adjuvant chemotherapy; Radiotherapy; Randomized trial

Core tip: Despite the benefit of adjuvant therapy has been clearly demonstrated, no general consensus has been still reached on the best treatment option. The narrow therapeutic index of adjuvant chemotherapy requires a careful assessment of expected risks and benefits for individual patients. Many issues, such as the role of postoperative radiotherapy and the best chemotherapy regimen, are still under investigation. Moreover, no prognostic or predictive factors beyond pathological stage have been prospectively validated. Despite researchers' efforts, this issue still represent an unmet medical need. In this review we describe the recently completed landmark studies and meta analyses, and we discuss the future challenges in this research field.

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INTRODUCTION

Gastric cancer (GC) is a major public health problem, because of its high incidence, morbidity and mortality rate. Despite a steady incidence decline over the last decades, GC still represents one of the major causes of cancer mortality worldwide^[1]. This is due to the high proportion of patients with metastatic disease at presentation or during the clinical course. Indeed, less than 5% of patients with advanced GC survive up to five years and the role of surgery as mainstay treatment is limited to approximately a quarter of all patients^[2].

Overall survival (OS) of patients who undergo surgery progressively diminishes as stage increases, ranging from 75% for stage I to 35% or less for stage II and beyond^[3]. Recurrences tend to occur at distant sites, suggesting the presence of micrometastatic disease at the time of surgery. Therefore, these observations led to the hypothesis that adjuvant chemotherapy should improve outcomes in curatively resected stage II-III GC.

Despite the benefit of adjuvant therapy has been clearly demonstrated, no general consensus has been still reached on the best treatment option. The narrow therapeutic index of adjuvant chemotherapy (*i.e.*, limited survival benefit with considerable toxicity) requires a careful assessment of expected risks and benefits for individual patients. Generally, surgery followed by chemoradiotherapy is the standard protocol in the United States, whereas perioperative or postoperative chemotherapy are recommended in the Europe and Asia. The difference of this approaches is mainly due to the fact that less than D2 lymph nodal dissection is routinely used in the United States, whereas D2 surgery is the standard treatment in Europe. Thus, optimal local control may be obtained by adding radiotherapy to D0-D1 surgery. Many issues, such as the role of postoperative radiotherapy and the best chemotherapy regimen, are still under investigation. Moreover, no prognostic or predictive factors beyond pathological stage have been prospectively validated. Despite researchers' efforts, this issue still represent an unmet medical need.

In this review we describe early randomized clinical trials (RCTs) of adjuvant chemotherapy for resected GC, with particular emphasis on the recently completed landmark studies and meta-analyses, and we discuss the future challenges in this research field.

CURRENT EVIDENCE

Role of D2 surgery

The extension of surgical dissection is an open issue in the treatment of potentially curable GC. Asian and Western surgeons have followed different paths in the last de-

acades in their approach to GC. D2 gastrectomy has been a standard of care in Eastern countries since the 1960s^[4]. In Europe this procedure became widely used after the publication of 15-year results of the Dutch D1D2 trial, showing better locoregional control and lower GC related deaths in the D2 arm^[5]. In 2008 Sasako *et al*^[6] published the results of a Japanese RCT comparing D2 lymphadenectomy alone *vs* D2 lymphadenectomy plus para-aortic nodal dissection, a procedure performed in Japan since the 1980s. However, patients undergoing wider, D3, dissection did not benefit in terms of disease-free survival (DFS) and OS and experienced more surgical complications. Nowadays, D2 resection is the recommended surgical approach for patients with resectable GC and it is the major determinant of patients' prognosis.

Adjuvant chemotherapy: An "historical overview"

The debate on surgical dissection is obviously directly linked to the use of adjuvant therapy.

Over the last few decades numerous RCTs have been conducted to evaluate the benefit of post-operative chemotherapy as compared to surgery alone^[7-10]. Most of them failed to demonstrate a statistically significant survival advantage for different reasons, including the lack of adequate statistical power to detect a survival difference, the use of obsolete surgical techniques or "suboptimal" chemotherapy regimens, and the delay in starting treatment after gastrectomy.

Among those RCTs demonstrating a benefit, most were performed in Asia and few in Western countries. For instance, a Spanish RCT evaluated the efficacy of the combination of mitomycin plus tegafur *vs* observation in patients with resected stage III GC^[11]. After a median follow-up of 37 mo, both OS and DFS were significantly better in the chemotherapy group. Five-year OS and DFS were 56% and 51% in the treatment group *vs* 36% and 31% in the control group.

Taking into consideration all the RCTs testing anthracycline-containing polychemotherapy regimens, disappointing results were reported. The only positive trial so far was a multi-institutional study conducted in Italy in the 90's which randomly assigned node-positive GC patients to receive epidoxorubicin, leucovorin and 5-fluorouracil for 7 mo or no treatment^[12]. After a median follow-up of 5 years, the median OS was 18 mo for untreated patients *vs* 31 mo for treated ones.

This positive experience opened the way to subsequent trials testing more intensive chemotherapy regimens in order to further improve clinical outcomes. The Italian cooperative research groups played a fundamental role in this scenario. In fact, three large RCTs were completed in the attempt of evaluating new polichemotherapy strategies for high-risk resected GC patients. The Italian Trials in Medical Oncology group conducted a RCT comparing D2 surgery alone *vs* D2 surgery followed by 2 cycles of etoposide, adriamycin, cisplatin and 2 cycles of Machover regimens. The results showed that at 5 years the sequential regimen led to a 7% re-

Table 1 Overall survival results of study based meta-analyses comparing post-operative chemotherapy *vs* surgery alone

Ref.	Studies analysed (n)	Pooled HR (95%CI)
Earle <i>et al</i> ^[16]	13	0.80 (0.66-0.97)
Mari <i>et al</i> ^[17]	20	0.82 (0.75-0.89)
Janunger <i>et al</i> ^[19]	21	0.84 (0.74-0.96)
Oba <i>et al</i> ^[20]	4	0.73 (0.60-0.89)
Liu <i>et al</i> ^[21]	19	0.85 (0.80-0.90)
Zhao <i>et al</i> ^[22]	15	0.90 (0.84-0.96)
Sun <i>et al</i> ^[23]	12	0.78 (0.71-0.85)

duction in mortality and 17% reduction in the disease relapse rate, neither of which were statistically significant. In fact the trial was designed to detect a 15% of difference in 5-year survival between the two arms. We want to emphasize in addition that the results obtained with an adequate surgical treatment were better than expected^[13].

The second trial was conducted by the Italian Oncology Group for Clinical Research and published in 2008^[14]. Patients with stage IB-IV, completely resected GC were randomized to receive chemotherapy with 4 cycles of cisplatin, epirubicin, and 5-FU/LV (PELF regimen) or follow-up alone. Ultimately, chemotherapy did not lead to a significant increase in either DFS (HR, in PELF arm *vs* follow-up arm = 0.92; 95%CI: 0.66-1.27) or OS (HR = 0.90; 95%CI: 0.64-1.26). In fact, 5-year OS was almost identical in chemotherapy and follow-up arms (47.6% *vs* 48.7%). Statistical concerns were raised for this trial, since it was underpowered to detect very modest differences in OS between the two arms. Higher than expected survival rates were registered in both groups. Similar results was obtained by a third study conducted by the Gruppo Oncologico dell'Italia Meridionale^[15].

The fourth study compared two different treatment arms: PELFw regimen, consisting of eight weekly administrations of cisplatin, leucovorin, epidoxorubicin, 5-fluorouracil, and glutathione with the support of filgrastim, and a regimen consisting of six monthly administrations of 5-fluorouracil and leucovorin (5-FU/LV)^[9]. Unfortunately, this study did not find any difference in mortality or relapse between treatment groups, failing to show any benefit from dose-dense or intensified strategies. Again, 5-year OS was unexpectedly high in both arms - approximately 50% - probably reflecting the high quality of resection procedures. Thus, an optimal surgery may have reduced the impact of chemotherapy on outcomes, as well as the critical planned difference in OS rates may have been inappropriate (expected 5-year survival of only 20% for the control arm).

Due to the large discordance in outcomes in published RCTs, subsequent study-based meta-analyses have been performed to evaluate to role of adjuvant chemotherapy and finally a survival benefit, albeit small, was demonstrated^[16-23]. Table 1 shows summary OS results of the meta-analyses in terms of pooled HRs comparing adjuvant chemotherapy *vs* surgery alone. All the studies

coherently showed a significant OS benefit for adjuvant chemotherapy; however, when analysing only the Western RCTs, the Janunger *et al*^[19] estimated a non-significant HR = 0.96 (95%CI: 0.83-1.12). On the opposite side, the Oba *et al*^[20] including only Japanese studies estimated a HR as low as 0.73.

Milestone meta-analysis

In 2010 the GASTRIC Group published a patient-level meta-analysis to quantify the potential benefit of adjuvant chemotherapy over curative surgery in terms of both OS and DFS^[10]. The results obtained using individual patient data are potentially more reliable than those carried out on aggregate data. Table 2 shows the summary results in terms of pooled HRs; the overall estimates were practically overlapping for the two end-points and demonstrated reduced risks in the chemotherapy group. The HRs were translated in a small absolute benefit: for OS, 5.8% at 5 years and 7.4% at 10 year, whereas for DFS the Authors could estimate only a 5.3% absolute benefit at 5 years. Sub-group analyses by type of regimen showed that the greatest benefit was associated with monotherapy; however, such estimates were based only on two RCTs, one of which was Japanese. Even if no significant heterogeneity was detected across Europe, Asia, and United States, as we have already pointed out, the HRs are usually lower in Asian RCTs as compared to Western ones.

In 2013 the Cochrane Collaboration published a further study-level meta-analysis reviewing RCTs of post-surgical chemotherapy *vs* surgery alone^[24]. A significant improvement of OS (HR = 0.85; 95%CI: 0.80-0.90; 34 studies) and DFS (HR = 0.79; 95%CI: 0.72-0.87; 15 studies) was confirmed for adjuvant chemotherapy. Based on these results, the Authors recommended to offer adjuvant chemotherapy as a routine option - when-ever possible - following GC curative resection.

If considering OS results, the HRs obtained in the three study-level meta-analyses with the highest number of RCTs^[17,19,24], were consistent with those obtained in the individual-level meta-analysis^[10].

From the literature to the bedside: new landmark studies

New insights confirming the effectiveness of fluoropyrimidine-based adjuvant chemotherapy were made available by two landmark Asian RCTs.

The ACTS-GC study was aimed at confirming the effectiveness on OS of 1-year adjuvant chemotherapy with the oral fluoropyrimidine S-1 following D2 gastrectomy^[25]. After a median follow-up of 3 years, 3-year OS was 80.1% in the S-1 group and 70.1% in the surgery alone group. S-1 reduced the risk of death by 32% (HR = 0.68; 95%CI: 0.52-0.87, *P* = 0.003). In the 5-year follow-up update, OS was 71.7% in the S-1 arm and 61.1% in the surgery-alone arm, therefore S-1 reduced the risk of death by 33% (HR = 0.67; 95%CI: 0.54-0.83). The 5-year relapse-free survival (RFS) was 65.4% in the S-1 arm and 53.1% in the surgery-only arm^[26]. The

Table 2 GASTRIC group meta-analysis^[10]

Studies (n)		Comparison	Pooled HR (95%CI)	
For OS analysis	For DFS analysis ¹		OS	DFS
17	14	Overall	0.82 (0.76-0.90)	0.82 (0.75-0.90)
2	1	Mono Chemotherapy <i>vs</i> surgery	0.60 (0.40-0.84)	0.49 (0.29-0.84)
3	2	Fluorouracil + mitomycin C + other without anthracyclines <i>vs</i> surgery	0.74 (0.58-0.95)	0.69 (0.48-0.98)
3	2	Fluorouracil + mitomycin C + anthracyclines <i>vs</i> surgery	0.82 (0.71-0.95)	0.80 (0.69-0.94)

¹Analyses were performed on randomized clinical trials with available disease-free survival (DFS) data. OS: Overall survival.

Authors raised some doubts about the possibility of translating the advantages of such treatment to Western population because of different pharmacodynamics and surgery practices. However, following the footsteps of the ACTS-GC trial, assessing the efficacy of combining S-1 with other potentially active drugs such as platinum-derivatives or taxanes could be an interesting perspective.

Similarly, the CLASSIC RCT was designed to compare the efficacy of adjuvant capecitabine plus oxaliplatin (XELOX regimen) with D2 surgery alone in stage II or III GC patients^[27,28]. Three-year DFS was 74% in the chemotherapy group and 59% in the surgery only group (HR = 0.56; 95%CI: 0.44-0.72, $P < 0.0001$); the 5-year analysis confirmed such results: DFS was 68% *vs* 53% (HR = 0.58; 95%CI: 0.47-0.72, $P < 0.0001$). As regards OS, the 5-year rates were 78% in the XELOX group and 69% in the surgery alone group (HR = 0.66; 95%CI: 0.51-0.85, $P = 0.002$). However, the greater limitation of this study was that the beneficial effect deriving from the addition of oxaliplatin to fluoropyrimidine should be assessed by a specific RCT. In fact, a control arm constituted by surgery alone is not appropriate for future trials since the benefits of adjuvant chemotherapy were clearly demonstrated^[10]. Indeed, the ongoing POTENT study is moving along this line^[29]. This is a RCT that started enrolling in early 2013 and it is randomizing patients to receive oxaliplatin and S-1 for six cycles or S-1 for 1 year after surgery. The primary end point is OS, while secondary end points are DFS and safety.

A further research topic in the adjuvant setting is the possibility to improve outcome through a sequential, non cross-resistant polychemotherapy. This strategy may allow to sequentially administer several active agents in order to exploit different mechanisms of drug activity in the context of a relatively chemoresistant disease. In such a perspective, ITACA-S was a multicentre, Italian RCT aimed at comparing two different regimens in GC patients eligible for adjuvant chemotherapy^[30]. Patients in arm A received a polychemotherapy with 4 cycles of irinotecan plus 5-FU/LV (FOLFIRI regimen) followed by cisplatin and docetaxel for 3 cycles, while patients in arm B received monotherapy with 5-FU/LV alone (De Gramont regimen) for 9 cycles. After a median follow up of 49 mo, no significant difference was observed between the two arms in terms of DFS (HR = 0.98; 95%CI: 0.83-1.16, $P = 0.830$) and OS (HR = 1.00; 95%CI: 0.83-1.20, $P = 0.980$). Toxicity was consistent with literature, as previously reported^[31], and significantly

higher in the polychemotherapy arm.

Similarly, the Japanese SAMIT RCT compared 4 different adjuvant regimens: in arm A patients received UFT alone, in arm B received S-1 alone, while arm C and arm D patients received sequential therapy with paclitaxel followed by either UFT or S-1, respectively^[32]. The trial aimed at comparing UFT with S-1, and both single agents with a sequential, taxane-based regimen. After a median follow-up of 1875 d and 728 events, the results failed to show a statistically significant difference of DFS in the sequential arms as compared to single agent fluoropyrimidine arms (HR = 0.92; 95%CI: 0.80-1.07, $P = 0.273$). Comparing the data in arms A + C *vs* B + D, UFT-based chemotherapy was clearly less effective than S-1-based one in the study population.

As a matter of fact, sequential polychemotherapy does not seem to be the best strategy to improve GC patients' outcome in the adjuvant setting and, since fluoropyrimidine and platinum salts have synergistic activity, their upfront combination may hopefully be more effective than a single agent regimen.

Role of adjuvant chemoradiotherapy

Due to the high risk of local recurrence, different studies have been evaluating the potential benefit of radiotherapy alone or combined to chemotherapy as adjuvant treatments for GC^[33,34].

Early studies of adjuvant radiotherapy demonstrated reductions of local failure rate despite of lack of OS benefit^[35].

Much more impact on modern management of GC had the large US Intergroup INT0116 study^[36]. This trial randomly assigned stage IB-IV GC patients to surgery plus postoperative chemoradiotherapy or surgery alone. Chemotherapy with bolus 5-FU/LV was intermingled by a "sandwich" chemoradiation phase in which 5-FU/LV was given on the first four and the last three days of radiotherapy. With a median follow-up of 5 years, median overall survival was 27 mo for surgery alone and 36 mo for adjuvant chemoradiation. Three-year OS was 41% for the surgery-alone group and 50% for surgery followed by chemoradiation group. Local failures were reduced from 29% to 19% with the addition of adjuvant chemoradiation. After more than 10 years of follow-up a persistent benefit was demonstrated for the experimental strategy in terms of both OS (HR = 1.32; $P = 0.004$) and RFS (HR = 1.51; $P < 0.001$)^[37].

This hallmark trial was largely criticized due to the

fact that only 10% of patients had a D2 dissection and more than half of patients did not even have clearance/examination of the D1 (perigastric) nodes. Furthermore, most of the patients on this study had T3/T4 disease, and 85% had nodal metastases. This resulted in a lack of accurate tumor staging and consequently in a non proper arm-allocation at randomization - likely contributing to inferior survival and a 64 percent relapse rate in the surgery alone arm. Finally, approximately one third of patients in the chemoradiation group had to stop treatment prematurely because of toxicity.

Despite all these issues, the adjuvant strategy as proposed in this trial became very popular in North America and still represents a gold standard treatment in this setting. Moreover, a meta-analysis including RCTs which compared postoperative chemoradiotherapy *vs* postoperative chemotherapy^[38] concluded that postoperative chemoradiotherapy improved local relapse-free survival (HR = 0.53; 95%CI: 0.32-0.87) and DFS (HR = 0.72; 95%CI: 0.59-0.89) but not OS (HR = 0.79; 95%CI: 0.61-1.03). However, the study was based only on three Asian RCTs and the results may be not extendable to Western patients.

Following the promising results of the INT00116 trial, the CALGB 80101 aimed at assessing whether replacing 5-FU/LV with Epirubicin, Cisplatin and 5-FU (ECF regimen) in the adjuvant chemoradiotherapy setting would improve OS^[39]. However, there was no significant benefit from adding this polychemotherapy regimen to standard 5-FU/LV chemoradiation in terms of OS ($P = 0.800$). Similarly, the ARTIST trial was designed to compare postoperative treatment after D2 dissection with capecitabine plus cisplatin (XP) *vs* XP plus capecitabine-based chemoradiation. There was no significant difference in DFS between the two arms, although chemoradiation arm was associated with significantly prolonged DFS in the retrospectively identified, lymph node-positive subgroup. Estimated 3 year-DFS rate was 78.2% in the experimental arm *vs* 74.2% in the control arm ($P = 0.086$), while estimates were 77.5% *vs* 72.3% ($P = 0.037$). An ongoing phase III trial (ARTIST-II) was designed to compare chemotherapy alone *vs* chemoradiation in lymph node-positive, resected GC, aiming at prospectively confirm the ARTIST trial hypothesis-generating data^[40].

In conclusion, adjuvant chemoradiation may be offered to patients to reduce the risk of locoregional failure in patients with node positive disease or suboptimal surgery.

FUTURE CHALLENGES

Economic analyses

Usually, few RCTs perform concurrent economic analyses; recently, recommendations regarding such an issue included guidelines for data collection of costs, efficacy and proper sample size^[41]. However, prospectively collected information on economic costs require ensuring

proper information extraction from source documents, leading to difficulties in conducting trials aimed at investigating both treatment efficacy and related costs. Besides, in the planning phase another challenge is represented by the sample size, considering that the statistical power adequate to test the main study end-point may be not sufficient to address also economic questions. Moving beyond RCTs, it is even more difficult to gather sufficient information on treatment direct and indirect costs^[42].

There are several kinds of economical evaluations for comparative evaluation of treatments. The two most used in clinical settings are the cost-effectiveness analysis (CEA) and the cost-utility analysis (CUA), both used when the interventions being assessed are not of equal effectiveness. CEA and CUA are aimed at comparing the effectiveness and costs of two (or more) interventions and usually the comparison measure is expressed in terms of ratio (Incremental Cost Effectiveness or Cost-Utility Ratio, generically referred to as ICER), where the denominator is the gain in effectiveness of an intervention *vs* its comparator and the numerator is the differential cost. Since health is a function of both length and quality of life, in CUA the outcome measure captures both survival and health-related quality of life. The latter is measured by means of the quality adjusted life year (QALY). QALYs are calculated by multiplying survival time by an utility weight to adjust for the health-related quality of life experienced during that survival time.

Formal economic evaluations of adjuvant therapy for GC are very few. Earle *et al*^[43] performed a systematic review of CUA applications in oncology; from 1975 and 1997 they found 40 CUAs pertaining to cancer and none to GC. *Health Technology Assessment (HTA)* has published a number of reviews on economic analyses of adjuvant therapy, mainly in terms of costs-effectiveness evaluations. The majority of the studies were related to breast cancer, colorectal cancer, and lung cancer^[44-46], but none of them has evaluated GC adjuvant treatments.

In the study by Wang *et al*^[47] a cost-effectiveness analysis by Hisashige *et al*^[48] of adjuvant chemoradiotherapy for resected GC was performed based on the favourable results of the Intergroup 0116 trial^[56]. The costs of adjuvant therapy accounted for included those for radiotherapy, chemotherapy and toxicity management. Carrying out the analyses out from a payer's perspective (3% discount rate, lifetime time horizon), it was estimated an ICER of \$38400/QALY, *i.e.* one would expect to gain one more year of life lived in perfect health (QALY) for each additional \$38400 spent when treated with chemoradiotherapy.

Recently, the results of a cost-effectiveness analyses by Hisashige *et al*^[48] evaluating S-1 adjuvant chemotherapy were published, using as evidence of effectiveness the results of the ACTS-GC trial^[25]. They included the costs incurred for resources used during the trial and subsequent follow-up, including costs of adverse events and recurrences, being the latter the major component

in each of the two groups. The analyses were carried out from a payer's perspective with a 3% discount rate. Over a lifetime time horizon, the mean QALYs per patient were greater in the S-1 arm than in the surgery arm (8.65 *vs* 7.41). On the other hand, the S-1 arm incurred greater costs than the surgery arm (mean costs per patient: \$13057 *vs* \$9346). The ICER was \$3016 per QALY gained. Braithwaite *et al*^[49] noticed that such ICER estimate was far below the Japan threshold of willingness to pay for additional QALY (from \$53000 to \$56000), very far from the threshold of \$109000/QALY suggested by a recent review, and could be ranked to the top of the league table of cost-utility in oncology^[43]. In the latter table, the Hisashige *et al*^[48] ICER estimate ranked immediately before a study of second line treatment with docetaxel *vs* paclitaxel for patients with metastatic breast cancer (ICER = \$4100/QALY)^[50], and also before a study of adjuvant chemotherapy *vs* surgery alone in Duke's B or C colorectal cancer patients (ICER = \$8100/QALY)^[51].

The issue of between study variability of ICER estimates is a current problem, especially because the choice of a threshold value for considering a treatment as cost-effective is depending on such variability. Hisashige *et al*^[48] estimated ICER was about 8% the value reported in the Wang *et al*^[47]. However, the two studies differentiate in many aspects; for instance, methodology, treatments administered and, besides, they have been performed in different locations, *i.e.*, United States and Japan, respectively. Location is one of most significant factors related to the ICER variability. The review by Bell *et al*^[52] examined cost-utility studies published between 1976 and 2001, 15% of which concerned neoplastic diseases. Most analyses reported favourable ICERs, which were statistically associated with location of the study (Europe, United States, Other), methodological quality (low, medium, high), and sponsorship (non-industry, industry, not specified). In particular, the likelihood to report ICERs below \$20000/QALY was two times more in studies industry sponsored than non-industry sponsored. Moreover, the studies conducted in Europe and the US rather than elsewhere were less likely to find ICERs below \$20000/QALY.

As noticed by Cleemput *et al*^[53], it is difficult to define a single ICER threshold value to be used as a policy-making tool, because it depends on many elements: who is making the decision, what the purpose of the analysis is, what the available resources are, thus different countries or studies reach disparate conclusions^[54]. Ternouth *et al*^[55] studied the trends in accepted ICER thresholds by disease type considering all published HTA appraisals from 2005 to 2010. Findings from Great Britain revealed that most accepted treatments have an ICER of about \$49000, but accepted ICERs for malignant disease cluster at a higher level, up to about \$102000. Data from Australian websites highlighted that for malignant disease the threshold tended to double.

Based on the above findings, the Wang *et al*^[47] ICER

of \$38400/QALY appears well in line with the Western studies and it is well below the thresholds accepted for malignant disease.

Prognostic and predictive factors

Prognostic factor are clinical or biologic characteristic measured at diagnosis proved to be associated with patients' prognosis (*i.e.*, recurrence rate, death rate, or other clinical outcomes) independently of treatment; they may be utilized for stratifying patients according to their risk with the aim of selectively administer adjuvant systemic treatments. Predictive factor are able to predict the likely benefit from treatment, either in terms of tumor shrinkage or survival, and can be utilized for identifying subpopulations of patients who are most likely to benefit from treatment. In summary, prognostic factors define the effects of patient or tumor characteristics on patient's outcome, whereas predictive factors define the effect of treatment on tumor^[56].

The prognostic stratification may be more effective when more factors are combined in a unique prognostic index. In two previous works of ours^[57,58] we have modified an existing index designed for prognostic classification of GC patients undergoing curative resection^[59]. Based on patient's age, tumor site, extent of wall invasion and nodal status, the original index classified patients in three prognostic categories: group I (5-year OS > 70%), group II (OS 30%-69%) and group III (OS < 30%). In the modified index we introduced the 1997 American Joint Commission on Cancer 4-level classification of nodal stage^[60]. The modified index was also internally and externally validated.

More advanced and complex tools are nowadays implemented for estimating patients' outcome, such as nomograms. One of the nomogram advantages is that it is possible to derive a "point" prediction of patient prognosis and, also, that there is no need to categorize continuous variables, such as patient's age or tumor size. One example in GC is the nomogram developed by Kattan *et al*^[61] which allows predicting the survival probability of GC patients up to nine years after R0 resection; the predictions were based on the following prognostic factors: patient's age and gender, tumor size, tumor primary location, tumor histology, depth of tumor invasion, percentage of positive nodes, percentage of negative nodes. Both the prognostic index^[57-59] and the nomogram^[61] were based on established clinical prognostic factors. However, such tools can potentially be improved by including powerful prognostic/predictive biomarkers.

Biomarker have great potential for use in clinical oncology; they can be different types of molecular entities (such as DNA, RNA or proteins), detected in different tissues or body fluids and associated with a disease process.

Many biomarkers are being evaluated in order to establish prognostic or predictive factors in GC and several have been identified for their potential key role, but their clinical use remains controversial^[62,63]. Indeed, both in

the setting of a single biomarker and of a multimarker predictive signature summarized by a categorical measure, the development and validation studies must be carefully designed. For prognostic biomarkers, provisional supportive data is possible through small retrospective studies, but it is difficult to achieve robust multi-site validation. For instance, Warneke *et al.*^[64] investigated several biomarkers in a retrospective series of about 500 patients and some (*KRAS* mutation, persistent *H. pylori* infection, Mucin 2 and PIK3CA) were found to be associated with patient survival. Bria *et al.*^[65] proposed a risk classification system comprising adenomatous polyposis coli gene, Fhit and HER2, together with 5 clinicopathological parameters. An external validation is warranted before applying the model in a clinical setting.

Our research group is conducting an ancillary study of the ITACA-S trial^[50], aiming at identifying the prognostic role of prospectively determined biomarkers on primary GC tissue. Among several candidates, our preliminary data showed that osteopontin (OPN) immunohistochemical expression is significantly associated with RFS and OS. Six-year RFS was 49.7%, in OPN negative group; 34.0% in OPN positive-focal and 22.9% in OPN positive-extended ($P < 0.001$). The corresponding figures for OS were 53.0%, 43.2% and 34.2% ($P = 0.002$). OPN was confirmed as significant prognostic factor also at multivariable analysis ($P = 0.001$ for RFS and 0.014 for OS), independently of treatment^[66].

Predictive biomarkers validation must be prospective in nature and requires more extensive data; the obvious strategy would be to conduct a properly designed RCT to test a biomarker by treatment interaction^[67]. In recent years, many molecular target agents have been investigated; however, at the moment no molecular biomarkers other than Human epidermal growth factor receptor type-2 (HER-2) for trastuzumab-based treatment^[68] have been validated.

Surrogate endpoints

In some situations, the end point of interest is expected to occur far into the future, making RCTs using such an end point infeasible. A surrogate end point is a substitute for the main clinical end point and potentially enable a more rapid assessment of intervention effectiveness, and, at times, with greater reliability and accuracy than classic end points such as survival. A surrogate end-point may be a different clinical end-point but also biomarkers may be employed as surrogate nonclinical end points in proof-of-concept studies. Surrogate end points are challenging to validate, and require data demonstrating both that the surrogate is prognostic for the true end point independently of treatment and that the effect of treatment on the surrogate reliably predicts its effect on the true end point^[67]. The statistical validation of biomarkers surrogacy presents major problems than validation of clinical surrogate end-points. Indeed, the supportive data for prognostic biomarkers is possible even through small retrospective studies, but it is more

difficult to demonstrate that the effect of treatment on the surrogate correlates with that of the true end point.

As regards GC, no biomarkers have been demonstrated as good surrogate end-point for OS. A meta-analysis by Oba *et al.*^[69] examined the use of a clinical end point, *i.e.*, DFS as a surrogate end point for OS in adjuvant trials of GC. The Authors used the data achieved in a previous patient-level meta-analysis of theirs^[10] using the 14 RCTs in which DFS information could be retrieved, and demonstrated that DFS is an appropriate surrogate for OS in studies of GC in the adjuvant setting. The study also estimated the “surrogate threshold effect” (STE), defined as the minimum treatment effect on DFS necessary to predict a nonzero effect on OS, equal to 0.92; a future trial would require the HR CI upper limit (UL) for DFS to fall below 0.92 STE to predict a nonzero effect on OS. The association between 5-year OS and 4 or 5-year DFS was good; however, at 2 and 3 years, the number of DFS events did not allow obtaining precise estimates of STE. However, considering for instance the CLASSIC trial^[27,28], in the 5-year analysis UL was $0.72 < 0.92$; moreover, the 3-year DFS and 5-year OS estimates were super impossible, both in terms of rates and HRs, thus giving support to the establishment that XELOX effect on 3-year DFS reliably predicts that on 5-year OS.

CONCLUSION

The role of adjuvant chemotherapy is now clearly established in patients with resected GC. Future studies are needed to clarify the roles of various chemotherapy combinations and the ideal dosing schedule and to determine which subgroups of patients obtain a significant treatment benefit. Despite significant advances in treatment, mortality from GC remains high, and preventing this disease through global public screening programs is of paramount importance. Medical oncologists should keep an open mind, and individual treatment decisions should be reached after an assessment of patient suitability for adjuvant chemotherapy and after a full discussion of the risk-benefit profile. In fact, the appropriate selection of patients for adjuvant therapy depends largely on performance status and accompanying co-morbid conditions. Treatment of the elderly patient with GC a frequently debated topic. Most recent opinions suggest that physiologic (not chronologic) age should dictate which patients are most appropriate for therapy. Whether this may extend to the adjuvant setting would require prospectively designed RCTs. Molecular biomarkers could better identify which patients should be treated with, or spared by, chemotherapy and which drugs should be better used (assuming a differential sensitivity to a particular cytotoxic agent or regimen). This could help clinicians to increase the therapeutic index of adjuvant treatment and avoid potentially harmful treatment to patients who are not likely to gain a significant benefit. However, most available studies were limited by the small sample size and retrospective nature, with consequent methodologi-

cal limitations, and difficult in distinguishing the predictive or prognostic nature of analyzed factors. Finally, in view of the evidence of benefit from trastuzumab-based chemotherapy in patients with metastatic, HER-2 positive GC^[68], the addition of molecularly targeted agents to chemotherapy seems to be a logical next step to improve outcomes in the adjuvant setting.

Neoadjuvant chemotherapy has recently received increasing attention in an attempt to increase the rate of complete tumor resection, to combat systemic metastases, and to prolong survival in patients with GC. The available data indicate that neoadjuvant chemotherapy is feasible, does not increase post-operative morbidity and mortality, and it is able to increase the rate of R0 resection. This finding appears to translate into a survival benefit for those patients who respond to chemotherapy and have subsequent complete tumour resection. Randomized, controlled, prospective trials are therefore clearly warranted in order to compare neoadjuvant or perioperative chemotherapy with adjuvant treatment.

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