

might predict that inclusion of tumor size and nodal status in prognostic models that also include proliferation-based genomic predictors will improve the prognostic accuracy of the model but could at the same time decrease its predictive value for chemotherapy benefit. Indeed, in the analysis by Tang et al,⁶ adding clinicopathologic measures to RS reduced its ability to predict benefit from adjuvant chemotherapy in the NSABP-B20 study, which illustrates the difficulties that we face in optimizing the performance of empirically derived survival predictors. Ideally, one would have purely prognostic models that predict survival in the absence of any systemic adjuvant therapy, do not interact with treatment effect, and also have distinct, purely predictive models that estimate the benefit from various treatment modalities but do not have prognostic value. Combined use of such markers would provide the necessary information to formulate the most effective therapeutic strategy. However, development of such independent models is logistically challenging.¹⁰

What is the potential clinical utility of the RSPC? The investigators convincingly reason that most patients (89%) with low RS remain in the low-risk category even when the RSPC is applied. Furthermore, low RS heralds minimal, if any, benefit from adjuvant chemotherapy, therefore reclassification of these individuals to groups at intermediate or high (that occurred rarely) prognostic risk may not have immediate therapeutic implications. Similarly, high RS implies greater benefit from adjuvant chemotherapy and reclassification of these individuals to intermediate risk with RSPC (few patients were reclassified into the low-risk group) may also not change treatment recommendations. The greatest potential clinical value may lie in the reclassification of patients with RS intermediate risk into the low-risk category by taking into account clinical pathologic variables.

However, currently, an RSPC score cannot be calculated for an individual patient as a result of the absence of a fully specified model, which was not included in the article, and the lack of a freely accessible Web site that could provide this function in the future. One important caveat needs to be mentioned: the accuracy of the RSPC has not yet been validated on independent data sets. The model performance was assessed on the same data that was used to develop the prognostic predictor. To some extent the NSABP-B14 and TransATAC data sets

served as independent validation sets for the models developed from each of these study cohorts separately, and therefore, the averaged RSPC risk estimates are likely to be close to the performance that could be expected in independent data. However, independent validation on a similar large, randomized trial would greatly increase confidence in this combined clinical and molecular predictor and could also more precisely define its future clinical role.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Gastric Cancer: Nagoya Is Not New York

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Adenocarcinoma of the stomach and gastroesophageal junction is a significant problem worldwide, with more than 900,000 cases occurring yearly.¹ In the United States, this disease occurred in 21,000 individuals and resulted in approximately 10,500 deaths in 2010.² The curative treatment of gastric cancer is based on surgical gastrectomy. However, after gastrectomy alone, relapse resulting in death from metastatic disease is relatively common. For this reason, adjunctive therapies to surgery have been extensively explored in clinical trials over the last 40 years.³ Some of these adjunctive therapies have been accepted as standards of care. In

North America and western Europe, patients with stages II-IV (M0) disease who have undergone gastrectomy benefit in disease-free and overall survival from postoperative chemoradiotherapy.^{4,5} In patients identified preoperatively as having resectable gastric cancer, pre- and postoperative cytotoxic chemotherapy,⁶ a strategy termed perioperative therapy, has been accepted as a standard of care on the basis of results from the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial published in 2006 by Cunningham et al.⁶ Many studies of postoperative adjuvant chemotherapy³ have been carried out in the United

States and Europe, and none of these trials has resulted in a regimen being accepted as a standard of care.

Although gastric cancer is an important cause of morbidity and mortality in the Western world, morbidity and death from this disease are much more common in Asia. For example, approximately 60% of the 900,000 cases occurring worldwide are seen in east Asia.⁷ For this reason, there has been great interest in improving the treatment of stomach cancer in Asia. Asian surgeons have developed carefully planned surgical protocols for gastric cancer resection, including well-defined systematic nodal dissection (D2 nodal dissection).⁸ These surgical procedures have been thought by some to improve the cure rate of stomach cancer, but when subjected to phase III trials in the West, more extensive resection did not result in increased cure rates compared with less radical surgery.⁹ The larger gastric resections (D2 gastrectomies) were also associated with more operative morbidity. Although cure rate was not increased with D2 nodal dissection, the precision of staging was markedly improved¹⁰ when compared with the less rigorous nodal dissections commonly performed in the United States.^{4,5}

As might be expected, there has been much interest in evaluating adjuvant therapy in Asia. In this issue of *JCO*, Sasako et al¹¹ report the 5-year results of a phase III trial of adjuvant chemotherapy in more than 1,000 Japanese patients with resected gastric cancer. This clinical trial, known as Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC), evaluated the oral fluoro-pyrimidine S-1 in patients with resected stage II/III stomach cancer.¹² This agent has been shown to potentially improve on the efficacy of oral fluorinated pyrimidines by combining the antineoplastic agent with two biologic modulators aimed at reducing bowel toxicity and increasing the anti-tumor efficacy of the fluoro-pyrimidine.

The ACTS-GC trial enrolled 1,034 patients with stages II-III resected gastric carcinoma. Patients all underwent D2 gastrectomies and then were randomly allocated to 1 year of S-1 therapy or to surgery alone. The results of ACTS-GC reporting 3-year survivals were first published in *New England Journal of Medicine* in November 2007.¹³ Eighty percent of S-1 patients were alive at 3 years after gastrectomy versus 70% of surgery-only patients. These survival differences were highly statistically significant and raised provocative questions not only about the activity of adjuvant chemotherapy in gastric cancer, but also about potential differences between stomach cancer in Asia compared with the same tumor histology in the West.

To Western oncologists, there are several striking findings concerning the ACTS-GC study and its outcomes. First, this phase III clinical trial is well designed and well powered. It is a prospectively randomized trial of oral therapy with S-1 monotherapy in patients who underwent D2 gastrectomy versus patients who underwent D2 gastrectomy with no adjuvant therapy. There were 1,034 patients randomly allocated on ACTS-GC, providing a statistical power to easily detect clinically important differences. The fact that monotherapy with S-1 was the treatment arm is unusual to oncologists in north America and western Europe, who generally use combination chemotherapy in advanced stomach cancer and assume that an active multidrug regimen would be the most likely candidate for success as adjuvant therapy. The most striking finding of ACTS-GC is the survival outcome in both the treatment and control arms. Table 1 compares the 5-year survival outcomes of the US Southwest Oncology Group Coordinated Intergroup trial (INT0116) of postoperative chemoradiation and the UK peri-

Table 1. Five-Year Survival Rates

Study	Surgery (%)	Chemoradiotherapy/ Chemotherapy (%)
INT0116	28	43
MAGIC	23	36
ACTS-GC	61	72

Abbreviations: ACTS-GC, Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer; INT0116, Intergroup 0116; MAGIC, Medical Research Council Adjuvant Gastric Infusional Chemotherapy.

operative chemotherapy trial (MAGIC) with the outcomes of ACTS-GC. As can be seen, the ACTS-GC results are strikingly better both for treatment (72% 5-year survival) and for the surgery-only controls (61% 5-year survival) than the MAGIC peri-operative chemotherapy results (36% and 23%, respectively) and INT0116 (43% and 28%, respectively). Western oncologists are particularly impressed with how well the patients treated with surgery only do. One could argue that the Japanese patients had lower stage disease at gastrectomy and therefore had better prognoses than the patients included in INT0116 and MAGIC. In that regard, Table 2 shows that ACTS-GC patients had somewhat more favorable T stage (45% T3/4 v 64% for MAGIC and 68% for INT0116). However, for the strong negative prognostic factor of lymph node metastases,⁵ one may see that ACTS-GC patients had more frequent nodal metastases (89%) than patients in MAGIC (72%) and INT0116 (85%). It appears from examining T stage and nodal dissemination that there are no marked prognostic disparities that could explain the excellent outcomes in both treated and control patients in ACTS-GC.

The patients on the MAGIC trial were identified preoperatively and may well have implicit differences in prognostic factors compared with patients identified after gastrectomy. Patients in ACTS-GC were identified after gastrectomy, as were the patients for INT0116. Therefore it makes sense to carefully investigate the patients in these two studies to look for reasons that may explain the striking outcome differences between the two trials. It is not fruitful to attempt to compare outcomes differences between ACTS-GC and INT0116 by pathologic stage because INT0116 accrued patients in the early to mid 1990s using an American Joint Committee on Cancer staging schema quite different from the current sixth-edition Union for International Cancer Control/American Joint Committee on Cancer used in ACTS-GC.

Tables 3 and 4 examine 5-year survival rates in INT0116 (Table 3) and ACTS-GC (Table 4). It is instructive to look at the surgery-only patients in these two tables. For example, in INT0116,

Table 2. Patient Characteristics

Characteristic	INT0116	MAGIC	ACTS-GC
No. of patients	554	503	1,034
T3/T4, %	68	64	45
Node positive, %	85	72	89

Abbreviations: ACTS-GC, Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer; INT0116, Intergroup 0116; MAGIC, Medical Research Council Adjuvant Gastric Infusional Chemotherapy.

Table 3. INT0116 5-Year Survival Estimates by T Stage and Nodal Status

Characteristic	Chemoradiotherapy (%)	Surgery Only (%)
Nodal status		
N0	60	44
N1-3	50	37
N > 4	30	17
Stage		
T1-2	56	38
T3	38	20

T3 patients, have a 20% survival. In ACTS-GC, T3 patient survivals vary from a high of 70.8% (stage II) to a low of 42.7% (stage IIIB). Likewise, in patients with advanced nodal metastases (stage IIIB), ACTS-GC survival is 40.1%. In INT0116 the roughly comparable group is patients with four or more nodal metastases. The survival of this group (Table 3) is only 17%. The conclusion that one draws from these data is that the ACTS-GC patients do better, sometimes markedly better, stage for stage than the North American patients enrolled onto INT0116. The inescapable conclusion is that the patient populations in these two studies are different and that the outcomes of adjuvant therapy cannot be generalized from one population to the other.

Why do Japanese patients have superior outcomes with resectable gastric cancer? As discussed above, it does not seem to be related to earlier stage at diagnosis. Could it be “better” surgery? There is no question that the consistent use of D2 resection improves the precision of staging,¹⁰ but randomized Western studies have not shown an overall survival benefit.⁹ It has been recognized for a number of years that there are disparities in the uses and outcomes of gastric cancer chemotherapy between Europe/North America and Asia.¹⁴ There may be differences in the toxicity/efficacy profile of S-1 between Asian and North American patients. Tolerable doses may be lower as a result of higher folate levels in North American populations and genetic differences¹⁵ in drug metabolism between Western and Asian populations. These differ-

ences make the application of the same regimens of treatment in the two populations even more complex.

Finally, how should the clinician look at the ACTS-CC results? First, this is a high-quality, well-designed and executed trial. Second, S-1 is a highly effective adjuvant therapy that may be administered with modest toxicity in the Japanese study population. S-1 should be considered a standard of care for such patients. Third, the S-1 therapy as used in ACTS-GC cannot be considered applicable to patients with gastric cancer in the West for the reasons mentioned in this editorial. There is no doubt that there are differences between adenocarcinomas of the stomach in Japan and North America. Finding out precisely what these differences are will hopefully allow us to enhance the outlook for gastric cancer patients throughout the world.

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Table 4. UICC/AJCC Sixth Edition: Survival Outcomes in ACTS-GC

Stage	5-Year Survival	
	S-1	Surgery Only (%)
II (T2N1, T3N0)	83.4	70.8
IIIA (T2N2, T3N1)	68.9	56.7
IIIB (T3N2)	43.7	40.1
IV (T4N1)	45.1	42.7

Abbreviations: ACTS-GC, Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer; AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control.