出術（開腹・腹腔鏡）を検討する．

血清プロテオミクス

早期卵巣癌を発見するための診断用血清バイオマーカーの探索が重要な課題であり，われわれはKKKS臨床プロテオミクス研究会（NPO）を組織して世界に先駆け子宮体癌での第1段階の解析を行った．卵巣癌に関しても報告はきわめて限られており[17]，現在，試験の準備中である．

おわりに

早期癌早期診断のポイントは以下の通りである．（1）卵巣癌の発症リスクを知る．（2）内科医などへの啓蒙（腹部超音波）．（3）婦人科受診時の内診・経腟超音波の重要性．（4）適切な検診システムの構築．（5）子宮内膜症への注意．そして，プロテオミクス研究の推進が必要である．

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【婦人科がん早期診断の要点・問題点　5】

卵管癌

三宅 貴仁*　　榎本 隆之

はじめに

卵管癌は婦人科腫瘍のなかでも非常に稀な疾患であり，その頻度は全婦人科腫瘍の約0.3％といわれている．組織学的な形態，特徴から卵管癌は卵巣癌と非常に類似しており，その診断，治療は卵巣癌と同様に行われる．大半は上皮由来であるが，肉腫を認めたという報告もある．

症　状

卵管癌は50歳代から60歳代にかけてみられることが多く，平均年齢は55歳から60歳である．典型的な三徴は水様帯下，下腹部痛，骨盤内腫瘤とされているが，これらすべての症状が認められる症例は15％以下である[1]．症状がなく，他疾患での子宮摘出，付属器摘出の際に偶然みつかることも多い．

最もよく認められる症状は性器出血，下腹部痛，骨盤痛であり，50％以上の症例で認められる．下腹部痛，骨盤痛は卵管壁の伸展に伴うもので，出血を伴う仙痛として自覚されることが多い．症状が長期間持続することも特徴的であり，半数以上の症例で症状が2か月以上持続していたという報告もある[2]．しかしながら，このような症状は非特異的であるため，症状出現から診断に至るまで4か月以上経過している症例が半数以上との報告もある[3]．

卵管癌の早期発見は非常に困難であるが，閉経後女性で原因不明の帯下増量を認め持続する場合，不正出血が持続する場合には卵管癌の存在も念頭に置いて精査を進める必要がある．

診　断

術前に卵管癌の診断がつくことは非常に稀である．約60％の症例に骨盤内の腫瘤を認め，病変が進行している場合には腹水も認められる．このために卵巣癌との鑑別が問題となるが，超音波画像，MRI，腫瘍マーカーなどで両者を鑑別することは困難なことが多い．

近年，卵管癌の診断にMRIやCTを使用した報告も認められる．術前診断が可能であった卵管癌症例のMRI画像を図1に示す．川上ら[4]は帯下増量や不正出血を認める症例で，付属器領域に小さく充実性で分葉状の腫瘤を認め，子宮内に液体貯留を認める場合には卵管癌も鑑別診断に挙げておくべきであると報告している．また，子宮筋腫，卵巣腫瘍などとの鑑別にはCTよりもMRIが有用であるとも報告している．

卵巣癌における超音波診断についてはあまり報告がないが，複雑な形態をした大部分が嚢腫状で，一部に壁在結節を認める付属器腫瘤，明らかに子宮から離れた部位に存在するソーセージ様腫瘤として描出されることが多いという報告がある[5,6]．当科で経験した卵管癌症例の超音波画像を図2に示す．血流ドプラを用いることで，腫瘍内の血管

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REVIEW ARTICLE

Disparities in Gastric Cancer Chemotherapy Between the East and West

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ABSTRACT

There are still remarkable disparities in the treatment of gastric cancer between the East and West. Treatment outcomes for this disease have improved in Japan due to early detection and surgical resection with systematic node dissections, such as D2, whereas gastric cancer remains a virulent disease in Western countries. Differences in the types of surgery and their outcomes affect how adjuvant trials are conducted and interpreted. Recent Western randomized trials demonstrated the significant survival benefit of adjuvant chemoradiotherapy or intensive combination chemotherapy. However, baseline surgical quality and outcomes were quite different from those in Japan, and Japanese surgical/medical oncologists have not accepted the Western results. Several disparities are also evident in the results of chemotherapy trials for advanced gastric cancer. Although similar results were obtained with randomized studies using older regimens, the interpretation of the results differed between Japan and other countries. A combination of cisplatin and fluorouracil was used as the reference arm in ongoing randomized trials in most countries, whereas single-agent fluorouracil or *S*-1 alone was used in Japanese trials. Two triplet regimens have already demonstrated significant prolongation of survival in Western studies. However, these benefits seem to be marginal and these regimens may be replaced by newer regimens, which will soon be available in Europe and Asia, where a total of 2,600 patients have been accrued. Although these disparities between regions must be overcome, it is time for both Eastern and Western investigators to pursue further benefits by incorporating new agents into treatment regimens.

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INTRODUCTION

According to global estimates of cancer incidence in the year 2002, gastric cancer is the second most frequent cancer-related cause of death after lung cancer. The incidence of gastric cancer was estimated to be 934,000 cases, with 56% of the new cases occurring in East Asia; 41% in China, and 11% in Japan.[1] Although the incidence of gastric cancer has decreased in recent years and its mortality rate in Japan is now lower than that of lung cancer, it still has the highest incidence.

Significant differences have been observed among the 5-year survival rates in Japan and other countries. Based on data from population-based cancer registries, the survival rate is higher in Japan (40% to 60%)[2,3] than in other countries (approximately 20%).[4,5] In Japan, a nationwide mass screening system has been developed that has resulted in the diagnosis of a large proportion of gastric cancers at an early stage: 53% of Japanese gastric cancers were localized when diagnosed, compared with only 27% of those in the United States population. Today in Japan, approximately 50% of patients with stage IA gastric cancer are treated with endoscopic mucosal resections, as has been documented precisely in a recent review in the *Journal of Clinical Oncology*.[6]

Another cause of the higher survival rate in Japan is thought to be the use of radical surgery. Gastrectomy with the systematic dissection of lymph nodes in the first tier (perigastric) and the second tier (along the celiac artery and its branches), known as D2 dissection, is the standard surgical technique used in Japan, whereas D1 dissection is used in Western countries. Two European randomized trials that compared D1 and D2 gastrectomy failed to demonstrate any survival benefit of D2 over D1.[7,8] However, this failure was predominantly caused by the high mortality rate in the D2 group, which exceeded 10%, a rate that most Japanese surgeons and medical oncologists find unacceptable. The Japanese nationwide registry reported an operative mortality rate of less than 2%,[9] and the recent report of a large randomized trial comparing D2 dissection with D2 plus para-aortic nodal dissection, by the Japan Clinical Oncology Group (JCOG 9501), showed a hospital mortality rate of only 0.8%.[10] One of the major criticisms of Japanese surgery is that most of the data from Japan have been based on retrospective or small studies. JCOG 9501 trial circumvents these criticisms. Japanese surgeons believe that D2 gastrectomy imposes a steep learning curve and may be associated with higher than expected operative morbidity and mortality. Furthermore, major US cancer centers with extensive experience have also achieved

low mortality rates of 1.7% to 3.6%.[11,12] The protracted debate regarding the survival benefit of lymphadenectomy persists between the West and Japan, and also Korea, where D2 gastrectomy has been well accepted with survival and mortality rates similar to those of Japan.[13,14] Although this issue should be clarified in future clinical trials, these marked differences in survival and morbidity and mortality rates after surgery have also caused the planning and interpretations of adjuvant and neoadjuvant trials to differ between Western countries and East Asia.

In contrast to the marked differences in the surgery used to treat gastric cancer, there seem to be fewer differences in the results of the chemotherapy used to treat metastatic gastric cancer. However, a few agents display ethnic differences, and there are some cultural and regulatory differences between the West and Japan in interpreting the results of clinical trials. The number of international studies has recently increased annually, and these regional differences are one of the major obstacles to be overcome in these studies. This review focuses on the disparities in the treatment of gastric cancer between the East and West, particularly in adjuvant and neoadjuvant and primary chemotherapy trials.

ADJUVANT AND NEOADJUVANT TRIALS

The survival benefits of adjuvant chemotherapy have long been argued. In 1993, Hermans et al[15] reported the results of a meta-analysis of 11 randomized trials that compared surgery alone with postoperative adjuvant chemotherapy. The analysis produced no definite evidence of significant survival benefit for adjuvant chemotherapy, but was followed by contrary results in an updated analysis.[16] Two recent reports of meta-analyses showed a significant survival benefit for adjuvant chemotherapy. However, the methodologies of these meta-analyses varied and the benefit of adjuvant chemotherapy was so small that there was insufficient evidence to recommend adjuvant chemotherapy as the standard treatment.

Historically, earlier adjuvant studies in Japan were carried out with mitomycin C (MMC) and/or oral fluorouracils. These studies produced conflicting results in terms of the survival benefit of adjuvant chemotherapy.[17-20] Possibly because of the immature infrastructure available for clinical trials, and particularly the quality control of the studies, the 5-year survival rate of the surgery-only group in each study varied, which might explain the conflicting results. Against this background, the JCOG undertook a large multi-institutional randomized study in the late 1980s that compared surgery alone with surgery plus adjuvant chemotherapy consisting of intravenous infusion of MMC + fluorouracil (FU) followed by oral uracil and tegafur (UFT; JCOG 8801) for patients with macroscopically defined T1 or T2 tumors, who had received curative resections.[21] With a median follow-up of 72 months, no significant differences in survival between the two groups were observed; the 5-year survival rates of the control and treatment groups were 82.9% and 85.8%, respectively. In this study, the 5-year survival rate of patients with T1 cancer in the control group was 94.9%, which led Japanese investigators to exclude these patients from the following adjuvant trials, and from programs of adjuvant chemotherapy in daily practice. The subsequent adjuvant randomized trials undertaken by the JCOG were divided into two studies: one targeted macroscopically serosa-negative cancers excluding T1N0 cancers (JCOG 9206-1), and the other targeted macroscopically serosa-positive gastric cancers (JCOG 9206-2). The former study (JCOG 9206-1) compared surgery alone with surgery plus intravenous MMC, FU, and cytarabine, followed by oral FU, and the results have already been published (Table 1).[22] Although there was a trend of increased survival in the adjuvant chemotherapy group, this study failed to demonstrate a significant difference in relapse-free or overall survival between the two arms. The 5-year relapse-free survival rates of the chemotherapy and control groups were 88.8% and 83.7%, respectively ($P = .14$), and their 5-year overall survival rates were 91.2% and 86.1%, respectively ($P = .13$). More recently, the positive results of another randomized trial by the National Surgical Adjuvant Study for

Table 1. Results of Recent Randomized Trials of Adjuvant Chemotherapy/Chemoradiotherapy Versus Surgery Alone

Study	Stage	Treatment	No. of Patients	5-Year RFS (%)	5-Year Survival (%)	*P*
Japanese trials						
Nashimoto et al[22] JCOG 9206-1	T1-2 excluding T1N0	FU + MMC + Ara C	128	88.8	91.2	NS
		Surgery alone (D2)	124	83.7	86.1	
Kinoshita et al[23] NSASGC	T2N1-2	UFT	93	84.5*	86.3*	.0176
		Surgery alone (D2)	95	68.1	73.6	
Miyashiro et al[24] JCOG 9206-2	T3-4	FU + CDDP/UFT	135	59.0	62.7	NS
		Surgery alone (D2)	133	57.1	61.6	
Western trials						
Bajetta et al[27] ITMO	N+ or T3-4	Etoposide + ADM + CDDP	137	49	52	NS
		Surgery alone (D2)	137	44	48	
Cunningham et al[28] MAGIC	Including GEJ/lower E	Epirubicin + FU + CDDP	250		36	.009
		Surgery alone	253		23	
MacDonald et al[30] INT 016	T1-4	FU/LV + RT (45 Gy)	281	48†	50†	.005
		Surgery alone (D0 > 1)	275	31	41	

Abbreviations: RFS, relapse-free survival; JCOG, Japan Clinical Oncology Group; FU, fluorouracil; MMC, mitomycin; Ara C, cytarabine; NS, not significant; NSASGC, National Surgical Adjuvant Study for Gastric Cancer; UFT, uracil and tegafur; CDDP, cisplatin; ITMO, the Italian Trials in Oncology Group; ADM, doxorubicin; MAGIC, MRC Adjuvant Gastic Cancer Infusional Chemotherapy; GEJ, gastroesophageal junction; E, esophagus; INT, US Intergroup study; LV, leucovorin; RT, radiation therapy

*At 4 years.

†At 3 years.

Gastric Cancer (NSASGC) have been reported in abstract form.[23] Patients with histologic T2 cancers (N1-2 in the Japanese staging system), who had been treated with curative gastrectomy, were eligible for this study and were randomly assigned to either surgery only or adjuvant chemotherapy comprising UFT alone for 16 months. This study was designed to accrue 244 patients, but closed with a total of 190 patients because of slow recruitment. In an interim planning analysis, the chemotherapy group demonstrated a significant survival benefit over the surgery alone group, in both relapse-free and overall survival. Four-year survival rates in the chemotherapy and control groups were 86.3% and 73.6%, respectively ($P = .0176$), and the relapse-free survival rates were 84.5% and 68.1%, respectively ($P = .0040$). Contrary to the results of the NSASGC study, the JCOG 9206-2 study, which targeted serosa-positive (T3 or T4) cancers, recently demonstrated no advantage for adjuvant chemotherapy.[24] This study compared surgery alone with surgery plus adjuvant chemotherapy consisting of intraperitoneally administered cisplatin (CDDP) at the time of surgery, one course of intravenous CDDP and FU, followed by oral administration of UFT for 12 months. A total of 268 patients were accrued; the 5-year overall survival rates in the chemotherapy and control groups were 62.7% and 61.6%, respectively ($P = .48$), and the relapse-free survival rates were 59.0% and 57.1%, respectively ($P = .5$).

Several criticisms can be made of these Japanese studies. These studies had limited statistical power to detect survival differences due to small sample sizes. For instance, in the JCOG 9206-1 study, the expected difference in 5-year survival between the two arms was 15%, which seems unrealistic when the power of chemotherapy is considered. Subdividing the stages in each study also contributed to the small sample sizes. In addition, the survival results of the control groups were inconsistent in each study. In JCOG 9206-1, the expected 5-year survival rate of the control group was estimated to be 70% based on the results of a previous study, whereas the actual 5-year survival rate was 83.7%. However, this increase seems to have been caused by an improvement in the quality control of the studies. As described in the report of another JCOG study, only selected surgeons with extensive experience could participate in the study.[10] This selection criterion might have improved the survival of the control group. A similar phenomenon was observed in adjuvant studies of cancers at other sites, such as colon cancer. The chemotherapy regimens and the doses used in each study varied and may have been inadequate. Most of the regimens used in these adjuvant trials in Japan were not based on sufficient evidence of their efficacy in treating metastatic disease. Moreover, the doses used in the studies (except the NSASGC study) were lower than usual doses. With respect to oral fluorouracils, oral FU (134 mg/m^2 per day) was administered in the JCOG 9206-1 study and oral UFT (267 mg/m^2 per day) in the JCOG 9206-2 study, which are considered to be insufficient doses for efficacy. The differences in the doses of UFT between the NSASGC and JCOG studies may have caused the contradictory results. The small sample size of the NSASGC study means that no definitive advantage of adjuvant chemotherapy following standard gastrectomy with D2 dissection has been demonstrated yet in Japan. However, these studies have confirmed the survival benefit of surgery, with a 5-year survival rate higher than 60%, even in patients with T3 or T4 cancers. Recently, a large-scale randomized trial of 1,000 patients that compared surgery alone with adjuvant chemotherapy using *S*-1 was undertaken in Japan and accrual has already been completed. This study targets a wide population with stage II and III cancers and uses standard doses of *S*-1. The results of this study will allow definitive conclusions to be drawn and should circumvent these criticisms.

In contrast, the usefulness of intensive adjuvant chemotherapies has been challenged in Western countries. Earlier Western randomized trials investigated the use of FU, doxorubicin, and MMC as adjuvant therapies. They failed to demonstrate a significant survival advantage of adjuvant chemotherapies over surgery alone.[25,26] Another trial, using an intensive combination regimen comprising etoposide, doxorubicin, and CDDP, was reported by an Italian group.[27] A total of 274 patients were randomly assigned to surgery alone or surgery plus two courses of etoposide, doxorubicin, and CDDP followed by FU + leucovorin. It is of note that this study used D2 dissection as the surgical procedure and the pathologic documentation of second tier nodes, consistent with Japanese guidelines. Although there were no significant differences in survival (5-year survival rates of the chemotherapy and control groups were 52% and 48%, respectively), Bajetta et al concluded that D2 surgery might have a favorable impact on survival because the 5-year survival rate observed in the control group was remarkably higher than expected (30%) when the protocol was designed. More recently, the Medical Research Council Adjuvant Gastric Cancer Infusional Chemotherapy (MAGIC) study in the United Kingdom reported the survival benefit of perioperative chemotherapy.[28] This study adopted a three-drug combination regimen consisting of epirubicin (50 mg/m^2) and CDDP (60 mg/m^2) every 3 weeks, and FU (200 mg/m^2 per day) for 3 weeks (ECF regimen), based on the positive results of a randomized trial for the treatment of metastatic gastric cancer.[29] Patients with operable adenocarcinoma of the stomach, gastroesophageal junction, or lower esophagus were randomized into either surgery alone or perioperative treatments with chemotherapy comprising three preoperative and three postoperative courses of ECF. With a median follow-up of longer than 3 years, the perioperative chemotherapy group showed significantly better survival and progression-free survival than the control group. The 5-year survival rates of the chemotherapy and control groups were 36% and 23%, respectively ($P = .009$).

Another approach to the improvement of survival in the United States, where locoregional recurrence rates are high, is with postoperative chemoradiotherapy, which has also been challenged. The U.S. Intergroup study INT0 116 was a large-scale randomized trial comparing surgery alone with surgery plus chemoradiotherapy consisting of FU + leucovorin and 45 Gy of radiation. The results of this study were published in 2001 and updated in 2004.[30,31] This study clearly demonstrated significantly better survival and locoregional control in the chemoradiotherapy group than in the control group. Median disease-free survival in the chemoradiotherapy and control groups was 30 and 19 months, respectively ($P < .001$) and overall survival was 35 and 26 months, respectively ($P = .006$).

Although the two reports from the West described above have demonstrated the positive impact of adjuvant therapies, several issues are still open to criticism, as in the Japanese studies. The biggest issue is the quality control of surgery in these studies, particularly in the INT0 116 study, in which only 10% of patients underwent D2 dissection and 54% of patients underwent D0 (not D1) dissection. Furthermore, retrospective analysis of this study demonstrated that surgical undertreatment reduced survival.[32] The 5-year survival rate was around 40%, even in the chemoradiotherapy group, which seems remarkably lower than that for D2 surgery alone in both the Japanese and the Italian studies.[27,33] In Japan, where D2 is the standard surgical procedure and locoregional recurrence is rare, the results of this trial would be interpreted as demonstrating that D0/1 plus chemoradiotherapy is better than D0/1

alone but probably no better than D2 alone. Due to the low incidence of locoregional recurrence in Japan, the role of radiotherapy in gastric cancer should be very limited. A similar criticism might be leveled at the MAGIC trial, although this study has only been reported in abstract form and the types of surgery evaluated were not specified. However, the chemotherapy group showed an even worse 5-year survival rate after D2 surgery alone than that reported in the Italian study. This study also included lower esophageal cancers, which confuses the interpretation of the trial. The staging system and types of surgery used to treat esophageal cancer are quite different from those used for gastric cancer in Japan, although adenocarcinoma of the lower esophagus is still rare. Whether the biologic behavior of this tumor is different from that of squamous cell carcinoma is unknown to Japanese investigators.

There are great disparities in the interpretation of adjuvant trials between the West and Japan, mostly caused by different baseline results of surgery. These differences appear to be caused not only by differences in surgical techniques but also by differences in diagnostic techniques. Japanese gastroenterologists and pathologists also have advanced techniques for the accurate estimation of the extension margin or staging. Although Western randomized trials comparing D1 with D2 have not demonstrated any superiority of D2, and stage migration might affect survival after D2, it seems unlikely that Japanese investigators will accept the results of Western trials. In this regard, the interpretation of adjuvant trials will differ, based on baseline types of surgery. Chemoradiotherapy could compensate for inadequate surgery, such as D0 dissection, and ECF could provide a survival advantage after D1 surgery, whereas the benefit of adjuvant chemotherapy after D2 surgery has yet to be confirmed. To identify a small increment in the cure rate caused by adjuvant chemotherapy, larger sample sizes are required in randomized studies, as observed in colorectal studies, for which international studies are now becoming common. Japanese investigators should also conduct international studies with other countries in which D2 is the standard surgical practice, such as Korea. Newer regimens, with more evidence of success with metastatic disease, as described in the following paragraph, should be included in future trials.

CHEMOTHERAPY TRIALS FOR ADVANCED DISEASE

Unresectable advanced or recurrent gastric cancers still have poor prognoses. Randomized trials have demonstrated that FU-based regimens provide superior survival and quality of life in patients with advanced gastric cancer when compared with the results of the best supportive care.[34-36] However, this survival advantage appears to be marginal and no standard regimens have yet been established worldwide.

DISPARITIES IN INTERPRETING THE RESULTS OF PREVIOUS RANDOMIZED CONTROLLED TRIALS

During the past two decades, various randomized trials have been performed to evaluate treatments for metastatic gastric cancer. Three randomized trials that included FU alone as the reference arm and compared it with older FU-based combination regimens have been reported in the United States, Korea, and Japan (Table 2).[37-39] All three trials had similar results. No combination regimen demonstrated survival prolongation compared with that of FU alone, whereas the response rates and progression-free survival in the CDDP + FU (CF) arm were better than those of single-agent FU in the Korean (median survival times [MSTs] of 8.5 and 6.9 months, respectively) and Japanese studies (MSTs of 7.3 and 7.1 months, respectively). However, the interpretation of these results, particularly when determining the reference arms of subsequent studies, differed between regions. Most countries other than Japan considered CF as a following reference arm, without definite evidence of superiority over single-agent FU, because this monotherapy had only limited activity, with a response rate of around 10% and median progression-free survival of approximately 2 months. It would be advantageous for CF that a higher response rate could improve the symptoms of the patients. In Japan, single-agent FU was selected as the subsequent reference arm, because no differences in overall survival were observed and the primary end point of the study was overall survival. The CF regimen provided significantly longer progression-free survival, but no better overall

Table 2. Results of Randomized Trials Using Older Regimens

Study	Treatment	No. of Patients	Response Rate (%)	Median Survival (months)	*P*
Korea[38]	FU	94	26	6.9	NS
	FU + ADM + MMC	98	25	6.6	
	FU + CDDP	103	51	8.5	
JCOG 9205[39]	FU	106	11	7.1	NS
	FU + CDDP	104	34	7.3	
	UFT + MMC	70	9	6.0	
EORTC[40]	FU + ADM + MMC	103	7	6.7	.004
	FU + ADM + MTX	105	33	9.6	
UK[42]	FU + ADM + MTX	130	21	5.7	.0009
	Epirubicin + CDDP + FU	126	45	8.9	
EORTC[41]	FU + CDDP	134	20	7.2	NS
	Etoposide + LV/FU	132	9	7.2	
	FU + ADM + MTX	133	12	6.7	

Abbreviations: FU, fluorouracil; NS, not significant; ADM, doxorubicin; MMC, mitomycin; CDDP, cisplatin; JCOG, Japan Clinical Oncology Group; UFT, uracil and tegafur; EORTC, European Organisation for Research and Treatment of Cancer; MTX, methotrexate; UK, United Kingdom; LV, leucovorin.

survival, and a significantly higher incidence of toxicity compared with that of the control arm, FU alone.

In Europe, triplet regimens have been commonly used. A combination of FU, doxorubicin, and high-dose methotrexate (FAMTX) used to be a standard regimen, based on European Organisation for Research and Treatment of Cancer trials.[40] However, this regimen failed to demonstrate any superiority to other combination regimens, such as CF or etoposide + FU + leucovorin, in the following European Organisation for Research and Treatment of Cancer randomized study.[41] Another randomized study in the United Kingdom revealed the superiority of a combination of epirubicin, cisplatin, and FU (ECF) over FAMTX in terms of survival,[29] whereas there was some debate about the methodologies of the clinical trials and the inconsistent results obtained with FAMTX during the European trials.[42,43] The survival results in these studies were limited, with an MST ranging from 6 to 8 months, and no improvement with the addition of epirubicin to CF has yet been confirmed. ECF still has limited acceptance as a standard treatment for metastatic gastric cancer. This regimen is used only in the United Kingdom and parts of Europe.

Although there are significant differences in the historical backgrounds and interpretations of results between regions, the results for CF in Europe, North America, Korea, and Japan are very similar, as shown in Table 3.[38,39,41,44] Median progression-free survival (PFS; given as the time to progression in two studies) ranged from 3.7 to 5.0 months, with MSTs ranging from 7.2 to 8.5 months. Contrary to the disparities in the adjuvant trials, there were no significant differences in the biologic responses to chemotherapy between regions.

RESULTS OF RECENT STUDIES WITH NEW REGIMENS

During the past decade, a new generation of agents has been developed, including irinotecan, S-1, capecitabine, docetaxel, paclitaxel, and oxaliplatin, which have shown promising activities in single-agent studies[45-50] and when investigated in combination with other agents. Numerous combinations have been reported as phase II settings, and promising regimens that have been included in recent ongoing randomized trials are summarized in Table 4.[51-55] These regimens have achieved better median times to progression (approximately 6 months) and MSTs (approximately 10 months) compared with those of older regimens, although definite conclusions should not be drawn until the results of randomized trials are available.

Recently reported and ongoing large-scale randomized trials are listed in Table 5. Most of the trials outside Japan used CF as the control arm and one trial used ECF as the control arm, whereas the Japanese studies used single-agent FU or S-1 as the control arm. These disparities are considered to result from the different interpretations of the results of previous randomized studies, as described in the preceding section.

Table 3. Treatment Results of Cisplatin/Fluorouracil for Advanced Disease in Randomized Trials

Trial	No. of Patients	Response Rate (%)	Median PFS (months)	Median Survival (months)
Japan[39]	105	34	3.9	7.3
Korea[38]	103	51	5.0	8.5
EU[41]	134	5.0*	4.1	7.2
US/EU[44]	112	23	3.7*	8.5

Abbreviations: PFS, progression-free survival; EU, Europe; US, United States.
*Estimated as median time to progression.

Table 4. Treatment Results of Newer Generation Included in Ongoing Randomized Trials

Regimen	No. of Patients	Response Rate (%)	Median TTP (months)	MST (months)
Irinotecan + CDDP[51]	38	58	5.6	9.0
Irinotecan + FU/LV[52]	59	42	6.5	10.7
S-1 + CDDP[53]	25	76	6.0	12.5
S-1 + Irinotecan[54]	24	50	6.0	NS
Capecitabine + CDDP[54]	42	55	6.3	10.1
Docetaxel + CDDP[55]	63	28	5.0	10.5
Docetaxel + CDDP + FU[55]	61	43	5.9	9.6

Abbreviations: TTP, time to progression; MST, median survival time; CDDP, cisplatin; FU, fluorouracil; LV, leucovorin; NS, not stated.

Recently, a large-scale international randomized controlled trial (V325) comparing docetaxel + CDDP + FU (DCF) with CF has been reported in abstract form (Table 6).[44] The initial phase II randomized part of this study, comparing docetaxel + CDDP with DCF, revealed a better response rate and time to progression with DCF.[55] The DCF regimen was then chosen as the experimental arm for the phase III stage. The doses and schedules for the DCF arm were docetaxel (75 mg/m^2) on day 1, CDDP (75 mg/m^2) on day 1, and FU (750 mg/m^2 per day) as a continuous infusion on days 1 through 5, repeated every 3 weeks. Those for the CF arm were CDDP (100 mg/m^2) on day 1 and FU (1,000 mg/m^2 per day) as a continuous infusion on days 1 through 5, given every 4 weeks. The primary end point was time to progression, whereas overall survival, duration of response, safety, and quality of life were secondary end points. A total of 457 chemotherapy-naive patients were registered. The final results of this study clearly demonstrated the superiority of DCF to CF: time to progression was longer for DCF, with a median of 5.6 months, than for CF (3.7 months; $P = .0004$). Overall survival was also longer for patients receiving DCF, with an MST of 9.2 months, than for those receiving CF (8.6 months; $P = .0201$). Neutropenic fever, infections, diarrhea, and mucositis were more frequent in the DCF group than in the CF group, whereas a better quality of life, including global health status, was maintained for a longer period with the DCF regimen. An open question remains in the interpretation of these results. The MST of the DCF arm was less than 10 months and survival improvement was less than 1 month as compared with CF, despite substantial toxicity. These facts cause many investigators to hesitate in accepting this regimen as the standard treatment. However, this study clearly demonstrated the efficacy of docetaxel, and this agent should constitute part of the frontline therapies for advanced gastric cancer.

Another international randomized phase II/III study (V306) has recently been reported. This study initially compared irinotecan + CDDP with irinotecan + infusional FU + leucovorin in the phase II part of the study, to determine the experimental arm of the phase III trial with CF.[52] In this study, irinotecan (200 mg/m^2) and CDDP (60 mg/m^2) were administered every 3 weeks, and compared with irinotecan (80 mg/m^2), leucovorin (LV; 500 mg/m^2), and FU (2,000 mg/m^2) administered as one 24-hour infusion per week for 6 weeks, followed

by a 1-week respite. The overall response rates for irinotecan + CDDP and irinotecan + FU + LV were 32% and 42%, respectively, and MSTs were 6.9 and 10.7 months, respectively. Toxicity results also revealed more favorable profiles for irinotecan + FU + LV than for irinotecan + CDDP. Therefore, the former regimen was chosen as the experimental arm for the phase III part of the study for comparison with the control arm of CF. In the full analysis population of 333 patients, the irinotecan-based regimen demonstrated a trend toward a longer time-to-progression and greater overall survival. However, these differences were not statistically significant (hazard ratios: 1.23 and 1.08, respectively).[56] Median times to progression for irinotecan + FU + LV and CF were 5.0 and 4.2 months, respectively, and the MSTs of both arms were less than 10 months. More patients withdrew from the study because of drug-related adverse events with CF than with irinotecan + FU + LV (21.5% and 10.0%, respectively; $P = .004$). Based on the results of the V306 study, irinotecan + FU + LV can be considered a reasonable alternative first-line treatment option without CDDP, but it provides no definite efficacy advantage over CF.

In the United Kingdom, where ECF is the standard treatment, the REAL-2 study is now underway. This study uses a 2 × 2 design to evaluate several modifications of ECF: substitution of capecitabine for FU and substitution of oxaliplatin for CDDP. Patients were randomly assigned to one of the four regimens: ECF, epirubicin + oxaliplatin + FU, epirubicin + CDDP + capecitabine, or epirubicin + oxaliplatin + capecitabine. The interim analysis with a total of 204 patients showed response rates of 31%, 39%, 35%, and 48% for ECF, epirubicin + oxaliplatin + FU, epirubicin + CDDP + capecitabine, and epirubicin + oxaliplatin + capecitabine, respectively.[57] The accrual of 1,000 patients has already been completed and the final results will appear in 2006. In Korea, where many combination phase II studies that include capecitabine have been developed, a randomized trial comparing capecitabine + CDDP with CF is now underway in collaboration with other Asian countries. This study has already achieved the final accrual of 300 patients and the results will be presented in 2006.

In contrast, three randomized trials using an S-1-based regimen are now being investigated in Japan. Following the results of the JCOG 9205 trial, the JCOG initiated three arm randomizations (JCOG 9912) comparing FU alone with a combination of irinotecan + CDDP and with S-1 alone, based on the promising results of phase II studies in Japan.[48,49,58] This study requires a sample size of 700 and its accrual has recently been completed. The other two studies use S-1 monotherapy as the control arm, for comparison with S-1 + CDDP[59] (Taiho trial) or S-1 + irinotecan[59] (Yakult-Daiichi trial), for which the accruals have also been completed, with 300 patients each. The primary end point of all three trials is overall survival and final data on the total 1,300 patients will be available early in 2007.

There are several disparities between the Eastern and Western trials that have evaluated treatments for advanced cancer, as seen in the adjuvant trials. CF or partial ECF were used as the control arms in the studies outside Japan, whereas monotherapies such as FU or S-1 alone were used in the Japanese studies. These differences arose from different interpretations of previous trials, as described above. Usually, more than 50% of patients receive second-line or additional chemotherapy after the failure of a first-line therapy. In this regard, the monotherapy arm could represent a sequential combination therapy and, therefore, monotherapy versus combination therapy can be regarded as sequential combination therapy versus simultaneous combination therapy. These debates should be resolved by the ongoing Japanese studies, and the impact of second- or higher line therapies with new generation agents can be estimated by comparing the results for the FU monotherapy arms between the JCOG 9205 and 9912 trials.

The primary end points also differed among the studies. The V325, V306, and Korean studies adopted time to progression as the primary end point, whereas the end points of the REAL-2 and Japanese studies were overall survival. There exists a debate over whether time to progression can be replaced by overall survival as the primary end point in randomized studies of gastric cancer. It seems difficult to achieve a prolongation of overall survival using only first-line treatments because of the influence of subsequent treatments, particularly in evaluating the efficacy of new agents. In the field of colorectal cancer, where definitive survival prolongation has recently been achieved, time to progression has now become the primary end point of randomized trials that evaluate the efficacy of newly developed agents. This change could arise from changes in the policies of regulatory authorities, and might differ between countries against different social, cultural, and economic backgrounds. Scientifically, the survival advantage of the second-line treatment has not yet been established for this disease and the prognosis for advanced disease is still limited to an MST of less than 10 months, even in recent randomized trials such as the V325 and V306 studies. Therefore, overall survival still seems to be the most reasonable primary end point. However, the median

Table 5. Recently Published and Ongoing Large Scale Randomized Phase III Trials for Advanced Gastric Cancer

Regimen	Target Accrual (patients)	Primary End Point
Western trials		
CDDP + FU *v* docetaxel + CDDP + FU	462	TTP
CDDP + FU *v* irinotecan + FU/LV	337	TTP
epirubicin + CDDP + FU *v* epirubicin + oxaliplatin + FU *v* epirubicin + CDDP + capecitabine *v* epirubicin + oxaliplatin + capecitabine	1,000	OS
CDDP + FU *v* CDDP + S-1	700	OS
Asian trials		
CDDP + FU *v* CDDP + capecitabine	300	TTP
Japanese trials		
FU *v* irinotecan + CDDP *v* S-1	700	OS
S-1 *v* S-1 + CDDP	300	OS
S-1 *v* S-1 + irinoetcan	300	OS

Abbreviations: CDDP, cisplatin; FU, fluorouracil; TTP, time to progression; LV, leucovorin; OS, overall survival.

Table 6. Summary of the Results of the V325 and V306 Trials

	V325[44]		V306[56]	
	DCF (n = 227)	CF (n = 230)	IF (n = 170)	CF (n = 163)
Response rate	37%	25%	32%	26%
Median TTP (months)	5 6	3.7	5.0	4 2
MST (months)	9 2	8.6	9.0	8.7
Grade 3/4 toxicity	81%	75%	40%	44%

Abbreviations: DCF, docetaxel + cisplatin + fluorouracil; CF, cisplatin + fluorouracil; IF, irinotecan + fluorouracil + leucovorin; TTP, time to progression; MST, median survival time.

time-to-progression in recent studies (or PFS in some studies) appears to be consistent: approximately 4 months for CF, and 5 to 6 months for modern combination regimens. Moreover, the more recent phase II studies have shown MSTs of more than 12 months. If these are confirmed in ongoing randomized trials throughout the world, the primary end point will be changed to time to progression, although quality controls of the studies and valid evaluations of time to progression are necessary.

The agents used in these randomized trials also differed between Japan and other countries. All the Japanese studies selected *S*-1 in either the control arm or the investigational arms, because this oral agent is now used most commonly in this country. The efficacy of this agent, particularly for survival advantage, has not yet been confirmed and must await the final results of the JCOG 9912 study, which compares *S*-1 with FU. In this regard, the Japanese investigators, pharmaceutical companies, and regulatory authorities may be criticized because they adopted *S*-1 as a control arm with no evidence from phase III studies. This agent also displays ethnic differences in its metabolism, leading to differential dose tolerance and toxicity. The tolerable dose of *S*-1 is substantially lower in Western patients, which has resulted in its lower acceptance in Western countries. Recent pharmacokinetic data have indicated that the polymorphisms of the *CYP2A6* gene may be responsible for such differences in FU area under the curve and discordant outcomes.[60] Despite different doses, preliminary results for the *S*-1 + CDDP combination have shown promising activity and will be followed by an ongoing randomized trial that compares it with CF in Western populations.[61] This will constitute a key trial for this agent. Capecitabine is a more globally accepted oral agent for the treatment of gastric cancer, and for colorectal cancer, although this agent is still not commercially available in Japan. When the results of Korean studies were compared with those of Western studies, there were no significant ethnic differences in outcomes with this agent between Western and Asian populations. Capecitabine combination therapies are now being evaluated in the REAL-2 and Korean studies, with a total of 1,300 patients, which is equal to the number in the Japanese studies that are evaluating *S*-1. These results will clarify the true impact of both agents and may provide comparative data. Although future direct comparisons between the effects of the two agents are desirable, such a study will be less meaningful. It seems preferable to examine the possible benefits of incorporating them with other new agents.

Another difference is evident in the results of irinotecan + CDDP therapy. In the first step of the V306 study, comparing this combination with irinotecan + FU + LV, the irinotecan + CDDP arm showed inferior survival, with an MST of only 6.9 months. The question was raised whether the JCOG study (JCOG 9912) should close accrual to the irinotecan + CDDP arm. However, the doses and schedules of this regimen differ: irinotecan (200 mg/m^2) and CDDP (60 mg/m^2) every 3 weeks in the V306 study, and irinotecan (70 mg/m^2) on days 1 and 15 and CDDP (80 mg/m^2) every 4 weeks in the JCOG study. Furthermore, the MST of this regimen in the V306 study was markedly worse than that reported in the Japanese phase II study. Moreover, the Data and Safety Monitoring Committee of the JCOG did not recommend the early termination of accrual to this arm at the interim analysis. Thus, the accrual to this arm was continued to the last patient.

Biologic differences between Western and Japanese patients might exist. Adenocarcinoma of the esophagus and gastroesophageal junction are increasing at a dramatic rate in Western countries,[62] whereas no such trend has yet been observed in Japan or East Asia.[1] Most recent Western studies have included gastroesophageal junction carcinomas in the eligibility criteria and the REAL-2 study extended this to include lower esophageal carcinomas.[57] There have also been discrepancies in selecting targeted patients. The REAL-2 study included approximately one third of patients with locally advanced disease, who have a greater chance of subsequent surgical resection. However, in Japan and Korea, a lower incidence of gastroesophageal junction carcinoma and locally advanced disease (probably due to earlier detection and more radical surgery) is evident in daily practice. These disparities may not only perturb future comparisons of the results of ongoing studies but also obstruct additional global studies.

RANDOMIZED TRIALS IN PATIENTS WITH PERITONEAL DISSEMINATION

Peritoneal metastasis is the major site of dissemination from gastric cancer. However, these patients usually have a poor general condition, impairment of oral intake, and complications such as bowel obstruction or hydronephrosis, which may retard the elimination of the agents, thereby limiting the use and doses of several agents. Patients with peritoneal dissemination are excluded from phase II studies because they usually have no measurable lesions. Therefore, specifically targeted studies should be conducted. A phase II study of the sequential combination of MTX + FU (JCOG 9603) has been carried out in patients with malignant ascites.[63] A total of 37 patients were registered. A marked decrease in ascites was observed in 13 patients (35%), including four patients (11%) in whom ascites disappeared, whereas two patients (5%) died of treatment-related toxicity. Based on these results, a phase III study comparing FU alone with MTX + FU (JCOG 0106) in patients with peritoneal dissemination has commenced and the accrual will be completed at the end of 2006. Another randomized trial undertaken by the JCOG to investigate the efficacy of paclitaxel as a second-line therapy for the treatment of this disease is now underway. These unique studies will provide a benchmark for the treatment of this disease.

FUTURE PERSPECTIVES

To date, only two triplet regimens, ECF and DCF, have demonstrated significant survival prolongation. However, the benefits seem to be marginal and the MSTs were limited to within 10 months. Survival results from the ongoing randomized trials, which will be obtained soon, are anticipated to produce MSTs that exceed 12 months. These results will determine the baseline cytotoxic regimen, although they may differ between regions or be considered as platinum-doublet or -triplet, for example. Whichever regimen is the best, new active agents will be required to achieve additional improvement. Although the number of trials has been limited so far, molecular targeting agents, particularly epidermal growth factor receptor- and vascular endothelial growth factor-targeting agents, are now being investigated. The use of gefitinib, an orally active EGFR tyrosine kinase inhibitor, has been investigated for the treatment of metastatic gastric cancer in a joint Japanese-European phase II study.[64] However, this study failed to demonstrate any activity, with a disease control rate of only 18% and

no objective response. Trastuzmab, an anti-HER2 antibody, is now being investigated in a global randomized study, predominantly in Asian and European countries, in combination with FU (or capecitabine, as oncologist's choice) + CDDP. The rationale of this study was based on the analysis of HER2 expression in surgically resected and biopsy specimens, using two commercial immunohistochemical kits and fluorescence in situ hybridization, which showed an HER2 overexpression rate of 23%.[65] Recently, promising results for bevacizumab, an anti-VEGF monoclonal antibody, in combination with irinotecan + CDDP has been reported in the United States. Shah et al[66,67] conducted a small multicenter phase II study of this combination for the treatment of metastatic disease. They reported a high response rate of 75%, although this combination was associated with a high incidence of thromboembolic events (6 of 24) and gastric perforation (2 of 24), suggesting it be used with caution. Although the efficacy of molecular targeting agents is still limited, these agents are the new hope for improving the efficacy of results, with lower toxicity than conventional cytotoxic agents. Understanding the biology of gastric cancer may result in better targets or cellular pathways that can be modified or blocked by therapeutic intervention. Improvements in clinical trial design and the introduction of molecular surrogates to clinical research will also lead to the development of better treatments. Both clinical and biologic research will become more important.

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REVIEW ARTICLE

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Current status of stereotactic body radiotherapy for lung cancer

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Abstract Stereotactic radiotherapy (SRT) for extracranial tumors has been recently performed to treat lung and liver cancers, and has subsequently been named stereotactic body radiotherapy (SBRT). The advantages of hypofractionated radiotherapy for treating lung tumors are a shortened treatment course that requires fewer trips to the clinic than a conventional program, and the adoption of a smaller irradiated volume allowed by greater setup precision. This treatment is possible because the lung and liver are considered parallel organs at risk. The preliminary clinical results, mostly reported on lung cancer, have been very promising, including a local control rate of more than 90%, and a relatively low complication rate. The final results of a few clinical trials are awaited. SBRT may be useful for the treatment of stage I lung tumors.

Key words Stereotactic body radiotherapy · Conformal radiotherapy · Lung cancer · Stereotactic body frame · Stereotactic radiotherapy · Extracranial tumors

Introduction

Stereotactic radiotherapy (SRT) for extracranial tumors has been recently performed to treat extracranial tumors, mainly lung and liver cancers, and has subsequently been named stereotactic body radiotherapy (SBRT) or extracranial stereotactic radiotherapy (ESRT). The advantages of hypofractionated radiotherapy for treating lung tumors are a shortened treatment course that requires fewer trips to the clinic than a conventional program, and the adoption of a smaller irradiated volume allowed by greater setup precision. This treatment is possible because the lung and liver are considered parallel organs at risk (OAR). The disadvantages of SBRT are the uncertain effects of altered fractionation and the theoretical risk of worsening the ratio of normal tissue to tumor tissue through the use of a high dose per fraction. In this article, the technical procedures and clinical results of SBRT, especially in lung cancer, are reviewed.

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Biology

The biological background of SBRT is important. There is no past clinical evidence for this kind of hypofractionated regimen to extracranial tumors; therefore, most clinical regimens should be based on biological estimations.

The two great issues in hypofractionated regimens are dose response for tumor control and toxicity to normal tissue. Can the conventional linear-quadratic (LQ) model be applied in the SBRT dose range? Can repopulation be avoided in the SBRT regimen? How great is the effect of hypoxia in SBRT?

Fowler et al.[1] answered these questions, which are mostly applicable to SBRT; however, they recommended that SBRT be performed three to five fractionated schedule rather than using single SRS. These biological speculations should be reconfirmed in the clinical setting.

Body fixation

The first body fixation device was introduced in clinical practice as a stereotactic body frame by Bromgren et al.[2] and Lax et al.[3] Patients were fixed in the stereotactic frame, using a vacuum pillow. The concept of this frame is to utilize the cranial SRT coordinates for extracranial SBRT. The difference between cranial SRT and extracranial SBRT is the accuracy of the setup. The Japanese national guidelines for SRT state that the allowance of setup error is 2 mm for cranial tumors and 5 mm for extracranial tumors.

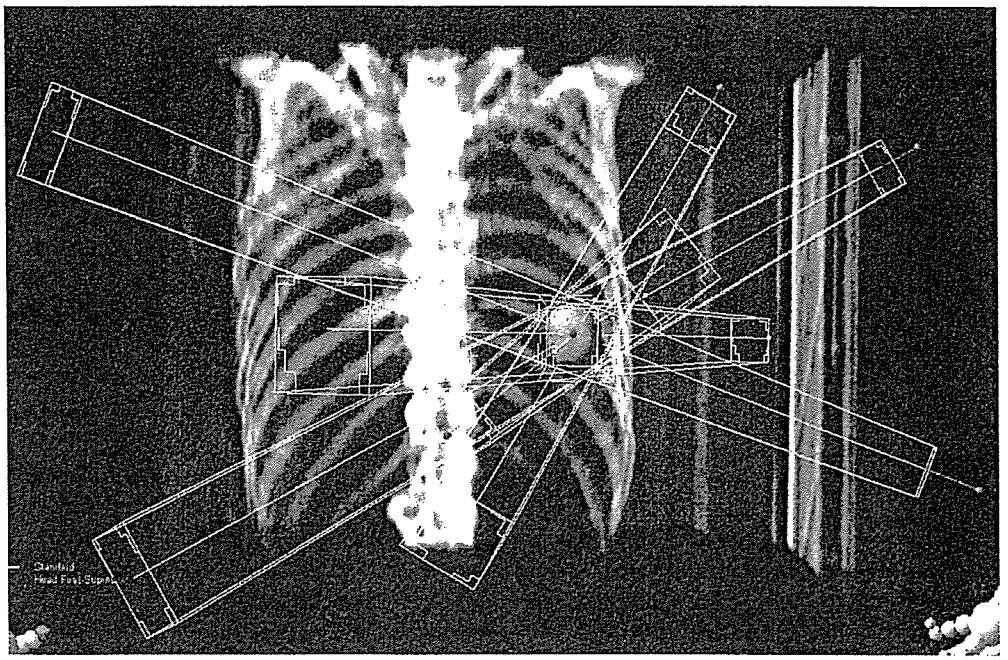

Fig. 1. Stereotactic body radiotherapy (SBRT) for lung cancer. In this image for treatment planning for left lung cancer, five beams are focused on the target

Some other fixing apparatuses using a vacuum sheet or thermoplastic shell are clinically available.

Respiratory monitoring

In the clinical practice of SBRT, the regulation of respiratory movement is essential. There are three ways to regulate the respiration of patients: respiratory holding, respiratory regulation, and respiratory gating.

The respiratory holding method is to ask patients to hold their breath for about 10s during radiation; therefore, radiation is performed intermittently four to ten times. Theoretically, this method can reduce the internal target volume (ITV). Holding can be done either voluntarily by patients or by using devices such as an active breathing control (ABC).

Respiratory regulation can be performed by exerting pressure on the abdomen using a plate like our diaphragm control or an abdominal belt.[4]

The respiratory gating method was originally developed in Japan. The gating sensors are a respiratory flow monitor, abdominal wall fiducials, and implanted gold fiducials.

Target definition

In computed tomography (CT) images taken under free-breathing long-scan (4–8s) conditions, the target outlines of the ITV are delineated. These CT images include the respiratory movement of the target. ITVs and Clinical Target Volume (CTV)s were not edited for anatomy.

If patients are irradiated with gated radiotherapy, the target outlines of CTV could be delineated under gating conditions.

The setup margins between the ITV and the planning target volume (PTV) must be determined at each institution. Our margins are 5mm for the anteroposterior (AP), 5mm for the lateral, and 8–10mm for the craniocaudal directions. Overlapping the outlines under inhale and exhale conditions is an alternative choice.

Treatment planning

There are two different concepts of Radiotherapy Treatment Planning (RTP) for SBRT. One concept, mainly used in Japan, is to maintain dose homogeneity within the target. In this case, the dose is usually prescribed at the isocenter. The other concept, mainly used in the United States, is not to maintain dose homogeneity. In this case, the dose is prescribed at the PTV margin. Our method adheres to the former concept, with selection of the optimal direction of noncoplanar beams, with the goal of the RTP being 6–10 portals for noncoplanar static beams, as shown in Fig. 1. The beam energy used was 6 MV and the isocenter was single for all beams. Four single treatments with 12Gy of radiation were prescribed at the isocenter. Using an LQ model,[5] the Biological Effective Dose (BED) was here defined to be nd (1 + d / alpha-beta) Gy, where n is the fractionation number, d is the daily dose, and the alpha-beta ratio for tumors was assumed to be 10. The value was 105.6Gy-BED for 48Gy in four fractions. The most important issue for RTP in SBRT is to maintain the dose constraints of OAR to avoid serious complications. The dose constraints of the OAR, including the spinal cord, pulmonary artery, bronchus, and heart, under the Japan Clinical Oncology Group (JCOG) 0403 protocol, are shown in Table 1.

Verification before radiation

In the clinical practice of SBRT for lung cancer, verification before each treatment is mandatory. In our institute, before each treatment, AP and lateral portal films are taken for verification. The position of each patient is verified by three experienced oncologists and technologists for each treatment. When the setup errors are larger than 2 mm between the X-ray simulation film and portal film in any direction, the patient is repositioned and portal films are taken and verified again. CT on rails and FOCAL units are also useful materials for verification before each treatment.

Clinical indications for SBRT

Currently, the eligibility criteria for patients with primary lung cancer are: (1) tumor size less than 5 cm in diameter without nodal and distant metastases (T14N0M0); (2) surgery was contraindicated or refused; (3) the patient could remain stable in the body frame for longer than 30 min (WHO performance status <=2); (4) no active interstitial pneumonitis; and (5) written informed consent was obtained. The criteria for patients with secondary lung cancer are: (1) tumor size less than 5 cm in diameter; (2) tumor number three or less; (3) no other metastases, and (4) local tumor is controlled.

Tumor size is an important factor when dose homogeneity within the target should be maintained. The dose constraints of mediastinal organs should be maintained; therefore, a central tumor could be less suitable for SBRT indications than a peripheral tumor.

Table 1. Dose constraints of various organs at risk, according to the JCOG 0403 protocol

Organ	Dose	Volume	Dose	Volume
Lung	40 Gy	<=100 cc	MLD	<=18 cc
	V15	<=25%	V20	<=20%
Spinal cord	25 Gy	Max		
Esophagus	40 Gy	<=1 cc	35 Gy	<=10 cc
Pulmonary artery	40 Gy	<=1 cc	35 Gy	<=10 cc
Stomach	36 Gy	<=10 cc	30 Gy	<=100 cc
Intestine	36 Gy	<=10 cc	30 Gy	<=100 cc
Trachea, main bronchus	40 Gy	<=10 cc		
Other organs (heart, etc)	48 Gy	<=1 cc	40 Gy	<=10 cc

18-Fluoro-deoxy-glucose (FDG)-positron emission tomography (PET)

18-Fluoro-deoxy-glucose (FDG)-PET scanning is an important examination both for the staging and the follow-up of lung cancer. For lung cancer staging, occult mediastinal and hilar lymph nodes, and distant metastases, are frequently found by FDG-PET.

In the follow-up of lung cancer after SBRT, radiation fibrotic change cannot be distinguished from residual tumor. FDG-PET is also useful in this situation.[6]

Clinical results

Local tumor response

The local control rates of primary lung cancer with SBRT have been previously reported by several authors, as shown in Table 2: 94 % (47/50) for 50–60 Gy in five fractions with a median follow-up of 36 months,[7] 92 % (22/24) for 60 Gy in 8 fractions with a median follow-up of 24 months,[8] 81% (30/37) for 60 Gy in three fractions with a median follow-up of 15 months,[9] 80% for 48–60 Gy in eight fractions with a median follow-up of 17 months,[10] 95% for 45–56.2 Gy in three fractions with a median follow-up of 10 months,[11] 90% for 30–40 Gy in four fractions with a median follow-up of 21 months,[12] and 98% (44/45) for 48 Gy in four fractions with a median follow-up of 30 months.[13] However, the definition of local control after radiotherapy is difficult because local tumor failure and Radiation Induced Lung Damage (RILD) cannot be clearly delineated. Even though the definition of local control is different in various trials, a BED larger than 100 Gy may be effective for the SRT of solitary lung cancer with a local control rate of above 85%.

Survival

The survival rates of stage IA (T1N0M0) lung cancer and stage IB (T2N0M0) lung cancer have not been separately reported by several authors. In our stage IA series, the 1-year and 5-year local relapse-free survival rates were 100% and 95%. The isease-free survival rates after 1, 3, and 5 years were 80%, 72%, and 72%, respectively, and the overall survival rates were 93%, 83%, and 83%, respectively. In our stage IB series, the 1-year local relapse-free survival

Table 2. Local control rates of stereotactic radiotherapy for primary lung cancer

Author (year)	Total dose (Gy)	Daily dose (Gy)	Reference point	Local control	Median follow-up (months)
Uematsu[7] (2001)	50–60	10	80% Margin	94% (47/50)	36
Arimoto[8] (1998)	60	7.5	Isocenter	92% (22/24)	24
Timmerman[9] (2003)	60	20	80% Margin	81% (30/37)	15
Onimaru[10] (2003)	48–60	6–7.5	Isocenter	80% (20/25)	17
Wulf[11] (2004)	45–56.2	15–15.4	80% Margin	95% (19/20)	10
Nagata[13] (2005)	48	12	Isocenter	98% (44/45)	30
Lee[12] (2003)	30–40	10	90% Margin	90% (8/9)	21

Table 3. Clinical toxicities after stereotactic radiotherapy for primary lung cancer

Author (year)	Number of cases	Lung >=grade 3	Lung grade 5	Other grade 5
Uematsu[7] (2001)	50	0%	0	
Arimoto[8] (1998)	24	NA	0	
Lee[12] (2003)	28	0	0%	
Onimaru[10] (2003)	45	2%	0%	Esophagus
Wulf[11] (2004)	61	0	0%	
Nagata[13] (2005)	45	0	0	
Timmerman[16] (2006)	70	20%	9%	Hemoptysis, pericarditis
J-CERG[5] (2006)	2106	NA	0.50%	Esophagus, hemoptysis

NA, not available

rate was 100%. The disease-free survivals after 1, 3, and 5-years were 92%, 71%, and 71%, respectively, and the overall survival rates were 82%, 72%, and 72%, respectively.[13] Onishi et al.[14] recently reported the results for 13 institutions in Japan, which summarized findings for 245 patients: 155 with stage IA lung cancer and 90 with stage IB lung cancer. There were 87 operable and 158 inoperable patients, and their results showed that the intercurrent death rate was especially high in the inoperable patient group. Moreover, the 5-year survival rates of operable patients irradiated with more than BED=100 Gy was 90% for stage IA and 84% for stage IB, and their clinical results were as good as those for surgery.

These survival rates should be compared with the results of surgery; however, the results of SBRT may differ depending on how many of the group are operable and how many are inoperable, and how many of the tumors are central and how many, peripheral.

Toxicities

The great concern of pulmonary toxicity with this SBRT treatment was relieved by the very low rates of complications in early studies. Most pulmonary complications were less than National Cancer Institute common toxicity criteria (NCI-CTC) version 2.0 grade 2. No other serious complications were reported, except for rib fracture, intercostals neuralgia, and mild dermatitis. However, recently, a few serious complications have been reported by several institutions in Japan.[15] These complications include grade 5 pulmonary complications, radiation pneumonitis, hemoptysis, and radiation esophagitis. Most cases of grade 5 radiation pneumonitis were associated with interstitial pneumonitis. Cases of interstitial pneumonitis should be carefully considered. Thoraco-cutaneous fistula was reported in a patient with previous tuberculosis history. Acute cholecystitis was reported in a patient with gallstones who had been pressed with an abdominal press board at the time of SBRT.

Another toxicity concern was the effect on the central bronchus, pulmonary artery, esophagus, heart, and spinal cord. The effects of a hypofractionated dose on the main bronchus, pulmonary artery, heart, and esophagus have not been followed up for a sufficiently long time. Lethal pulmonary bleeding and esophageal ulcer have been reported previously by several authors. Timmerman et al.[16] recently reported a series of complications with SBRT. Central hilar tumors adjacent to mediastinal organs should be carefully considered.[17] Table 3 shows the toxicities reported by various groups.

Ongoing clinical trials

Recently, a multi-institutional phase II study of SBRT for T1N0M0 non-small cell lung cancer under JCOG (http://www.jcog.jp/) protocol 0403 was started in Japan. Sixteen institutions entered together and started the same 48-Gy SBRT dose at the isocenter in four fractions for T1N0M0 lung cancer. One hundred patients have been registered. The results of SBRT for both inoperable and operable stage I lung cancer patients are awaited.

A new dose-escalation study of SBRT for T2N0M0 lung cancer is also planned, under the JCOG.

Timmerman et al.[9] concluded that a 60-Gy marginal dose in three fractions was the limiting dose, and the Radiation Therapy Oncology Group (RTOG) study 0239 for inoperable patients is already closed. There are a few other reports so far.[18–23] The coming RTOG protocols for operable patients, central tumors, and lung metastases are awaited.

Future directions

Both a new IGRT technique and four-dimensional RTP are future directions of SBRT. Systemic chemotherapy may be considered when the local tumor is well controlled and regional/distant metastases are frequent.

The primary indication for stereotactic radiotherapy in lung cancer could be a stage 1A (T1N0M0) patient. Very early-stage lung cancer can now be detected by screening CT examination, and these cases are also good indications for SRT; however, the issue in these cases is histological confirmation. In our clinical experience, 7 of a total of 95 SRT cases could not be finally confirmed histologically. Of course, these 7 cases were not included in our study.[13] They could not be histologically confirmed because of failure or difficulty in CT-guided biopsy or transbronchoscopic lung biopsy (TBLB). Currently, CT screening has revealed very early-stage lung cancer with ground glass opacity (GGO) and some patients with severe emphysema could be contraindicated for biopsy. Therefore, the indication for SRT for

these cases without histological confirmation should be discussed in the future. When the tumor is larger than 3 cm in diameter, which corresponds to stage 1B (T2N0M0), SRT is possible; however, the intratumor dose becomes less homogeneous, and the rate of occult distant metastases may increase. Therefore, extension of the indication of this technique for T2 tumors requires more consideration for dose escalation or adjuvant chemotherapy.

The current standard choice for stage IA lung cancer treatment is lobectomy;[24] however, for many patients this is not indicated because of accompanying diseases, such as chronic obstructive pulmonary disease (COPD), cardiac disease, and diabetes. For such patients, various minimal surgical techniques are indicated, including wedge resection and video-assisted thoracoscopic surgery (VATS), as well as ablation. The local control rates of various other modalities for primary stage I lung cancer previously reported were 93% for wedge resection and 83%-95% for VATS, and the 5-year survival rates were 82% and 50%-70%, respectively. A further randomized trial comparing SBRT with surgery should be considered.

Conclusion

SBRT is a safe and effective treatment method for stage I lung tumors. Further clinical studies are therefore warranted.

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Diagnostic accuracy of CT-guided percutaneous cutting needle biopsy for thymic tumours

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AIM: To determine the diagnostic accuracy of computed tomography (CT)-guided percutaneous cutting needle biopsy (PCNB) for thymic tumours in accordance with the World Health Organization (WHO) classification.

MATERIAL AND METHODS: We retrospectively analysed a consecutive series of 138 cases in which CT-guided PCNB had been performed for an anterior mediastinal tumour. Its sensitivity and specificity for thymic epithelial tumours were evaluated, and the concordance between the histopathological diagnosis according to the WHO classification of thymic tumours based on PCNB and the diagnosis is based on the surgical specimens was assessed by Kappa statistic.

RESULTS: The diagnostic sensitivity and specificity of CT-guided PCNB for thymic tumours were 93.3 and 100%, respectively. The overall concordance between the diagnosis according to the WHO classification established by PCNB specimen and by the surgical specimen was 79.4% (weighted kappa = 0.79).

CONCLUSION: CT-guided PCNB is a reliable method of diagnosing thymic tumours, and there was good concordance for the WHO classification between the diagnosis based on CT-guided PCNB specimen and that based on the surgical specimen.

Introduction

Percutaneous needle biopsy (PNB) is used in the diagnosis of pulmonary, pleural, and mediastinal tumours. There are well-established methods for guiding mediastinal tumour biopsy, including fluoroscopy, ultrasonography, and computed tomography (CT),[1–6] but as most mediastinal tumours are located adjacent to major vessels and important structures, CT-guidance is preferred over guidance by fluoroscopy or sonography.[7]

The percutaneous cutting needle biopsy (PCNB) technique has become safer and more accurate with the use of 18 to 20 G needles, improvements in imaging techniques used for guidance (especially CT), and advances in pathological interpretation of the specimens.[8] Previous studies have reported that larger cutting needles allow sufficient tissue to be obtained for histological examination, and that biopsy with such needles might be more useful than aspiration biopsy for the diagnosis of malignant or non-malignant lesions.[5,7,9,10]

Previous studies on mediastinal tumours have reported that PNB is highly reliable for the diagnosis of metastatic carcinoma and germ cell tumours, but less reliable for that of thymic epithelial tumours and lymphomas.[7,9,11–13] The World Health Organization (WHO) Consensus Committee recently published a histological classification system for tumours of the thymus.[14] It stratifies thymic epithelial tumours into six categories (types A, AB, B1, B2, B3, and thymic carcinoma) based on the epithelial cell morphology and the lymphocyte: epithelial cell ratio. However, no studies to date have assessed the

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reliability of CT-guided PCNB for the diagnosis of thymic epithelial tumours according to the WHO classification.

The aims of this study were: (1) to evaluate the diagnostic accuracy of CT-guided PCNB for thymic epithelial tumours, and (2) to evaluate the concordance of the WHO classification between the diagnoses based on CT-guided PCNB specimen and based on the surgical specimen.

Materials and methods

CT-guided PCNB for an intra-thoracic mass was performed in a total of 541 patients at our hospital between November 1997 and November 2004, and in the present study 138 cases were retrospectively reviewed in which CT-guided PCNB was performed for an anterior mediastinal tumour.

CT was performed using a helical CT machine (X-Vigor, Aquillion, Toshiba Medical Systems, Tokyo, Japan) in all patients before the CT-guided PCNB. The biopsies were performed by experienced thoracic radiologists or thoracic radiologist fellows under the supervision of an experienced thoracic radiologist. Informed consent was obtained from the patient before each procedure. Localization was performed in the supine position by CT imaging with laser lights and a grid system. The helical imaging was performed at 3.0 mm collimation for individual examinations of the entire thorax (120 kVp, 150 mA), and reconstruction was performed using a standard algorithm.

Local anaesthesia was achieved by subcutaneous injection of 1% lidocaine (Xylocaine; AstraZeneca, London, UK). All biopsies were performed by a coaxial technique with 150 mm long 18 G cutting needles (Urocut; TSK laboratory, Tochigi, Japan) consisting of an outer and inner cutting needle. The needles were guided to the target lesion by CT. The inner cutting needle was manually advanced a fixed distance of 25 mm, and the outer cutting needle was then manually advanced same distance to obtain a 17-mm core specimen. CT images were obtained to document successful placement of the cutting needle beside the lesion and within the lesion. If a sufficient core of tissue was obtained, only a single pass was used, but if only small fragments of tissue were obtained, two passes were made. After withdrawing the biopsy needle, the patients were examined by CT for complications. All the patients remained in the hospital overnight for observation, and a chest radiograph was obtained the next day. The specimens obtained were immersed in 10% buffered formalin and later stained for histological and immunohistochemical examination. After the publication of the classification system by the WHO, the pathologists made their histological diagnoses based on the WHO classification of thymic epithelial tumours.[14] After the diagnosis based on examination of the CT-guided PCNB specimen, surgical resection or open surgical biopsy was performed when necessary.

To evaluate the diagnostic accuracy of CT-guided PCNB for thymic epithelial tumours, we retrospectively compared the results of the CT-guided PCNB with the final diagnosis made during clinical and radiological follow-up in the inoperable cases and with the histological diagnosis based on histopathological examination of the surgically resected specimens in the operable cases. Diagnostic concordance was assessed by comparing the diagnosis according to the WHO classification of thymic epithelial tumours that was made based on examination of the specimens obtained by CT-guided PCNB and based on histopathological examination of the surgical specimens. For evaluation of the weighted Kappa statistic analysis, the WHO classification of thymic epithelial tumours was divided into four categories based on the clinical and oncological information[15,16]: (1) types A and AB, (2) types B1 and B2, (3) type B3, and (4) thymic carcinoma. The weighted kappa analysis was used to evaluate the overall concordance with the set of weights

$$w_{ij} = 1 - (i-j)^2/(l-1)$$

used, where i and j are indices of the categories being used, and l is the number of categories. The concordance for the diagnosis according to the WHO classification system between CT-guided specimen and surgical specimen was also analysed by this method. The concordance level was graded based on the weighted kappa value, thus; <0.20 = very poor; 0.21–0.40 = poor; 0.41–0.60 = fair; 0.61–0.80 = good; >0.80 = excellent. The statistical analysis was performed with SAS version 8.2, software (SAS Institute, Cary, NC, USA).

Results

During the study period CT-guided PCNB was performed for an anterior mediastinal tumour in 138 patients, 72 males and 66 females, and their median age was 56 years (range, 12–80 years). CT was performed during and after the procedure in all 138 patients, and no patients developed severe complications, such as pneumothorax and bleeding, that needed treatment.

The final diagnosis was thymic epithelial tumour in 60 cases (43.5%), malignant lymphoma in 26 cases (18.8%), metastatic carcinoma in 26 cases (18.8%), germ cell tumour in 12 cases (8.7%), benign tumour in six cases (4.4%), miscellaneous malignancy in six cases, (4.4%), and thymic hyperplasia in two cases (1.5%).

The results of the analysis of the results of CT-guided PCNB for the diagnosis of thymic epithelial tumours in all 138 cases revealed a sensitivity of 91.7% [95% confidence interval (CI): 81.6–97.2%], specificity of 100% (95% CI: 95.4–100%), positive predictive value of 100% (95% CI: 93.5–100%), negative predictive value of 94.0% (95% CI: 86.5–98.0%), and overall accuracy of 96.4% (95% CI: 91.7–98.8%).

The diagnosis of both CT-guided PCNB specimens and surgical resection specimens was made in accordance with the WHO classification in 29 of the 60 patients diagnosed after its publication. The WHO classification concordance between the diagnoses based on CT-guided PCNB specimen and based on the surgical specimen and weighted kappa values were 79.4% and 0.79 (95% CI: 64.7–94.1%, 0.63–0.95, Table 1). A definitive diagnosis could not be made by CT-guided PCNB in four of the 29 patients with thymic epithelial tumours, and there was a discrepancy between the diagnosis of the CT-guided PCNB specimen and diagnosis of the surgical specimen in two cases.

A false-negative diagnosis of thymic epithelial tumour was made in five of the 60 patients, and the overall false-negative rate was 8.3% (95%CI: 2.0–13.5%). The results of the diagnoses of the CT-guided PCNB specimen and the final diagnoses in the five false-negative cases are summarized in Table 2. Sufficient material for diagnosis could not be obtained by CT-guided PCNB in these five cases, including the two cases suspected of having a malignant tumour (Fig. 1). Repeat CT-guided PCNB was not performed in any of the five patients. There were no false-positive diagnoses of thymic epithelial tumour.

Table 1 Concordance between the diagnosis established by computed tomography-guided percutaneous cutting needle biopsy and diagnosis of the surgical specimen in patients with a thymic epithelial tumour classified according to the World Health Organization classification system

CT-PCNB diagnosis	Diagnosis of the surgical specimen					Total
	Non-tumour[a]	A or AB	B1 or B2	B3	Ca	
Non-tumour*	–	2	2[b]	–	–	4
A or AB	–	9	–	1	–	10
B1 or B2	–	1	5	–	–	6
B3	–	–	–	1	–	1
Thymic carcinoma	–	–	–	–	8	8
Total	–	12	7	2	8	29

[a] For the weighted Kappa statistic analysis, we defined the non-tumour category consisted of thymic hyperplasia, thymic tissue, fibroadipose tissue, and insufficient material for diagnosis.

[b] Including one case with atypical cells, suspected of being thymic carcinoma.

Discussion

This study revealed high sensitivity and specificity of CT-guided PCNB, and good concordance of the WHO classification of thymic epithelial tumours between the diagnosis based on CT-guided PCNB specimen and based on surgical specimen. Thus, CT-guided PCNB is not only a reliable and safe procedure for the diagnosis of thymic tumours, but obviates the need for open surgical biopsy in patients with non-resectable thymic epithelial tumours.

Many previous studies have reported that PNB is not very useful for the diagnosis of thymic epithelial tumours, and its sensitivity has been reported to range from 44–83%.[1,7,11,13,17–19] However, relatively few patients were evaluated in most of the studies. There were only two studies of patients with thymic epithelial tumours where there were sufficient cases evaluated to allow a statistical assessment of the diagnostic utility of the procedure.[11,13] In both of these previous studies, fine-needle aspiration biopsy or 20 or 21 G needle biopsy was used and they reported a sensitivity of 61% and 71%, respectively, for the diagnosis of thymic epithelial tumours. Thus, the published results suggest that the diagnostic role of PCNB in patients with suspected thymic epithelial tumours is mainly to exclude other types of non-surgical lesions.[9] However, the results of the present study revealed a high sensitivity and specificity of CT-guided PCNB for thymic epithelial tumours, and the procedure was also found to be reliable for diagnosis according to the WHO classification. Therefore, CT-guided PCNB performed under local anaesthesia is a useful procedure for the diagnosis of thymic epithelial tumours, and it may also obviate the need for an open surgical diagnostic procedure.

A false-negative result was obtained by CT-guided PCNB in five cases of thymic epithelial tumours in the present study. Based on the results of the present study and those of a previous study,[13] the diagnostic yield was relatively low for tumours that tended to undergo extensive

Table 2 Summary of cases of thymic epithelial tumour in which a false-negative diagnosis was made by computed tomography-guided percutaneous cutting needle biopsy (PCNB).

No./Sex/Age	Size (cm)	PCNB diagnosis	Final diagnosis
1/F/61	4.0 × 2.5	Specimen insufficient for diagnosis	Thymoma AB
2/F/60	6.1 × 2.9	Necrotic tissue	Thymoma B2*
3/M/59	3.6 × 3.4	Atypical cells, suspicion of thymic carcinoma	Thymoma B1
4/F/55	5.6 × 2.6	Lymphoepithelial tissue, no definite tumour	Thymoma B2
5/F/55	3.5 × 2.0	Fibrous tissue	Thymoma AB

*Although patient 2 underwent surgery before publication of the WHO classification of thymic epithelial tumour, we retrospectively reviewed the slides prepared from the surgical specimen and made the diagnosis according to the latest WHO classification.[14]

necrotic or cystic degeneration from which it was difficult to obtain sufficient material for histopathological diagnosis (Fig. 1).

Previous studies have reported difficulty in differentiating thymomas from malignant lymphomas.[11,13] Herman et al.,[11] described five cases of lymphoma that were misdiagnosed as thymoma and two cases of thymoma (lymphocytic type) that were misdiagnosed as lymphoma. These misdiagnoses were ascribed to the use of cytological methods alone without immunohistochemical study. Moulton and Moore[10] reported that more accurate diagnosis could be achieved by cutting needle biopsy than by aspiration biopsy in cases of lymphoma. The CT-guided PCNB in the present study had high diagnostic sensitivity and specificity and did not result in diagnostic confusion between thymic epithelial tumours and lymphomas, because it allowed histological evaluation of the tissue architecture as well as immunohistochemical analysis. Immunohistochemical examination was useful in making the diagnosis of mediastinal lymphoma.[20] In addition, as CD5 and CD117 are expressed in approximately 80% of thymic carcinomas,[21–23] immunohistochemical analysis enable differentiation between thymic carcinomas and thymomas.

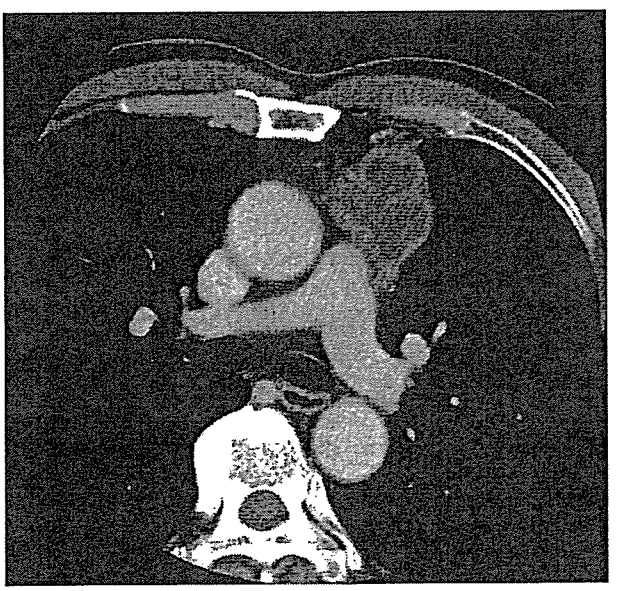

Figure 1 CT images from a patient with a false-negative diagnosis of thymic epithelial tumour by CT-guided PCNB. Enhanced transaxial CT image showing a heterogeneous attenuation with a peripheral irregularly enhancing wall in the left anterior mediastinum. Histological examination revealed thymoma B1 with extensive necrosis (case 3 in Table 2).

Several studies have assessed the value of the WHO classification system of thymic epithelial tumours. It has been reported that the WHO classification may be an independent prognostic factor and have a correlation with the disease-free survival and overall survival.[15,16,24,25] In one study the 10-year disease-free survival rate was 100% for types A and AB, 83% for types B1 and B2, 36% for type B3, and 26% for thymic carcinoma,[15] and similar results have been obtained in another study.[16] Most type A and type AB thymomas follow a benign clinical course, but they are not all benign. Type B1 and type B2 thymomas are borderline between benign and malignant. Type B3 tumours exhibit malignant behaviour, and thymic carcinoma displays more aggressive behaviour.[15,16] The outcome of the patient was affected by the histological types, and it was not a simple matter of tumour progression according to Masaoka's clinical stage.[16] Therefore, the histological type together with the stage is important in deciding on the therapeutic strategy.[16,25] Several studies on the treatment of thymic epithelial tumours have suggested that the complete resection rate and survival rate may be improved by a multidisciplinary approach (e.g., surgery, neo-adjuvant or adjuvant chemotherapy, and radiation therapy).[25,26] As the results of the present study indicated that CT-guided PCNB may allow reliable diagnosis of thymic epithelial tumours, including diagnosis in accordance with the WHO classification system, its use may contribute to optimizing the multidisciplinary approach for each patient.