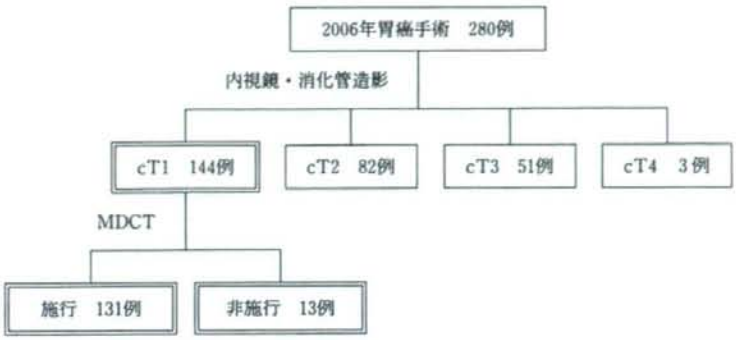


図1　症例の内訳

表1　MDCTによる早期胃癌術前のリンパ節転移診断能

| | 病理組織診 | |
|---|---|---|
| | リンパ節転移あり | リンパ節転移なし |
| 術前MDCTにて<br>リンパ節転移あり | 1<br>(pN1) | 3 |
| 術前MDCTにて<br>リンパ節転移なし | 14<br>(pN1：13例/pN2：1例) | 113 |

感度＝7％
特異度＝97%
陽性適中率＝25%
陰性適中率＝89%
正診率＝87%

科・内科・外科合同の術前カンファレンスにて最終確認した．

## 結　果

144例全例において，開腹下にリンパ節郭清を伴う根治的手術が行われた．組織学的にpT1であったのは134例で，10例がpT2であった．全144例中MDCTが行われたのは131例で（図1），全例に静注造影剤が使用されていた．そのうち4例がMDCTにてリンパ節転移ありと術前診断されたが，この中で実際にリンパ節転移を認めたのは1例のみであった(pN1)．また，術前MDCTでリンパ節転移なしと診断された127例中14例に病理所見でリンパ節転移を認めた（pN1が13例・pN2が1例）．リンパ節転移診断の感度は7％，特異度は97%，陽性適中率25%，陰性適中率89%，正診率87%であった（表1）．

ルーチンの術前MDCTにて検出された他疾患は胆嚢疾患（結石・ポリープ・腺筋症），肝疾患（血管腫・嚢胞），膵疾患（嚢胞），腎疾患（嚢胞・結石・血管筋脂肪腫），副腎疾患（腫瘍），骨盤内疾患（子宮筋腫・卵巣嚢腫・総腸骨動脈壁在血栓）であった．MDCTおよび超音波検査が両方施行された102例の検討では，胆嚢結石・胆嚢ポリープで同時に胆嚢摘出術を施行した9例以外は術式決定に影響を及ぼさず，またその多くが超音波検査でも検出可能であった（表2）．

この期間内にMDCTの所見を理由に手術を中止・延期した症例は認めず，また術前MDCTを省略した13例には省略したことに起因する術中・術後の問題点は一切認めなかった．

## 考　察

早期胃癌で起こりうるほとんどの転移形態はリンパ節転移であり[12]，最も重要な予後因子とされている[13]．このため治療法の選択にあたっては術前にリンパ節転移を正確に把握することが重要で，MDCTを術前に行う大きな理由の一つである．胃癌治療ガイドラインにおいても，深達度T1における治療選択はリンパ節転移度に応じて多岐に渡る[1]．しかし大きさ，形状，造影効果に頼った現状の術前リンパ節転移診断には限界があり，過去の報告から早期胃癌におけるリンパ節転移

表2　術前 MDCT にて検出された他疾患の詳細

| | 検出した検査法 | | | |
|---|---|---|---|---|
| | MDCT および超音波 | MDCT のみ | 超音波のみ | |
| 胆嚢疾患（結石・ポリープ・腺筋症） | 6 | 3 | 6 | → 9例が同時に胆摘を付加 |
| 肝疾患（血管腫・嚢胞） | 18 | 18 | 7 | → 全例経過観察 |
| 膵疾患（嚢胞） | 0 | 1 | 1 | |
| 腎疾患（嚢胞・結石・血管筋脂肪腫） | 5 | 6 | 11 | |
| 副腎疾患（腫瘍） | 2 | 1 | 0 | |
| 骨盤内疾患（子宮筋腫・卵巣嚢腫・総腸骨動脈壁在血栓） | 0 | 6 | 0 | |

診断についての満足すべき結果は得られていない[6)14)~20)]．診断に multiplanar reformation（MPR）像を組み合わせることによりリンパ節と胃周囲血管の区別がより明瞭になるとの最近の報告があるが，それでも正診率の向上は不十分とされている[21)]．また，今回の検討結果からも早期胃癌におけるリンパ節転移診断の感度は7％と低く，術前 MDCT にてリンパ節転移度を正確に把握することは困難と考えられるため，現時点では術前 MDCT の有用性は示されなかった．特異度が97％と高い割に感度が7％と低い理由としては，リンパ節転移の診断基準が狭すぎる可能性が示唆され，結果的に131例中14例(11％)が understaging に陥っていた．また，MDCT における胃癌の深達度診断については，進行癌では有用だが早期癌では精度が低いとする報告が多く，この点においても早期胃癌に対する術前 MDCT の有用性は示されていない[8)~10)]．

腹腔内に並存する他疾患の検索も，胃癌術前に MDCT を行う目的の重要な一つに挙げられる．高齢化社会においては胃癌手術を受ける患者にも高齢化を認め，それに伴い併存疾患を有する症例の割合は年代を経るごとに増えてきている．術前にこれらの併存疾患を確実に把握し，先行手術や同時手術，あるいは術式の変更など，個々の患者の状況に応じて適切に対応することがテーラーメイド医療として求められる．しかし，今回の検討において検出された併存疾患は胆嚢結石・胆嚢ポリープを手術時に同時切除した症例を9例（9％）認めた以外は治療方針や術式決定に影響を及ぼさず，また胆嚢疾患の殆どが超音波検査でも検出可能であった．この点においても術前にルーチンで行う MDCT の有用性は低いと考えられ，まずは全例に対し超音波検査を行い，何か異常所見を認めた場合にのみ MDCT を行うという検査位置づけが効率的ではないかと思われた．

また，胃周囲の血管走行の詳細な把握により術前シミュレーションに利用できることも MDCT の利点の一つとされる．MDCT により得られたスライスデータをワークステーションに転送して処理することにより，術中のイメージに即したリアルな三次元画像を得ることができる[22)~24)]．徳永ら[25)]は安全で正確な手術のためには血管走行の確実な把握が必須と述べ，MDCT および血管再構築（3D-CT angiography）にて術前診断した Adachi VI型の手術症例を報告している．また Okabayashi ら[26)]は後胃動脈の走行を術前に把握することが外科治療に有用と述べている．確かに血管走行の把握は手術の一助となりうるが，手術症例全例に thin-slice の MDCT および3D-CT angiography を施行するのは人的労力および経費の問題から困難であり，通常は腹腔鏡手術や拡大郭清を予定する症例に限って施行しているのが実状と考えられる．しかし腹腔鏡下手術などに際し術前に行われる thin-slice の MDCT や3D-CT angiography の有用性が期待される一方で，5 mm スライス厚での MDCT で指摘し得なかった血管走行の異常は術中にしばしば経験することがある．開腹下手術に限っては実際に術中初めて血管の走行異常に気付いても慎重かつ臨機応変な対応により安全な D2郭清手術は可能である．

以上，今回の検討では早期胃癌におけるルーチンで行われる術前 MDCT の有用性は低いことが示唆された．近年の著しい普及により広く MDCT が行われている現状があるが，早期胃癌の必要十分な術前検査として，医療費節約の観点，患者への過剰な放射線被爆の問題からもまずは超音波検査を行うことで多くの症

例でMDCTが省略可能ではないかと考えられた．当然ながら全症例に対し超音波検査で代用可能という訳ではなく，肥満など体型的な問題から腹部超音波検査による腹腔内の描出が不良な場合や，また超音波検査で胃壁肥厚や胃周囲リンパ節腫大が疑われた場合などは，躊躇なくMDCTを追加し，さらなる術前評価を行うべきと考える．

## 結　語

今回の検討から現状では内視鏡検査，上部消化管造影検査を行って胃癌と診断されたときに深達度SM以浅と考えられる早期胃癌の術前検査においてはルーチンで行われるMDCTの有用性は低いことが示唆された．まずは超音波検査を行い，必要と思われる症例に限りMDCTを追加施行することが効率で有効と考えられた．

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## DIAGNOSTIC PERFORMANCE OF MDCT FOR EARLY GASTRIC CANCER

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Background : To completely remove tumors or to avoid excessive treatments, a precise assessment of cancer spread before surgery is important to determine the best treatment strategy for patients with early gastric cancer (EGC). However, previous results of preoperative staging on EGC have not been satisfactory. Purpose : The purposes of this study were to assess the diagnostic performance of multidetector-row computed tomography (MDCT) and to examine whether routine MDCT was necessary for preoperative diagnosis of EGC. Patients and method : During 1-year period, 280 consecutive patients with gastric cancer underwent surgery in our institution. Among these 280 patients, 144 were diagnosed preoperatively as EGC with gastroscopy and upper gastrointestinal series. MDCT findings were compared with operative findings and histopathologic studies of the resected specimens. Results : Among 144 patients, 131 underwent preoperative MDCT. The sensitivity, specificity and accuracy of MDCT for detection of lymph node metastasis were 7%, 97% AND 87%, respectively. Cholelithiasis, liver hemangioma, liver cyst, renal cyst were detected with routine MDCT. According to the result of MDCT cholecystectomy was added on 9 patients. Conclusions : MDCT was insufficient for assessing regional lymph node metastasis. It is suggested that we could omit MDCT from preoperative examinations for patients with EGC.

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# Prospective Evaluation of Selection Criteria for Active Surveillance in Japanese Patients with Stage T1cN0M0 Prostate Cancer

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**Objective:** Selection criteria for active surveillance (AS) program of localized prostate cancer remain to be standardized. The purpose was to evaluate the validity of selection criteria and investigate the feasibility of this AS program.

**Methods:** Patients meeting the criteria (i) stage T1cN0M0, (ii) age 50–80, (iii) serum prostate-specific antigen (PSA) ≤20 ng/ml, (iv) one or two positive cores per 6–12 systematic biopsy cores, (v) Gleason score ≤6, and (vi) cancer involvement in positive core ≤50% were enrolled and encouraged to start AS for at least 6 months during the period between January 2002 and December 2003. PSA was measured bimonthly for 6 months and every 3 months thereafter. Trigger of treatment recommendation was PSA-doubling time (PSADT) of ≤2 years or pathological progression at re-biopsy. Primary endpoint was '%PSADT > 2y', which was defined as the proportion of patients who showed PSADT assessed at 6 months >2 years out of all the patients who chose AS. Point estimate of '%PSADT > 2y' was expected to be >80%.

**Results:** One hundred and eighteen patients opted for AS and 16 chose immediate treatment at enrollment. PSADT for the initial 6 months based on four measurements could be assessed in 106 patients. Intent-to-treat analysis of '%PSADT > 2y' was 71.2% (84/118, 95% CI: 62.1–79.2). Pathological progression rate at 1-year re-biopsy was 33%. Fifty-four (46%) patients remained on AS for maximal observation of 54 months. General health-related QOL in patients undergoing AS was not impaired.

**Conclusions:** The primary endpoint, '%PSADT > 2y', did not meet the pre-specified decision criteria. Further prospective study with revised program and endpoint is needed.

*Key words: active surveillance – prostate cancer – PSA-doubling time*

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## INTRODUCTION

Widespread use of prostate-specific antigen (PSA) testing in Japan has resulted in a marked increase in the incidence of 'favorable risk' cancer, as has been seen in Western countries. Subsets of prostate cancers detected by PSA screening, however, might not have adversely affected patients' life span if they were to remain undetected. Etzioni et al. (1) estimated over-diagnosis rates under PSA screening in Caucasian and African-American men as 18–44%, but the rate still remains unclear in Japanese men. Minimal cancer (tumor volume $<0.5$ ml, organ-confined, no Gleason pattern 4 or 5) was found in 31.6% in the first round and 42.6% in the second round (4-year interval) in the screening arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC), Section Rotterdam (2). In contrast, Loeb et al. (3) detected only 5–10% of clinically insignificant cancer in their longitudinal prostate-cancer screening study. To avoid over-treatment without compromising lifetime, active surveillance (AS) with selective delayed intervention seems a practical treatment option for favorable risk patients, although selection criteria remain to be standardized.

Selection criteria so far published were based on biopsy features and PSA levels at diagnosis, although they have not yet been validated in a prospective trial (4,5). Organ-confined cancers with tumor volume $>0.5$ ml of Gleason score $\leq 6$ have been considered as indolent or clinically unimportant. This standard, however, was arbitrarily defined (6). What is clinically more important is tumor growth velocity. The only way so far applicable for the prediction of tumor growth velocity is to utilize PSA kinetics. In men with untreated prostate cancer, serum PSA appears to increase exponentially over time (7). Therefore, PSA-doubling time (PSADT), calculated using log-linear regression, may be an appropriate measure of cancer growth.

In this study, we have prospectively evaluated the selection criteria for AS with selective delayed intervention in patients with favorable risk prostate cancer using PSADT that was calculated with four consecutive PSA points for 6 months as a primary endpoint.

## PATIENTS AND METHODS

This was a multi-center prospective non-randomized study. Seven cancer center hospitals and six university hospitals participated in this study. The institutional review board of each participating institution approved the study protocol and all the patients gave written informed consent.

### Study Population and Enrollment Criteria

Patients with newly detected stage T1cN0M0 prostate cancer harboring the biopsy features described subsequently were enrolled during the period between January 2002 and December 2003. In order to be eligible for the study, participants should have met the following criteria: (i) age ranging between 50 and 80, (ii) initial serum PSA being $\leq 20$ ng/ml, (iii) number of positive core being one or two per 6–12 systematic biopsy cores, (iv) Gleason score being $\leq 6$ and (v) $\leq 50\%$ cancer involvement in any of the positive cores. Patients who had past history of cerebral infarction, unstable angina, diabetes uncontrollable with insulin, severe hypertension or suffered myocardial infarction within 6 months were excluded from this study. In the first step, candidate patients in whom the biopsy criteria of (iii), (iv) and (v) were confirmed by the central pathologist were asked to give their written consent to participate in this study. Then the patients were encouraged to start AS for at least 6 months according to the program described subsequently. Those who did not want to opt for AS immediately started treatments including radical prostatectomy (RP), external beam radiation (EBRT) and androgen-deprivation therapy (ADT).

### The AS Program

In patients who opted for the AS program, serum PSA was monitored every 2 months for 6 months and every 3 months thereafter. Those who showed PSADT of $\leq 2$ years (y) after 6 months were recommended to start aggressive treatment. After the initial checkpoint, patients undergoing AS were recommended to start treatment when either PSADT assessed with all PSA measurements or PSADT assessed with PSA points measured within 1 year was $\leq 2$ years. The patients who remained on AS for 1 year were recommended to undergo re-biopsy and those who did not fit the initial pathology criteria were also recommended to start aggressive treatment.

### PSA Assay and PSADT

All PSA determinations were made centrally using the Tandem-R monoclonal immuno-radiometric assay (Hybritech Inc., San Diego, CA, USA). PSADT was assessed with the assumption that PSA changed with time in simple exponential fashion, which was precisely described elsewhere (8). PSADT was calculated as the natural log of 2 divided by the slope, if PSA values were distributed on the $y$-axis of a scatter plot and time on the $x$-axis. It was a line function that fitted the PSA values over time and the PSA slope was calculated using least-squared regression. Outlier of PSA values was excluded from regression calculation when clinical manifestation of prostate inflammation was apparent. These calculations were performed with the software specifically developed for this study.

When an unnatural increase in serum PSA was found during AS, re-measurement of PSA was allowed within 3 months. Then, the principal investigator, the secretary of the study office and the duty doctor discussed whether the pending PSA value could be omitted from the PSADT evaluation.

### Histopathological Review

In addition to the eligibility criteria (iii), (iv) and (v) described earlier, the maximal tumor length was recorded for all positive cores by the central pathologist. For radical prostatectomy specimens, stepwise serial sections were made and subjected to thorough pathological review. Pathological T-stage was described according to the UICC TNM-classification 1997 (9).

### QOL Assessment

The patient-reported health-related quality of life (HRQOL) was assessed at the time of registration and 1 year later. General HRQOL was evaluated with the Japanese version RAND SF-36 (10), and disease-related QOL was assessed with the Japanese version UCLA Prostate Cancer Index (UCLA PCI) (11). Each scale of SF-36 was standardized to the Japanese population normative values, with a mean score of 50 and an SD of 10. The function and bother scores of urinary, bowel and sexual domains of UCLA PCI were calculated according to the scoring instructions (12).

### Endpoints and Sample Size

Primary endpoint was '%PSADT > 2y' defined as a proportion (%) of AS patients showing PSADT >2 years at the initial 6-month assessment out of all the patients who opted for AS at registration. The secondary endpoints were defined as follows: (i) proportion (%) of AS patients who met the initial pathology criteria at the time of re-biopsy, (ii) proportion (%) of the non-organ-confined rate in patients who chose radical prostatectomy as an initial strategy, (iii) adverse events in patients who chose aggressive treatment as an initial strategy, (iv) impairment of HRQOL in AS patients and other treatment patients, (v) overall survival of AS patients and other treatment patients and (vi) metastasis-free survival of AS patients and other treatment patients. The planned sample size was 100 patients who opted for AS, which was determined based on the precision of estimate to give the width of 95% confidence intervals for '%PSADT > 2y' within 10%.

### Follow-up

The local progression in AS patient was examined with digital rectal examination (DRE) and transrectal ultrasonography at least twice per year and at the suspicion because of rising PSA. Chest X-ray, CT scan or MRI for abdominal/pelvic cavity and bone scintigraphy were performed at least once every two years to rule out the presence of metastasis.

### Statistical Analysis

This study was designed to evaluate the validity of our selection criteria for AS. Point estimate of the primary endpoint was expected to be >80% for validating the selection criteria. The point estimates and 95% confidence intervals calculated by the exact method were carried out for proportions. For QOL analysis, subscale scores were compared with the Japanese population normative values and differences of subscale scores within patients were assessed. The Student's *t*-test and paired *t*-test were carried out accordingly in QOL analysis for exploratory purpose.

## RESULTS

### Participants

One hundred and thirty-four patients were enrolled into this study, and 118 chose the AS program and 13 chose RP, 2 chose EBRT and 1 chose ADT as an initial treatment. Table 1 shows clinical and pathological characteristics of each treatment group.

### PSADT in AS Patients and Primary Endpoint

Among 118 patients who chose the AS program, 7 changed the treatment strategy immediately after registration and 5 patients missed at least 1 PSA determination during the first 6 months. Therefore, PSADT at 6 months was completely calculated in 106 AS patients. Fortunately, there was no unnatural increase in PSA possibly due to prostate inflammation during the initial 6-month evaluation, although it was found in 11 patients thereafter. Distribution of PSADT at 6 months in the 106 patients is shown in Fig. 1. Twenty-two patients showed PSADT to be <2 years, whereas 59 patients showed PSADT to be >10 years or negative PSA slope. On the basis of the intent-to-treat analysis, the primary endpoint, '%PSADT > 2y' at 6 months, was 71.2% (95% CI: 62.1–79.2%).

### Prediction of 'Rapid Riser'

Among 106 AS patients in whom PSADT at 6 months was completely calculated, 22 (20.8%) patients were so-called rapid risers (PSADT ≤2 years) as described earlier. In order to analyse the proportion of rapid riser in the setting of more stringent criteria, one more condition could be added to the original criteria. Either one of following conditions could be added: (i) PSA density <0.15, (ii) maximum tumor length <3 mm, (iii) initial PSA <10 ng/ml or (iv) only one positive core per 6–12 systematic cores. Distribution of PSADT ≤2 years, 2 years <PSADT <10 years and PSADT ≥10 years under the four sets of criteria was compared (Table 2). Distribution of PSADT, however, did not prove to be statistically different between any of the subgroups and the original AS cohort, and the proportion of rapid risers under more stringent condition was not reduced.

**Table 1.** Baseline data in each treatment group

| | AS | RP | EBRT | ADT | Total |
|---|---|---|---|---|---|
| Age | | | | | |
| 50–59 | 5 | 0 | 0 | 0 | 5 |
| 60–69 | 51 | 6 | 0 | 0 | 57 |
| 70–74 | 44 | 6 | 1 | 0 | 51 |
| 75–80 | 18 | 1 | 1 | 1 | 21 |
| Initial PSA (ng/ml) | | | | | |
| <10 | 95 | 11 | 1 | 1 | 108 |
| ≥10 | 23 | 2 | 1 | 0 | 26 |
| Mean | 7.2 | 7.1 | 11.2 | 4.6 | 7.3 |
| Core no. at biopsy | | | | | |
| 6 | 37 | 5 | 0 | 0 | 42 |
| 7–8 | 33 | 7 | 1 | 1 | 40 |
| 9–10 | 21 | 2 | 1 | 0 | 24 |
| 11–12 | 27 | 1 | 0 | 0 | 28 |
| Positive core no. | | | | | |
| 1 | 91 | 10 | 1 | 1 | 103 |
| 2 | 27 | 3 | 1 | 0 | 31 |
| Gleason sum | | | | | |
| 5 | 13 | 2 | 0 | 0 | 15 |
| 6 | 105 | 11 | 2 | 1 | 119 |
| Max. % cancer | | | | | |
| Mean | 13.6 | 9.4 | 16.8 | 11.1 | 13.5 |
| Median | 11.2 | 9.0 | 16.8 | 11.1 | 11.1 |
| Max | 46.7 | 35 | 23.3 | 11.1 | 46.7 |
| Max. tumor length (mm) | | | | | |
| <3 | 103 | 12 | 1 | 1 | 117 |
| ≥3 | 15 | 1 | 1 | 0 | 17 |
| Mean | 1.6 | 1.5 | 2.5 | 1.0 | 1.6 |
| Median | 1.4 | 1.5 | 2.5 | 1.0 | 1.5 |
| Max | 5.8 | 3.5 | 3.5 | 1.0 | 5.8 |

One patient who chose EBRT at registration underwent RP soon after registration.
ADT: androgen-deprivation therapy
AS: active surveillance
PSA: prostate-specific antigen
RP: radical prostatectomy
EBRT: external beam radiation

### The 6-Month PSADT Versus the 12-Month PSADT

For 99 patients undergoing AS for ≥1 year including 12 patients who wanted to remain on AS in spite of short PSADT at 6 months (≤2 years), the initial 6-month PSADT was compared with the 12-month PSADT that was assessed using all PSA determinations for 1 year after registration, as shown in Fig. 2. Eight of the 12 patients who wanted to remain on AS in spite of short PSADT (PSADT ≤2 years) at 6 months showed the 12-month PSADT to be >2 years.

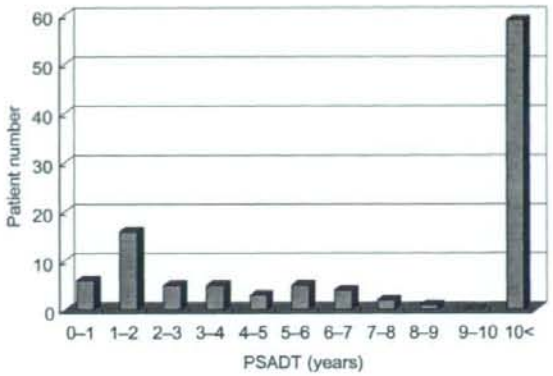


**Figure 1.** Distribution of the initial 6-month prostate-specific antigen doubling time (PSADT). PSADT >10 years or those which showed negative slope is categorized as PSADT >10 years.

In contrast, among 58 patients with PSADT estimated at 6 months being >10 years ('stable PSA'), only two patients showed PSADT <2 years at 12 months.

### Re-biopsy

As a rule of the present study, re-biopsy was recommended to the patients who remained on AS for 1 year and showed PSADT >2 years at the 12-month evaluation, although a few wanted to continue AS in spite of short PSADT. Sixty-six out of 99 patients who remained on AS at least for 1 year agreed to undergo re-biopsy. Among the 66 patients, four patients wanted to remain on AS in spite of PSADT <2 years. The pathological evaluation revealed that 44 out of 66 patients (66.7%, 95% CI: 54.0–77.8) were eligible for the pathological selection criteria again, including 25 patients in whom the second-round biopsy turned negative. Among the 22 patients who did not meet the criteria, three or more positive cores were found in 15 patients, Gleason score ≥7 was observed in 13 and >50% cancer occupation in a positive core was found in 7 as shown in Table 3. There was no association of PSADT with the aggressive findings. Two of four who had PSADT <2 years showed the aggressive findings and the remaining two met the pathological criteria again. After confirmation of deviation from the pathological criteria at re-biopsy, 15 of 22 patients immediately underwent treatment (10: RP; 3: EBRT with or without ADT; 1: seed implantation; 1: ADT) and showed no clinical recurrence until 31 October 2006. In contrast, seven patients wanted to continue AS despite the aggressive pathological findings at re-biopsy. Six remained on AS uneventfully, whereas one patient who started ADT 1 year later showed re-elevation of PSA on 31 October 2006.

### Prostatectomy Specimens

Thirteen patients chose RP as the initial treatment and one patient who chose EBRT at registration underwent RP

**Table 2.** Distribution of the initial 6-month PSADT in subgroups that fit the original selection criteria or that with one additional restriction

| PSADT at 6 months | Original criteria (%) | Additional restriction (%) | | | |
|---|---|---|---|---|---|
| | | Initial PSA <10 | PSAD ≤0.15 | One positive core | Max. length <3 mm |
| Rapid | 22 (20.8) | 18 (21.7) | 10 (23.8) | 17 (20.5) | 21 (22.6) |
| Intermediate | 25 (23.5) | 23 (27.7) | 12 (28.5) | 20 (24.1) | 21 (22.6) |
| Stable | 59 (55.7) | 42 (50.6) | 20 (47.6) | 46 (55.4) | 51 (54.8) |
| Patient number | 106 | 83 | 42 | 83 | 93 |

Rapid: PSADT was ≤2 years; intermediate: PSADT was between 2 years and 10 years; stable: PSADT was ≥10 years.
PSADT: prostate-specific antigen doubling time

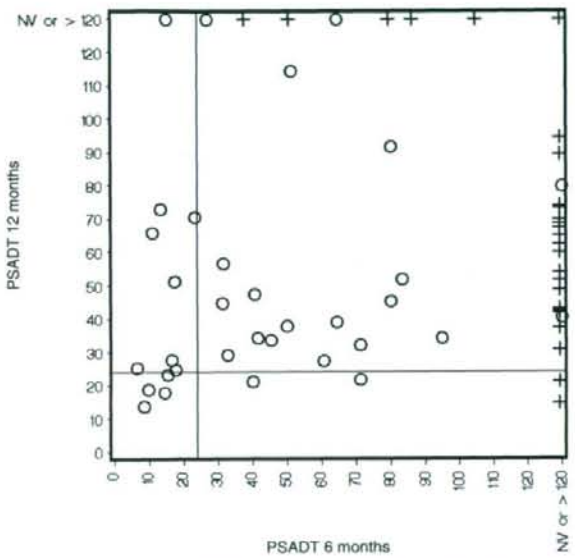


**Figure 2.** Comparison of the 6-month with the 12-month PSADT in 99 patients who remained on active surveillance (AS) for at least 1 year. '+' indicates PSADT >10 years. 'O' indicates PSADT ≤10 years.

immediately after enrollment. Non-organ-confined cancer, positive surgical margins and peri-neural invasion were found in 1, 3 and 4 patients, respectively. There was no lymphatic, vascular and seminal vesicle invasion. Invasion to the bladder wall, the urethral mucosa and the rectal wall were also not found (data not shown).

### HRQOL in AS Patients

Baseline HRQOL was measured in 128 patients (AS: 114; RP: 11; EBRT: 2; ADT: 1). As to the general HRQOL measured with SF-36, the physical functioning, bodily pain and vitality scores in patients who chose the AS program were better than the age-adjusted Japanese population normative values ($P < 0.05$, Student's $t$-test) as shown in Fig. 3A. There was no difference in the baseline scores of both SF-36 and UCLA-PCI between those who remained on AS and those who started other treatment within 1 year. HRQOL of 1 year after AS was measured in 95 patients, and the subscale scores of SF-36 were not statistically different from the baseline scores. Bodily pain, vitality and mental health scales in patients remaining on AS for 1 year were better than the age-adjusted Japanese population normative values ($P < 0.05$, Student's $t$-test), as shown in Fig. 3B. In AS patients, however, the urinary function, sexual function and bowel bother scores measured with UCLA-PCI were worse than the baseline scores ($P < 0.05$, paired $t$-test).

**Table 3.** Pathological findings of re-biopsy at 1 year after AS and deviation rates from the selection criteria

| Pathological criteria | | | | | | Deviation rate (%) |
|---|---|---|---|---|---|---|
| Number of positive core | 0 | 1 | 2 | 3 | 4 or more | |
| Patient number | 25 | 13 | 13 | 12 | 3 | 22.7 |
| % Cancer/ positive core | 0 | 1–25 | 25–50 | 50–75 | 75–100 | |
| Patient number | 25 | 28 | 6 | 5 | 2 | 10.6 |
| Gleason score | No score | 5 | 6 | 7 | 8–10 | |
| Patient number | 25 | 2 | 28 | 9 | 4 | 19.7 |

Number of patients who deviated each pathology criterion was divided with number of AS patients who agreed with re-biopsy ($n = 66$).

### Follow-up after Registration

Of all participants, neither manifestation of metastasis nor cancer death was observed until 31 October 2006, and three died of other disease and five did not turn up for follow-up. Of the 118 patients who chose AS, 54 (46%) remained on AS for maximal observation of 54 months, with 3-year actuarial AS-remaining rate being 48.9%. The reasons for

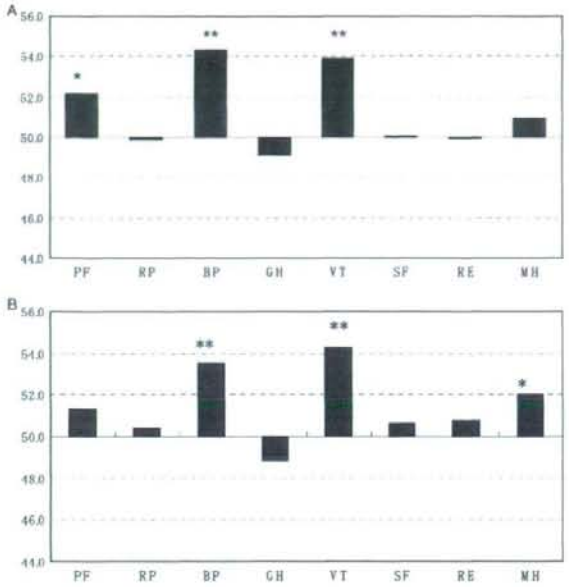


**Figure 3.** (**A**) Norm-based scoring of general health-related quality of life (HRQOL) at registration assessed with SF-36 in patients who chose AS. $^{*}P < 0.001$, $^{**}P < 0.0001$. (**B**) Norm-based scoring of general HRQOL 1 year after AS. PF, physical function; RP, role physical; BP, bodily pain; GH, general health perception; VT, vitality; SF, social function; RE, role emotional; MH, mental health. $^{*}P < 0.05$, $^{**}P < 0.01$.

leaving AS in the 64 patients were as follows: PSADT $\leq$2 years in 17, pathology progression in 16 and change in T-stage (T1c–T2a) in one. The remaining 30 patients have left AS either due to patient's preference ($n = 15$), co-morbidities ($n = 8$) or for some unknown reason ($n = 7$). Among the 15 patients who wanted to leave the AS program without PSA rise or progression, eight complained of aggravating difficulty in urinary voiding due to accompanying benign prostate hyperplasia (BPH), resulting in undergoing cancer treatment (RP: 4; EBRT: 1; ADT: 1) or transurethral resection of BPH ($n = 2$). Of 16 patients who chose immediate treatment, 15 have been alive without metastasis and one died of lung cancer. Through the observation period, no serious adverse event has been observed in both the AS program group and those who chose immediate treatment.

## DISCUSSION

This is the first prospective study on AS in Japanese patients with prostate cancer detected only with PSA elevation. Until the time we started this study, AS had not yet been generally accepted treatment option in Japan, where a randomized study comparing AS with non-AS could hardly been accepted. We therefore designed this study as a phase II setting to assess the validity and feasibility of our AS program. We enrolled 118 AS patients from 13 institutions, which was fewer than the expectation from viewpoint of the most current urology practice. In the early 2000s, however, the annual average number of stage T1cN0M0 patients newly treated at a university hospital or a cancer center hospital in Japan was estimated to be 20–40. Among them, 10–20% of stage T1c might have met the Hopkins pathology criteria for indolent cancer. Under these circumstances, the number of enrollment and those opting for AS suggests high motivation of participants in this study.

PSADT assessed with four serial measurements for 6 months was used as the primary endpoint in this study, although it was a surrogate for survival endpoint. In the calculating PSADT, one critical issue to be solved is how we should handle unnatural surges possibly due to prostate inflammation. Particularly, the number of PSA determinants was relatively small; the influence of measurement error upon estimation of PSADT would be strong. In this study, there was fortunately no unnatural increase in PSA during the initial 6-month evaluation, which might have influence on the primary endpoint. As to the point estimate of '%PSADT > 2y', it was expected to be >80% when this study was designed under the following backgrounds. In 43 untreated cases including 15 non-organ-confined cancers at Stanford University series, 79% showed PSADT to be >2 years (7). In 48 Japanese untreated localized cancers (T1-3N0M0 including 40% of Gleason score $\geq$7), 71% showed PSADT to be >2 years (13). Our previous retrospective study in 78 Japanese untreated patients (T1N0M0: 53, T2-3N0M0: 25) found that 91% showed PSADT >2 years (14). On the basis of these retrospective studies, although all were small in size, we expected '%PSADT > 2 y' to be $\geq$80% for the validation of the selection criteria because candidate patients with this selection criteria harbored more favorable biopsy features than those described earlier.

'%PSADT > 2 y'did not reach 80%, and the selection criteria were not validated. We, however, do not consider that major revision of the selection criteria is needed. In the next study, we rather consider that the primary endpoint should be assessed after a longer period ($\geq$1 year) of observation. Comparison of the 6-month PSADT with the 12-month PSADT in the present AS patients strongly suggests the possibility of overestimation as to PSADT estimated at 6 months. The Toronto AS experience demonstrated that the optimal time to determine whether to start a definitive treatment was 2.3 years after starting AS in most of the cases (15,16). In D'Amico et al.'s (17) PSA velocity study, most of the cohort were followed for median of >5 years prior to prostatectomy, but cancer-death rate at 7 years was only 1.75% in Gleason score $\leq$6 patients. These data warrant a prospective study of AS in which 1–2 years are allowed for observing PSA kinetics. It also remains undetermined whether the critical point of recommendation to start treatment should be PSADT $\leq$2 years or PSADT $\leq$3 years. The Toronto AS program has recently revised the timing of

treatment recommendation from PSADT ≤2 years to PSADT ≤3 years (16).

The present study demonstrates the limitation of the current systematic biopsy with regard to select low-risk cancers. The upgrading rate (19.7%) was slightly higher than that (12.9%) seen in the Johns Hopkins series (18). Under-estimation of biopsy has also been demonstrated in the patients who chose RP immediately after registration. These results indicate the necessity to incorporate re-biopsy into AS program, although patients who opt for AS seem to be reluctant to undergo re-biopsy.

The Scandinavian randomized trial did not indicate any significant impairment of HR-QOL at 5 years in the watchful waiting arm (19). Similarly, in the present study, any of the SF-36 subscales was not impaired after 1 year of AS. Although 54% of the patients left the AS program and started therapy to the prostate with maximal observation of 4.5 years, 14% stopped AS due to aggravation of physical condition unrelated to prostate cancer. In particular, it should be noted that 7% of AS patients left AS due to voiding difficulty caused by accompanying BPH.

In conclusion, the results obtained here together with those in similar AS programs being conducted in North America and Europe warrant a prospective analysis of AS program in Japanese patients with modified protocol in which selection criteria and primary endpoint are revised.

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### Conflict of interest statement

None declared.

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# Adjuvant and Neoadjuvant Therapy of Gastric Cancer: A Comparison of Three Pivotal Studies

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In the past, the role of adjuvant therapy for gastric cancer was indefinite. However, three large, randomized controlled trials have recently shown the survival benefit of adjuvant therapy over surgery alone: the American INT 0116 trial, with adjuvant chemoradiation therapy; the European MAGIC trial, with perioperative combination chemotherapy; and the Japanese ACTS-GC trial, with adjuvant monotherapy. Because the patient populations and surgical approaches are considerably different among these trials, it is not sensible to simply compare survival rates to determine the best modality. In the time since these pivotal trials, various innovative studies have been planned and launched to evaluate treatment factors including modality (chemotherapy or chemoradiation), timing (before and/or after surgery), and different surgical extent (D1 or D2 lymphadenectomy). Because the East and West have different backgrounds and treatments for localized gastric cancer, each region should design its own clinical trial to determine the best evidence-based treatment regimens.

## Introduction

Adjuvant therapy aims to improve survival by eliminating residual micrometastatic disease after curative resection of solid tumors. Gastric cancer has long been a focus of adjuvant studies; however, numerous past trials failed to prove the benefit of adjuvant therapy. Although some meta-analyses showed statistically significant superiority of adjuvant chemotherapy, they could not provide clinically significant conclusions due to the heterogeneity in therapeutic regimens, disease stages, and quality of surgery among the studied trials [1,2]; all phase 3 trials thus needed a control arm of surgery alone to produce evidence. The absence of a pivotal trial in adjuvant therapy for gastric cancer could be attributed to two reasons: 1) the absence of powerful treatment regimens to improve survival, and 2) the difficulty in conducting a large-scale, randomized controlled trial with sufficient statistical power for this disease.

Recently, three different modalities of adjuvant therapy for localized gastric cancer were proven to improve survival in three large-scale, randomized controlled trials conducted in three different regions in the world. These trials, the SWOG 9008/INT 0116 trial (INT 0116) of adjuvant chemoradiation in the United States [3], the MAGIC trial of perioperative three-agent chemotherapy in Europe [4••], and the ACTS-GC trial of adjuvant S-1 monotherapy in Japan [5••] have led to a new phase in this field of study.

Because these studies have different patient populations and surgical approaches, cross-trial comparisons of the survival results are not easy. In this review, these trials are carefully compared with special reference to the patient selection and the role of surgery. Currently active clinical trials and future directions are also discussed.

## Overview of the Three Trials

### The INT 0116 trial

The eligibility criteria for the INT 0116 study included stage IB through IV M0 adenocarcinoma of the stomach or gastroesophageal junction, with registration occurring 20 to 41 days after complete resection with free resection-line involvement. Of the 603 patients registered between 1991 and 1998, 556 were eligible and randomly assigned to surgery only ($n$ = 275) or to surgery plus chemoradiotherapy ($n$ = 281). The adjuvant regimen consisted of 5-fluorouracil (5-FU) (425 mg/m$^2$) plus leucovorin (20 mg/m$^2$) for 5 days, followed by a total of 45-Gy radiation given for 5 weeks with modified doses of 5-FU/leucovorin, and two 5-day cycles of 5-FU (425 mg/m$^2$) plus leucovorin (20 mg/m$^2$). Chemoradiotherapy was completed as planned in 64% of patients; it was stopped in 25% because of toxic effects or patient declination. Three patients (1%) died of toxic effects.

More than half the tumors were located in the antrum, and about 20% were in the cardia. Sixty-nine percent of the tumors were T3 or T4, and 85% had nodal metastases. The review of the surgical records of 552 patients showed that, although the study protocol had recommended D2 lymphadenectomy, the majority underwent limited resection (54% D0, 36% D1, 10% D2). With a median follow-up of 5 years, the median survival time and the 3-year survival rates of the surgery and surgery-plus-chemoradiation groups were 27 months (41%) and 36 months (50%), respectively. The first site of recurrence was more local-regional in the surgery-only group than in the adjuvant group.

### The MAGIC trial

The eligibility criteria for the MAGIC trial included stage II or higher M0 adenocarcinoma of the stomach or lower third of the esophagus that was deemed resectable. Between 1994 and 2002, 503 patients were randomly assigned to surgery alone ($n$ = 253) or to perioperative chemotherapy and surgery ($n$ = 250). The chemotherapy consisted of three preoperative and three postoperative cycles of ECF: epirubicin (50 mg/m$^2$) plus cisplatin (60 mg/m$^2$) on day 1 and a continuous intravenous infusion of 5-FU (200 mg/m$^2$) for 21 days. Of the 237 patients who started preoperative chemotherapy, 215 (90.7%) completed it, and 209 of this subset proceeded to surgery. Postoperative chemotherapy was started in 137 patients and was completed in 104 patients (41.6% of the chemotherapy group).

Surgery was performed in 91.6% of the chemotherapy group and in 96.4% of the surgery group. Resection was curative in 69.3% of the chemotherapy group and 66.4% of the surgery group. The extent of lymphadenectomy was not specified in the protocol and was decided by the surgeon. The postoperative mortality rates were similar between the two groups (5.6% and 5.9%). In the surgery group, 63.2% of tumors were T3 or T4, and 73.1% had lymph node metastases. In the chemotherapy group, the tumor diameter was smaller, the proportion of T1 and T2 was greater, and the proportion of N0 and N1 was greater than in the surgery group, suggesting the downstaging effect of preoperative chemotherapy.

With a median follow-up of 47 to 49 months, the overall and progression-free survival rates in the chemotherapy group were significantly better than those in the surgery group. The 5-year survival rates were 36.3% in the chemotherapy group and 23.0% in the surgery group. Both local and distant recurrences were more frequently seen in the surgery group.

### The ACTS-GC trial

The eligibility criteria for the ACTS-GC trial included stage II (excluding T1), IIIA, or IIIB adenocarcinoma of the stomach, after D2 or more extensive curative surgery, with no tumor cells in the peritoneal lavage cytology; patients were also no older than 80 years of age. Between 2001 and 2004, 1059 patients were registered from 109 high-volume hospitals in Japan and were randomly assigned to surgery only ($n$ = 530) or to adjuvant chemotherapy ($n$ = 529). The chemotherapy consisted of 6-week cycles of S-1 (an orally active fluoropyrimidine [6–8]; 80 mg/m$^2$ for 4 weeks followed by 2-week rest) for 1 year starting within 6 weeks postoperatively. This regimen was continued for at least 3 months in 87.4% of patients, for 6 months in 70.8%, and for 12 months in 65.8%. Dose modification due to toxicity was necessary in 42.4% of patients. The tumors were predominantly located in the distal stomach; 58% were treated by distal gastrectomy. Forty-six percent of the tumors were T3 or T4, and 89% had lymph node metastasis.

The study was designed to compare the 5-year overall survival, but the first interim analysis with a median follow-up of 2 years showed a significant difference in overall and relapse-free survival in favor of the chemotherapy group, and the trial was discontinued. In the published data, with a median follow-up of 2.9 years, the 3-year overall survival rates were 80.1% in the chemotherapy group and 70.1% in the surgery group. Fewer relapses in peritoneum and lymph nodes were observed in the chemotherapy group. Subgroup analyses showed no interaction between any studied variables.

## Comparison of the Three Trials

### Patient population

*Curability*

The patient population was essentially different between the MAGIC trial and the other two trials. MAGIC recruited cases deemed to be resectable, whereas the other two studies included only patients after curative gastrectomy. It has been well established that R0 resection without gross or microscopic residual disease is one of the most important prognostic determinants of gastric cancer [9,10].

Curability of gastric cancer without apparent distant metastasis largely depends on peritoneal dissemination. Staging laparoscopy with biopsy is the only method available to diagnose this before definitive surgery. In the MAGIC trial, laparoscopy was listed as a staging method but did not seem to have been employed in many patients: in 28% of the patients assigned to the surgery group, the operation turned out to be noncurative at laparotomy, and half of these individuals underwent nonresectional surgery.

Contamination of noncurative cases is inevitable in neoadjuvant trials but should be avoided with every effort. It is especially important to exclude individuals with peritoneal metastasis that is most refractory to chemotherapy. In current ongoing trials for neoadjuvant therapy, staging laparoscopy is usually mandatory to exclude peritoneal disease and is useful to select patients who may truly benefit from the treatment [11•].

*Tumor stage*

In the INT 0116 and ACTS-GC trials, only patients with pathologically confirmed stages after curative resection were recruited. More T3/T4 tumors were included in INT 0116 (69%) than in ACTS-GC (46%), but lymph node metastasis was less frequently detected in INT 0116 (85%) than in ACTS-GC (89%). It is well established that incidence and extent of nodal metastasis closely correlate with T stage of the primary tumor [12]; therefore, the above observation may appear contradictory. This may be explained by the fact that lymphadenectomy and postoperative nodal retrieval are more extensively performed in Japan; thus, small nodal disease possibly overlooked in the US trial could be detected.

In the MAGIC trial, it is difficult to determine the exact proportions of T and N stages of gastric cancer from the published data, partly because they were presented together with esophageal cancers and partly because there are several missing or "unknown" data. Nodal status is available in 156 of 187 gastric cancer patients in the surgery group, and only 114 (73%) had nodal metastasis, which is considerably lower than the other two trials (85% for INT 0116 and 89% for ACTS-GC). However, this is likely to be an underestimation because nonresectable cases with high probability of nodal metastasis were not included in this calculation.

A notable eligibility criterion used in ACTS-GC was the negative result of peritoneal cytology. Free cancer cells detected in the lavage fluid at the beginning of laparotomy or staging laparoscopy are a strong indicator of poor prognosis [13•], and the Japanese Classification [14] includes this as a determinant of the disease stage (ie, a tumor with positive cytology is staged as IV regardless of the T or N status). Exclusion of patients with positive cytology facilitates selection of patients with minimal residual disease who thus may benefit from adjuvant chemotherapy.

In all, Japanese patients in ACTS-GC were a highly selective population with the best prognosis among the three trials. Patients in MAGIC had the poorest prognosis at the time of registration because a considerable proportion had noncurative, even unresectable, disease. American patients in INT 0116 had more advanced T3/T4 disease than the Japanese patients but with better prognosis than the MAGIC population because they had undergone at least grossly curative resection.

*Tumor site and type of surgery*

Today, there is a remarkable difference between the East and the West in regard to the anatomical location of gastric cancer; in the West, a prominent shift to the proximal stomach exists [15,16]. Nevertheless, most tumors in the INT 0116 trial were located in the distal stomach, and 60% of the patients underwent distal gastrectomy. It is interesting that this rate of distal gastrectomy was very similar to that in the Japanese ACTS-GC trial (58%).

The MAGIC trial initially recruited only patients with gastric cancer, but extended the inclusion criteria to those with adenocarcinoma of the lower esophagus in the last 3 of the 8 accrual years. Fourteen percent of the tumors in the trial were lower esophageal cancer, and 22% of the patients in the surgery group underwent esophagogastrectomy. Of the other 146 gastric resections in this group, distal gastrectomy accounted only for 37%, indicating the predominance of proximal tumors in the trial.

The predominance of distal tumors in ACTS-GC and that of proximal tumors in MAGIC appears to reflect the general background of the disease in each region, although the patients in the INT 0116 trial may not represent American gastric cancer patients. The strict eligibility criteria of curative gastrectomy may have excluded many proximal or esophagogastric junction tumors which are, in general, locally more aggressive than distal tumors [17].

**Lymphadenectomy**

In adjuvant trials, surgery does not draw much attention because it is not a tested variable; rather it is a constant that is supposed to be the same or alike between the compared arms. However, when the results of separate studies are compared or combined for meta-analysis, the quality of surgery should be considered with great attention. In most solid tumors, including gastric cancer, surgery still plays the key role for cure, and the extent of surgery can easily alter the volume of residual tumor burden. If an adjuvant therapy aims at the systemically scattered cancer cells, the difference of surgery does not much matter. However, if the local residual disease is an important prognostic determinant to be targeted by adjuvant therapy, as in INT 0116, extent of surgery should be strictly controlled because it will directly affect the trial end points.

In the ACTS-GC trial, great attention was given to the quality assurance of surgery. Only high-volume centers participated in the study, the extent of lymphadenectomy was carefully reviewed, and the minimum requirement of D2 was confirmed before registration. In a D2 lymphadenectomy, the perigastric (N1) nodes and those along the branches of the celiac artery (N2) are completely removed [14].

In the INT 0116 trial, the operative records were reviewed in terms of lymphadenectomy, and it was found that the vast majority (90%) of patients had undergone limited lymphadenectomy [18]. Considering the high incidence of pathological nodal involvement in these patients (85%), microscopic disease must have remained in the nodes around the celiac artery in a considerable proportion of cases. In the subset analysis of the long-term results, chemoradiation did not improve survival of patients undergoing D2 lymphadenectomy [19]. Thus, the positive results of this study could be interpreted to mean that chemoradiation therapy was effective in eradicating the residual local disease, thereby reducing local recurrence and subsequent systemic metastasis.

**Table 1. Survival data of three pivotal trials**

| | INT 0116 | MAGIC* | ACTS-GC |
|---|---|---|---|
| **Surgery group** | | | |
| 3-year overall survival, % | 41 | 31 | 70.1 |
| 3-year relapse-free survival, % | 31 | 25 | 59.6 |
| **Chemo(radiation) group** | | | |
| 3-year overall survival, % | 50 | 44 | 80.1 |
| 3-year relapse-free survival, % | 48 | 40 | 72.2 |
| **Hazard ratios between arms** | | | |
| Death | 0.74 | 0.75 | 0.68 |
| Progression | 0.66 | 0.66 | 0.62 |

*Three-year survival rates in MAGIC trial were not shown (Cunningham et al. [4••]). The listed figures were estimations obtained from the survival curves presented.

In the MAGIC trial, the extent of lymphadenectomy was at the surgeon's discretion. Cunningham et al. [4••] reported that D2 lymphadenectomy was performed more frequently than D1 (96 and 50 cases, respectively, in the surgery group); however, this cannot be accepted at face value. First, these terms were used inaccurately (the researchers incorrectly termed "D1" as denoting limited lymph node dissection, and "D2" as denoting extended lymph node dissection), suggesting that a precise review of operative records, such as in the INT 0116 study, did not occur. Second, D2 lymphadenectomy, in its properly defined context, was not the standard of surgery in Europe at the time of the trial. Extremely high hospital mortality rates following D2 lymphadenectomy in both the Dutch D1/D2 trial and the British D1/D2 trial (10% and 13%, respectively) had been recently published (1995 and 1996) [20,21] at the time of MAGIC trial accrual (between 1994 and 2002); therefore, surgeons participating in the MAGIC trial had no strong reason to perform this dangerous surgery, especially after intensive chemotherapy. Indeed, the operative mortality of the MAGIC trial (5.4% in the chemotherapy group and 5.9% in the surgery group) was even lower than that of D1 group in the British D1/D2 trial (6.5%). Therefore, it seems inappropriate to consider that the surgery was more radical in MAGIC than in INT 0116 [22].

### Survival

The survival data of the three trials are summarized in Table 1. Following publication of the INT 0116 and MAGIC trial data, many discussions have arisen regarding which therapy—adjuvant or perioperative—is superior in terms of survival [23]. However, this comparison requires special attention because these trials had essentially different populations in terms of curability and disease stages, as discussed above. Despite the difference in the survival rates between the two trials, the hazard ratios for both death and progression between the surgery and treatment arms were exactly the same.

There was a strikingly large difference in baseline survival between the Japanese study and the other two trials. The 3-year overall and relapse-free survival rates in the surgery group of ACTS-GC were almost twice as high as those in INT 0116 and MAGIC. Again, this should be attributed to the population differences discussed above. A more aggressive surgical approach in Japan may also have contributed to this survival difference. However, the 3-year survival of gastrectomy plus chemoradiation in INT 0116 (50%), which could be considered a result of optimal local therapy, was still far inferior to that of the Japanese surgery-only group (70.1%); the difference in local control alone cannot explain such a large survival difference.

## Other Recently Concluded and Currently Ongoing Studies

In the time since the three pivotal studies discussed previously, other clinical studies in the United States, Europe, and East Asia have recently concluded or are ongoing (Table 2).

### Studies in the United States

Following INT 0116, adjuvant chemoradiotherapy has become a standard treatment option in the United States; all ongoing clinical trials for localized gastric cancer now include chemoradiation. In a phase 3 trial (CALGB-80101), the chemoradiation regimen used in the INT 0116 trial is being compared with one in which the ECF regimen of the MAGIC trial is used rather than 5-FU/leucovorin [24].

Neoadjuvant chemoradiation is a new subject drawing great attention. A phase 2 trial (RTOG 9904) in a cooperative study setting tested a regimen consisting of 5-FU/leucovorin/cisplatin induction followed by concurrent 45-Gy radiation and 5-FU, as well as weekly paclitaxel prior to surgical resection. Results showed pathological complete response in 26% and favorable survival of responders [11•]. Other chemotherapeutic regimens currently being evaluated in combination with radiation include capecitabine and oxaliplatin (SWOG-S0425) [25].

**Table 2. Currently active phase 3 trials on (neo)adjuvant therapy for gastric cancer**

| Study | Country | Patients, *n* | Disease | Therapeutic modes |
|---|---|---|---|---|
| CALGB-80101 [24] | USA | 824 | Stage Ib–IV M0 | Surgery + chemoradiation (RT + 5-FU/leucovorin) vs surgery + chemoradiation (ECF) |
| MRC-ST03 [29] | United Kingdom | 1100 | Stage Ib–IV M0 | ECX + surgery + ECX vs ECX/bevacizumab + surgery + ECX/bevacizumab + bevacizumab |
| CRITICS [30] | The Netherlands | 788 | Stage Ib–IVa M0 | ECC + surgery + ECC vs ECC + surgery + chemoradiation (RT + capecitabine/cisplatin) |
| CLASSIC [31] | Korea | 1024 | Stage II, III | Surgery vs surgery + capecitabine/oxaliplatin |
| SMC IRB [33] | Korea | 490 | Stage Ib–IV M0 | Surgery + capecitabine/cisplatin vs surgery + chemoradiation (RT + capecitabine/cisplatin) |
| SAMIT [34•] | Japan | 1480 | T3–4, N0–2 | Surgery + UFT vs surgery + S-1 vs surgery + paclitaxel + UFT vs surgery + paclitaxel + S-1 |
| JCOG 501 [36] | Japan | 316 | Linitis plastica/large ulcerative tumor | Surgery + S-1 vs S-1/cisplatin + surgery + S-1 |

The ECC and ECX regimens comprise the same chemotherapy elements; however, because different trials use these agents in different doses or timings, the abbreviations have been set to match the original expressions used in the respective citation and/or trial registration.
5-FU—fluorouracil; ECC/ECX—epirubicin, cisplatin, capecitabine; ECF—epirubicin, cisplatin, 5-FU; RT—radiation therapy; UFT—tegafur–uracil.

### Studies in Europe

The results of a French neoadjuvant randomized controlled trial were presented at the American Society of Clinical Oncology meeting in 2007 [26]. A total of 224 patients with adenocarcinoma of the lower esophagus (11%), esophagogastric junction (64%), or stomach (25%) were enrolled between 1995 and 2003. The chemotherapy group received two to three courses of 5-FU/cisplatin before surgery, whereas the surgery group immediately proceeded to surgery without additional chemotherapy. The responders of the neoadjuvant group also received postoperative chemotherapy. The 5-year overall survival rate was 38% in the chemotherapy group and 24% in the surgery group (HR 0.69; $P = 0.02$). Although the publication of the details is awaited, this can be considered supportive evidence for the MAGIC trial.

The ECF regimen is now undergoing modifications, as the UK National Cancer Research Institute REAL-2 study for advanced disease showed noninferiority of oral capecitabine to infusional 5-FU [27]. In the "MAGIC-B" trial (MRC-ST03), the 5-FU component of ECF is substituted by capecitabine (ECX). The perioperative ECX is to be compared with ECX plus bevacizumab in a phase 3 setting [28•,29].

Adjuvant chemoradiation is also being tested in Europe. In the Dutch CRITICS trial, patients with resectable gastric cancer receive neoadjuvant ECC and surgery, and then either adjuvant ECC or adjuvant 45-Gy radiation with cisplatin and capecitabine [30].

### Studies in East Asia

In Korea, where D2 gastrectomy is routinely performed as in Japan, an adjuvant randomized controlled trial is currently evaluating capecitabine/oxaliplatin after curative surgery for stage II and III gastric cancer (CLASSIC trial) [31]. This is an international study involving institutions in China and Taiwan, and would be the last large-scale randomized controlled trial with a control arm of surgery alone (as further discussed in the Future Perspectives section). Adjuvant chemoradiotherapy is being evaluated in the Samsung Medical Center (Seoul, South Korea) a mega-volume center for gastric cancer surgery (1000 gastrectomies/year). The center published a nonrandomized study using the same regimen as the INT 0116 trial, and results suggested the survival benefit of this regimen even after D2 gastrectomy [32•]. Currently, a randomized controlled trial in a single-institutional setting is under way at the Samsung Medical Center to compare D2 gastrectomy plus adjuvant capecitabine/cisplatin with D2 plus chemoradiation [33].

Following the ACTS-GC trial, adjuvant S-1 has become a standard treatment in Japan, and various trials are active or being planned with S-1 as the reference arm. An adjuvant study (SAMIT) is evaluating the sequential use of paclitaxel and S-1 or oral UFT (tegafur–uracil) for T3/T4 gastric cancer in a 2 × 2 factorial design, expecting that adding paclitaxel to a fluoropyrimidine may reduce peritoneal recurrence [34•]. Following the SPIRITS trial, in which the superiority of S-1/cisplatin to S-1 alone was proven for advanced gastric cancer [35], a phase 2 trial is under way to confirm the feasibility of adjuvant S-1/cisplatin after D2 curative gastrectomy for stage III gastric cancer.

Neoadjuvant chemotherapy has also been evaluated in phase 2 settings. The Japan Clinical Oncology Group (JCOG) completed four trials recruiting high-risk gastric cancer patients (ie, linitis plastica, large diffuse ulcerative tumors, or tumors with bulky nodal metastasis). Three regimens were used: S-1 alone, cisplatin/irinotecan, and S-1/cisplatin. A high pathological response rate with low toxicity was observed with S-1/cisplatin, and a phase 3

trial (JCOG 0501) has started to compare immediate D2 gastrectomy plus adjuvant S-1 with neoadjuvant S-1/cisplatin followed by D2 gastrectomy plus adjuvant S-1 [36].

## Future Perspectives

Although the treatment modalities and populations studied were all different, the three trials clearly showed a survival benefit of adjuvant or perioperative therapy for gastric cancer. With the exception of the Korean CLASSIC trial, a control arm of surgery alone has already disappeared in recently launched randomized controlled trials [31]. Large-scale trials will be conducted to compare various combinations of chemotherapy and radiotherapy before and/or after surgery, possibly including new molecular targeting agents.

In the West, the American principle of adjuvant chemoradiation and European principle of perioperative chemotherapy will certainly merge in the near future through cooperative randomized controlled trials. The Dutch CRITICS trial is such an example [30]. International cooperation may become mandatory in the West because of the relatively low incidence of gastric cancers, especially those that are localized.

The increasing trend of esophageal adenocarcinoma and esophagogastric junction tumors in the West are also expected to change the target population. In the middle of the trial, MAGIC extended its inclusion criteria to include esophageal cancer. Currently, there are several phase 2 studies that recruit patients with only esophageal and junctional adenocarcinomas. Application of the results of these trials to stomach cancer merits attention.

In Eastern Asia, the evolution of adjuvant therapy is also awaited, but from a different standpoint. In the INT 0116 and MAGIC trials, the 5-year overall survival rates of the surgery groups are less than 30%, even after curative resection. For a population with such a poor prognosis, toxic combination therapy is warranted even despite the possibility of treatment-related death. However, for a population in which a majority survives by surgery alone, physicians may hesitate about the blind use of highly toxic therapy for all patients, especially before surgery. These physicians would likely prefer primary D2 gastrectomy, careful pathological staging, and selection of high-risk tumors for adjuvant therapy. Simple regimens with high compliance and low toxicity are desirable, and in this regard, oral S-1 monotherapy is acceptable.

According to the Japanese Gastric Cancer Association's nationwide registry of gastric cancer, the 5-year overall survival rate of resected stage IIIb and IV tumors (International Union Against Cancer's TNM [tumor, node, metastasis] staging) was 30.5% and 9.9%, respectively; for resected linitis plastica tumors, it was 16.2% [37•]. Together, these populations would have a comparable prognosis to those of the INT 0116/MAGIC trials, and will likely become a target of toxic combination therapy before and/or after surgery. The JCOG 0501 is such an example [36]. Thus, (neo)adjuvant regimens in Japan and Korea will probably evolve depending on tumor stages, based on the premise that D2 gastrectomy provides sufficient local tumor control and accurate staging.

## Conclusions

As a result of three pivotal trials, adjuvant and neoadjuvant therapies for gastric cancer have entered a new era. Large-scale, randomized controlled trials should further produce evidence of benefits from various combination regimens. The East and the West have different patient populations and surgical approaches with different baseline survival rates; therefore, despite some cross-over, their studies are likely to move forward in separate directions. Research on molecular prognostic/predictive markers may be helpful in bridging the gap.

## Clinical Trials Acronyms

ACTS-GC—Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer; CALGB—Cancer and Leukemia Group B; CLASSIC—Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer; CRITICS—Chemoradiotherapy after Induction Chemotherapy in Cancer of the Stomach; INT—Intergroup; JCOG—Japanese Clinical Oncology Group; MAGIC—Medical Research Council Adjuvant Gastric Infusional Chemotherapy; MRC-ST—Medical Research Council Study; REAL—Revised European American Lymphoma Classification; RTOG—Radiation Therapy Oncology Group; SAMIT—Stomach Cancer Adjuvant Multi-institutional Trial; SMC IRB—Samsung Medical Center Institutional Review Board; SPIRITS—S-1 Plus Cisplatin vs S-1 in RCT in the Treatment of Stomach Cancer; SWOG—Southwest Oncology Group.

## Disclosure

No potential conflict of interest relevant to this article was reported.

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The follow-up data of 7935 gastric cancer patients treated in Japanese leading hospitals were analyzed. This is useful as a reference database of the disease.