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Cine MRI enables better therapeutic planning than CT in cases of possible lung cancer chest wall invasion

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ABSTRACT

The objective: To evaluate the hypothesis that lung cancer treatment planning (whether or not to use induction therapy) can be improved if respiratory dynamic cine magnetic resonance imaging (RD MR) is used.
Method: We studied 100 lung cancer patients, 76 men and 21 women, scheduled for thoracotomies between May 1997 and December 2006 wherein it was unclear preoperatively whether chest wall invasion would be found. We evaluated the accuracy of RD MR as compared with the findings at operation and postoperative pathology. The accuracy of RD MRI for evaluating chest wall invasion was compared with the efficacy of CT and MRI within our own group of patients and with data from the studies of other investigators.
Results: Concerning the evaluation of chest wall invasion, conventional computed tomography (CT) had 43.9% specificity, 60.0% sensitivity and 47.1% accuracy, while RD MR had 68.5% specificity, 100.0% sensitivity and 77.0% accuracy. RD MRI was particularly useful in the evaluation of cancers around 5 cm in diameter that were located adjacent to the diaphragm. Postoperative evaluation of superior sulcus tumor cases that had received induction therapy also showed that the RD MR procedure enabled an accurate decision in 87.5% of cases, and there were no false negative cases.
Conclusions: RD MR is more useful than CT or standard MRI for evaluating thoracic wall invasion. This noninvasive method enhances the reliability of deciding whether induction therapy should be employed.

1. Introduction

Since accurate evaluation of chest wall invasion by lung cancer is essential for precise staging and therapeutic strategy planning, there have been several studies using computed tomography (CT) or magnetic resonance (MRI) [1–7].

The recently developed high-speed respiratory dynamic MRI (RD MR) has the potential to provide accurate information on chest wall invasion and contribute to deciding on lung cancer staging, which might avoid the need to change surgical strategy intraoperatively, with attendant prolongation of operation time [8,9]. This is of particular importance when deciding on the indications of induction chemoradiotherapy in cases of superior sulcus tumor (SST) [10].

Simple contact of tumor and adjacent chest wall does not necessarily mean invasion, and even CT or conventional MR findings can be ambiguous concerning thoracic invasion.

On breathing, the chest wall and lungs move independently of each other. However, when a tumor invades only as far as the pulmonary pleura, it moves along the chest wall synchronously with breathing, while chest wall movement is limited when tumor invades the chest wall.

We therefore performed a prospective study to determine whether respiratory dynamic cine MRI (RD MR) could provide accurate and reliable information concerning pleural or chest wall invasion in lung cancer.

Abbreviations: CT, computed tomography; ED CT, expiratory dynamic computer tomography; Ef, therapeutic effect; FDG-PET, 18F-fluorodeoxyglucose-positron emission tomography; MRI, magnetic resonance image; NPV, negative predictive value; PPV, positive predictive value; RD MR, respiratory dynamic cine MRI; SST, superior sulcus tumor; SUV, standard uptake value; US, ultrasound.

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2. Materials and methods

In order to evaluate the usefulness of RD MR, we set out to evaluate information on all of the first 100 patients meeting the inclusion criteria and examined by this method, immediately after the equipment was introduced in May 1997 completing the study in December 2006. We enrolled only those in whom it was unclear whether there was invasion to the chest wall, in cases of peripheral lung cancer found to be abutting the pleural surface on a previous conventional static CT scan or MRI.

All cases in which rib destruction or infiltration into the soft tissues of the chest wall was identified by a CT scan or MR imaging were excluded from this study, because chest wall invasion was already clearly demonstrated by those findings. It was assumed that chest wall invasion had already taken place. We felt that once a decision on the status of the chest wall involvement had been made, it would be unethical to expose patients to the greater dose of radiation involved in RD MR. Another 43 patients were excluded because they did not undergo surgery due to distant metastasis or poor respiratory function. The method was developed by the second author of this paper, Dr. Akata. The first 100 patients meeting all our enrolment criteria (non-small cell carcinoma of the lung, suspected to have chest wall invasion, and ultimately operated cases with pathologically verifiable results) and giving written informed consent consisted of 76 men and 24 women, ranging in age from 30 to 84 years (mean 63.0). There were 42 adenocarcinomas, 40 squamous cell carcinomas, 14 large cell carcinomas, 2 adenosquamous cell carcinomas and 2 unclassified adenocarcinomas. The pathological stage of disease was IA in 9 cases, IB in 36 cases, IIA in 1 case, IIB in 20 cases, IIIA in 19 cases, IIIB in 10 cases and IV in 5 cases. Of the 100 cases, 13 were pathological T1, 56 pT2, 24 pT3 and 7 pT4. Almost half, 43 cases, were P0, 17 in P1, 13 in P2, 27 in P3. Tumors were located in the right upper lobe in 35, the right lower lobe in 27, the left upper lobe in 20, the left lower lobe in 17 and one was a multiple primary lung cancer case. Tumors ranged in size from 1.0 to 13.0 (mean 4.93) cm in diameter and only 22 cases were 3 cm in diameter or less. The tumor diameter was larger than 3 cm in 78 cases.

We used 1.5 T MR equipment (MAGNEX 150; Shimadzu Medical Systems, Kyoto, Japan) since 1997. RD MR was acquired with a body coil or spine coil by fast gradient echo sequence (TR = 8 ms, TE = 3 ms, FA = 10°). This sequence has a rewind gradient in phase direction after the completion of readout to maintain a steady state of magnetization. The slice thickness was 10 mm, the matrix was 128 × 128, the number of acquisitions was 2, and 25 consecutive images of the same slice, perpendicular to the abutting point on the chest wall, were taken while the patients breathed deeply.

After 2004, RD MR images were acquired using real-time true fast imaging with steady state precession (True-FISP) cine (Magnetom Symphony; Siemens Medical Systems, Erlangen, Germany), employing a body coil or spine coil with a real-time True-FISP cine sequence (TR = 2.24 ms, TE = 1.12 ms, FA = 74°). This sequence has a rewinding gradient in the phase direction after completion of readout, to maintain the status state of magnetization. The slice thickness was 8 mm, the matrix was 192 × 192 (80%), the number of acquisitions was 1, and 80 consecutive images, same slice obtained from perpendicular to the abutting point on the chest wall, while patients breathed deeply. The image time for 1 slide was 0.3 s and one loop was taken in 24 s. We also used CT scans (ProSeed SA, Yokogawa Medical, Tokyo, Japan) at 1 cm intervals with section thicknesses of 1 cm throughout the entire chest (120 kV, 200 mA, 0.8 s, HP 1.0). Intravenous contrast material iopamidol (Iopamiron 300; Nihon Schering, Osaka, Japan) was used in all cases. Several RD MR loops were taken, changing both the position and direction of the slides at least 3 times depending on the extent of the contact with the chest wall. Patients rehearsed breathing before the examinations which were performed within 3 weeks before surgery. Subjects took few deep breaths slowly for 30 s. MRI sagittal section and tangential projection scans were obtained without employing contrast medium.

The results of RD MR were analyzed to evaluate tumor movement relative to the chest wall, by 3 experienced radiologists blinded to the CT results who reached their conclusions by means of consensus. Chest wall invasion was considered absent if the tumor moved along the chest wall in synchrony with breathing (Fig. 1a). However, when tumor movement was restricted by the chest wall, chest wall invasion was considered present (Fig. 1b).

Lung tumor movement of more than half the height of a vertebra or of the width of a rib was considered to be substantial. Results of all RD MR examinations were analyzed before surgery and then

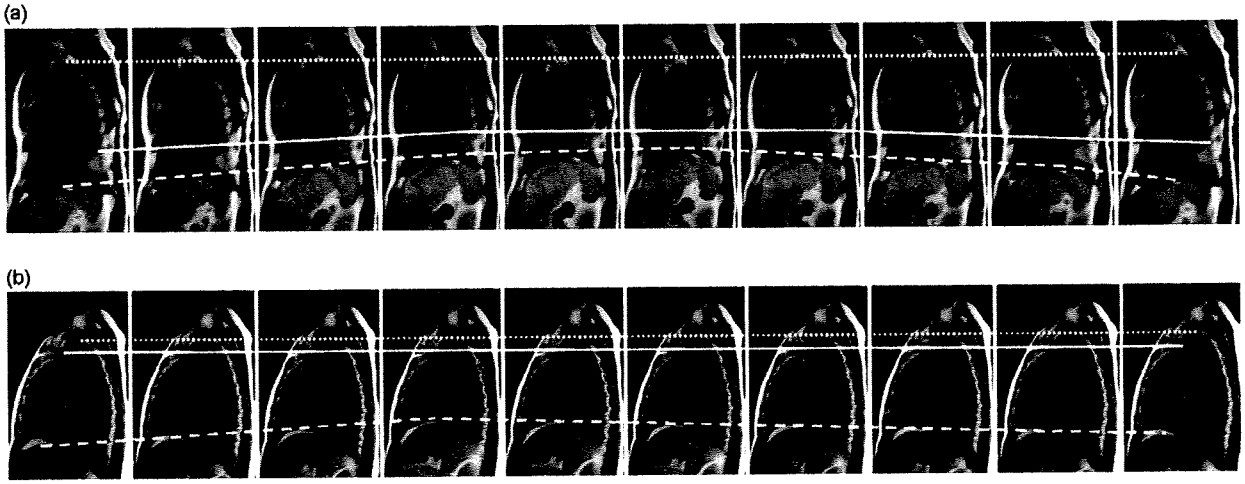

Fig. 1. The tumor on RD MR. (a) On RD MR, the tumor moves along the chest wall in synchrony with breathing. The dashed line connects the top of the diaphragm on 10 consecutive images. During deep breathing, it moves up and down. The unbroken straight line connects the tumor on the 10 consecutive images. During deep breathing, it goes up and down in (a). The dotted line connecting the apex of the lung shows that, during deep breathing, it does not move. Chest wall invasion was ruled out and the absence of invasion to the parietal pleura or chest wall was confirmed during operation. (b) On RD MR, no tumor movement along the chest wall is recognized during respiration. The lines connecting the 10 consecutive images are as described in (a). The unbroken straight line connecting the tumor on the 10 consecutive images shows that it did not move during deep breathing. Invasion was therefore considered likely. On thoracotomy, the adjacent parietal pleura and chest wall were resected in continuity with the primary lesion, and tumor invasion to the chest wall was shown pathologically.

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Table 1
Histopathological findings of chest wall invasion and pathologic Ef according to the General Rules for Clinical and Pathological Records of Lung Cancer of the Japan Lung Cancer Society.

Histopathological findings
p0: Cancer did not extend beyond the elastic membrane of the visceral pleura
p1: Cancer reached the elastic membrane of the visceral pleura
p2: Cancer present on the surface of the visceral pleura
p3: Cancer invaded the chest wall or mediastinum
Pathologic therapeutic effect (Ef) Ef 0: No effect
Ef 1a: Extremely mild effect
Ef 1b: Mild effect
Ef 2: Moderate effect
Ef 3: Complete response

the results were compared with the interoperative findings and the results of gross and microscopic pathologic examination of the resected specimens.

Histopathologic findings were described based on the World Health Organization classification for cell types [12]. Pathological stages were determined based on the TNM classification of the International Union Against Cancer (UICC) [13].

Pathological therapeutic effects were recorded according to the General Rules for Clinical and Pathological Records of Lung Cancer of the Japan Lung Cancer Society to evaluate the response to treatment in solid tumors (Table 1) [14].

All patients provided their written consent to the procedures which were all performed as part of the regular preoperative workup (and since all data are retrospective) and no patient's identity is revealed. Our Institutional Review Board approved data collection and analyses.

3. Results

In 50 of 100 patients, the RD MR showed that the tumor moved along the chest wall in synchrony with breathing (Fig. 2a: case 1). These cases were considered not to have invaded or at most only to the visceral pleura, but not into the chest wall, which was subsequently confirmed during surgery in all cases.

The other 50 patients all appeared to have chest wall invasion on RD MR, because tumor movement was restricted by the chest wall (Fig. 2b: case 2), suggesting possible invasion. However, this was corroborated by pathological examination in only 27/50 cases. In the remaining 23/50 lesions, no invasion was found pathologically, despite the suspicion of invasion on RD MR findings.

Thus, in the 50 cases that appeared to have no chest wall invasion on RD MR, absence of invasion was corroborated on pathological examination (Table 3). Another 23 appearing to have invasion, on RD MR were found not to have invasion pathologically. Of these, 8 (34.8%) were SSTs. The other 27 appearing to have invasion on RD MR were proved to have invasion on resected specimens. No case in which RD MR suggested the absence of invasion i.e. the tumor moved in synchrony with breathing, was found to have invasion or non-malignant fibrous adhesion pathologically.

Pathological examination of all cases showing false-positive RD MR findings of thoracic invasion revealed the cause to be non-malignant fibrous adhesion between the tumor and chest wall in all such cases. Even when tumor and chest wall appeared to form a mass on the RD MR image (Fig. 2c: case 3), the carcinoma sometimes did not invade the chest wall.

In this study, 31 of 100 patients underwent combined resection of the lung and surrounding structures, including resection of the parietal pleura in 9 and the chest wall in 16, and other organs in 6, including vessels, diaphragm, and vertebral bodies.

Induction therapy was performed in 20 stage IIIA cases. Among these, there were 7 SST cases in which concurrent chemoradiotherapy was performed. Pathologically evaluated therapeutic effect (Ef) after induction therapy is shown in Table 2.

Table 2
Effectiveness of chemotherapy.

	After chemotherapy	After concurrent chemoradiotherapy
Ef 0	23.00%	0%
Ef 1a	7.7%	14.3%
Ef 1b	30.80%	14.30%
Ef 2	30.80%	57.10%
Ef 3	7.70%	14.30%

Table 3
The results of specificity, sensitivity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) by conventional static CT and RD MR on the basis of pathological findings.

	Comparison between CT and pathological diagnosis	Comparison between RD MR and pathological diagnosis
Specificity	43.90%	68.50%
Sensitivity	60.0%	100%
Accuracy	47.10%	77.00%
PPV	20.70%	54.00%
NPV	81.80%	100%

The diagnoses based on RD MR and pathologic findings of the surgical specimen are compared in Table 3. For cases of chest wall invasion, the sensitivity and negative predictive value of RD MR were both 100%.

The results shown in Fig. 3 were obtained by the results from the characteristics (histopathology, localization, pathological T-factor, the maximal tumor dimension) of each resected lung specimen according to the results of RD MR.

The factors most related to accurate evaluation on RD MR were appropriate tumor size and suitable location to evaluate tumor movement.

4. Discussion

We set out to determine whether RD MR is a reliable and effective method for detecting the presence of chest wall invasion in cases of peripheral type non-small cell lung cancer. This information is extremely important since it can determine the necessity and type of preoperative treatment and the operative strategy, and, if accurate, can obviate the need for intraoperative change in surgical strategy. We believe that this important information is imperative to decide on the indications of induction chemoradiotherapy when we suspect SST. Rusch et al. [10] reported that in cases of SST, it is essential for cases with invasion to the chest wall to receive induction chemoradiotherapy to extend survival. Therefore one of the purposes of the present study was to determine whether invasion to the chest wall by SST could be accurately determined by RD MR, which is generally considered more accurate than static MR for this purpose [11].

We found that sufficient size and location of the tumor were important factors in deciding on whether the tumor invades surrounding tissue (chest wall, mediastinal pleura, diaphragm, vertebral body) or not. Invasion to surrounding structures can generally be determined in solitary tumors around 5 cm in maximum dimension. Perhaps, the accuracy is lower for tumors larger than 10 cm, because the weight of large tumors limits their mobility even if they are not invading the chest wall. Tumor invasion to the chest wall in the apical area (particularly on the left side) is hard to judge, even by RD MR, because the anatomical architecture tends to limit tumor movement.

Since tumors near the diaphragm are easily affected by respiratory movement, it is relatively simple to evaluate invasion to surrounding structures.

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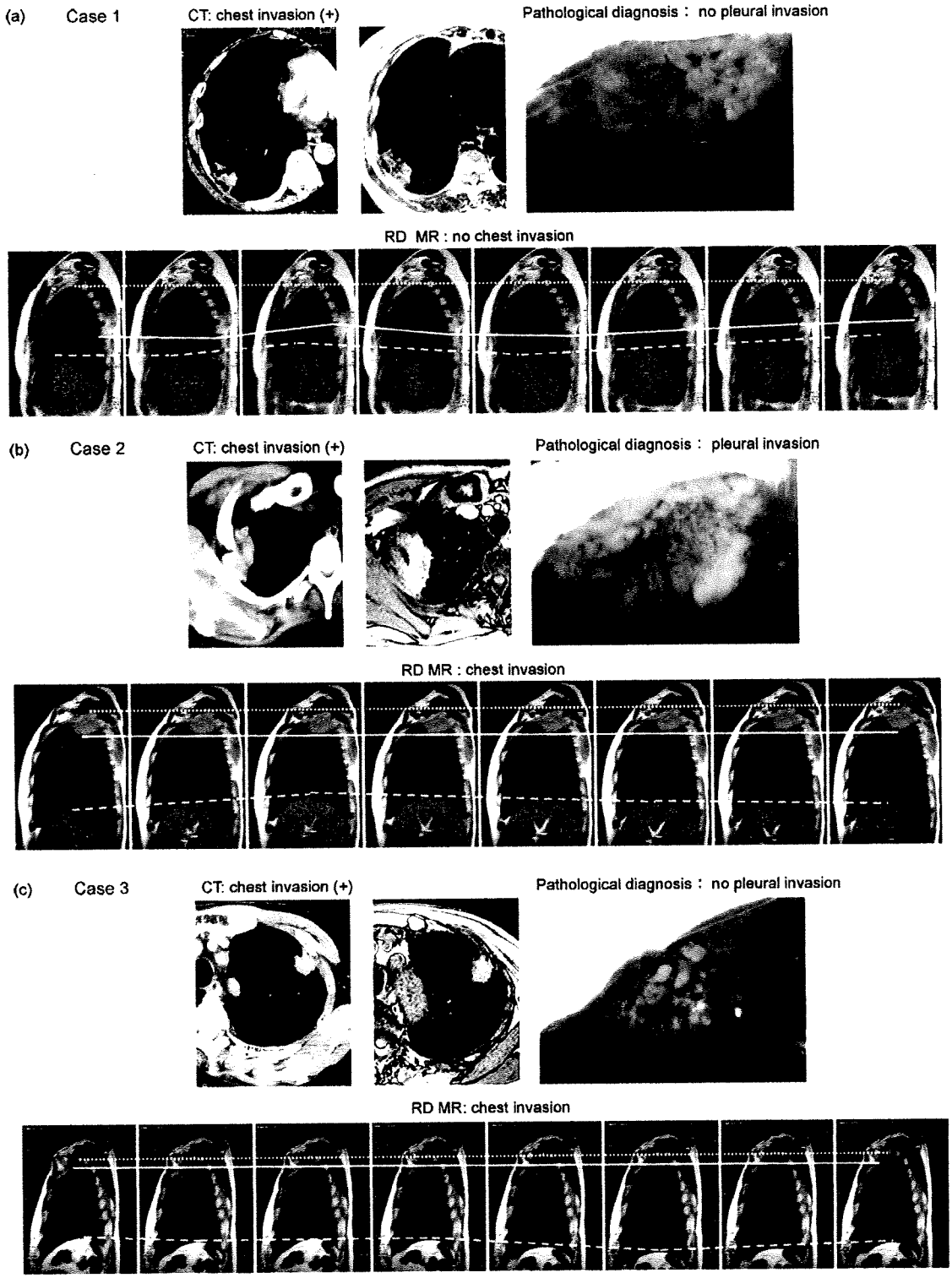

Fig. 2. Comparison between CT and MRI and pathological findings. (a) Case 1: A 79-year-old woman with adenocarcinoma in the right lower lobe. On RD MR, the tumor moves along the chest wall in synchrony with respiration. Chest wall invasion was ruled out and no invasion into the parietal pleura or chest wall was confirmed during operation, and after operation the pathological stage was pT1N0M0 stage IA. In the sectioned surface, the border is indistinct with white and an elliptic form. (b) Case 2: A 40-year-old woman with large cell carcinoma in the right upper lobe. On RD MR, lack of tumor movement along the chest wall during respiration was considered to indicate invasion by the surgeons. The adjacent parietal pleura and chest wall are resected in continuity with the primary lesion. The pathological stage was pT3N0M0 stage IIB. In the sectioned surface, tumor invasion to the chest wall was found histologically (p3). (c) Case 3: A 73-year-old man with adenocarcinoma in the left upper lobe immediately below the pleura. On RD MR, no tumor movement along the chest wall was recognized during respiration. Pathologically, no tumor invasion to the parietal pleura or chest wall was found, but the tumor showed non-malignant adhesion with the parietal pleura. The pathological stage was pT1N0M0 stage IA. In the sectioned surface, the border is indistinct, the tumor appears white and elliptic, and it is accompanied with a cavity. The pleura adhered to the tumor, but no pleural invasion of the tumor was found histologically (p0).

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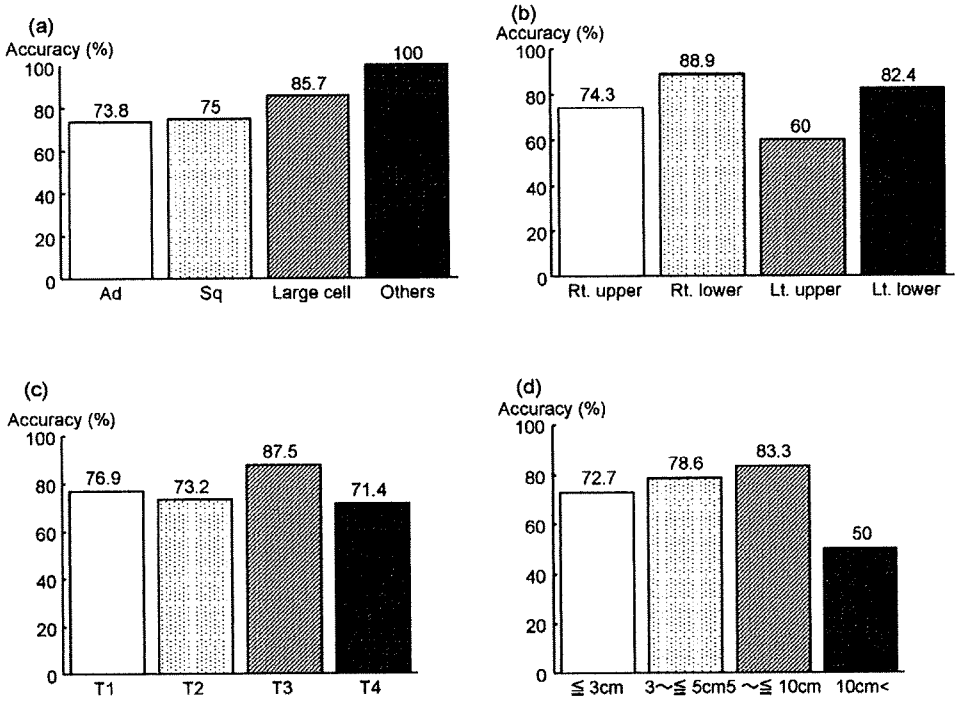

Fig. 3. (a) Accuracy of RD MR in relation to histopathology. (b) Accuracy in relation to tumor's site. (c) Accuracy in relation to T-factor. (d) Accuracy in relation to maximum tumor dimension.

Many studies using conventional CT scan or static MRI have been performed but limitations concerning their ability to detect chest wall invasion have been reported [7,15–18]. The report of Glazer et al. [1], which proposed the effectiveness of the combination of 2 or 3 CT criteria, suggested a method that, although quite sensitive, is not very specific.

Therefore in Table 3, we compared the results of pathological diagnosis and CT examinations by the criteria of Glazer and the results of RD MR. Our prospective study, based on confirmation by examination of resected specimens, showed that RD MR had better results than conventional static CT, using the evaluation method of Glazer, in terms of specificity, sensitivity and accuracy.

Shiotani et al. [19] reported that the detection of the presence or absence of minute amounts of pleural fluid between the lung cancer tumor and chest wall is a key criterion for the determination of chest wall invasion, but this method requires an extremely high level of radiological technique and expertise available only in few institutions. Other methods have been suggested, such as multi-section expiratory dynamic computer tomography (ED CT), using ultrafast CT, and this method, when used for the assessment of tumor movement along the chest wall in cine mode yielded an accuracy of 100%, but that report only described 15 cases [20]. The fact that ultrafast CT is available at only a limited number of institutions, plus the high amount of exposure to radiation, are both drawbacks for this method [20].

Dynamic evaluation using ultrasound (US) has also been reported to have a sensitivity and specificity of 100% and 98% [21]. However dynamic evaluation with US has a limited observation range, and the accuracy of the evaluation depends greatly on the skill and experience of the examiner.

Pneumothorax CT was reported to be useful in assessing chest wall invasion of lung cancer in 43 patients with an accuracy rate of 100% for chest wall invasion and 76% for mediastinal invasion [22]. However, this procedure had the drawback of significant complications (pneumothorax) in 4 patients (9%), one of whom (2%) suffered subcutaneous emphysema. In addition, failure to induce artificial pneumothorax was reported in 3 of those cases [22].

RD MR, although a noninvasive and simple technique, which can be performed in addition to the routine MR examination, is not always totally accurate in distinguishing invasion and non-malignant adhesion to the chest by the tumor. However, this limitation is also present in breathing dynamic ultrafast MRI, ED CT, US and pneumothorax CT, and therefore this problem is common to all these procedures [19–22]. In SST, the accuracy of RD MR was 87.5%.

One limitation of this study was the inability in cases of induction chemotherapy to accurately determine to conversion to non-malignant adhesion of malignant tumor invasion.

The following two useful methods can help to distinguish non-malignant adhesion from the invasion of malignant tumor preoperatively after induction chemotherapy. First is the method of imaging using multi-detector CT (MD-CT) in combination with 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET), which allows evaluation of accumulation of FDG with a quantitative standard uptake value (SUV). The combination of the FDG-PET image which images the function and the MD-CT image which images the form provides understanding of each peculiar feature of the findings of each imaging method and interpretation precision improves [23,24].

The second is CT-guided needle biopsy of the area of adhesion. This confirmation method is generally accurate, but there is the possibility of complications [25–27]. If the site is found to consist only of non-malignant adhesion by either of the above methods, induction therapy can be implemented, followed by operation.

One other limitation of RD MR is that MRI is generally contraindicated in patients who have ferromagnetic materials in certain locations (e.g. cerebral aneurysm clips, intraorbital metallic foreign bodies, and pacemakers).

However, it is clear that RD MR is a simple noninvasive examination that can demonstrate restriction of tumor movement along the chest wall during deep breathing. This method improves the

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precision of diagnosis of chest wall invasion in cases of peripheral type lung cancer abutting on the pleura, in comparison with conventional CT or static MR.

Conflict of interest

The authors declare no conflict of interest.

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Individualized Adjuvant Chemotherapy for Surgically Resected Lung Cancer and the Roles of Biomarkers

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Review

Individualized Adjuvant Chemotherapy for Surgically Resected Lung Cancer and the Roles of Biomarkers

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Several prospective randomized trials for patients with completely resected stages II and IIIA nonsmall cell lung cancer have confirmed a survival benefit with cisplatin-based adjuvant chemotherapy. The Lung Adjuvant Cisplatin Evaluation, which is based on pooled analyses of five randomized trials, has demonstrated a 4.2% absolute survival benefit at 5 years. The stage is the benchmark standard used to decide the indication for adjuvant chemotherapy; however, it is important to identify and select the patients who would benefit from adjuvant chemotherapy and to choose the optimal regimen for each case. The translational research was performed using specimens obtained in the above adjuvant trials also to obtain information concerning biomarkers and subsets of patients who would benefit from adjuvant chemotherapy. The extent to which individualized treatment of lung cancer can be provided, especially adjuvant chemotherapy, is discussed in this manuscript. (Ann Thorac Cardiovasc Surg 2009; 15: 144–149)

Key words: lung cancer, adjuvant chemotherapy, individualized treatment, biomarker

Introduction

Surgery is considered to be the standard treatment for early-stage nonsmall cell lung cancer (NSCLC). However, distant metastasis occurred in nearly 60% of patients with stages I to IIIA NSCLC after complete resection. Micrometastasis of the tumor is generally regarded as the cause of recurrence; therefore systemic chemotherapy after surgery is a rational strategy to reduce the risk of recurrence and metastasis.

Recent large-scale randomized trials have confirmed a survival benefit of adjuvant cisplatin-based chemotherapy following complete surgical resection of NSCLC (Table 1). The Lung Adjuvant Cisplatin Evaluation (LACE) study was based on a pooled meta-analysis of individual patient data from 5 trials (Adjuvant Lung Project Italy [ALPI];[1] Adjuvant Navelbine International Trialist Association [ANITA];[2] Big Lung Trial [BLT];[3] International Adjuvant Lung Cancer Trial [IALT];[4] and JBR.10[5]). The overall hazard ratio (HR) of death was 0.89 (95% confidence interval [CI]; 0.82–0.96; p <0.005), which corresponds to a 5-year survival benefit of 4.2% with chemotherapy.[6] The survival benefit varied with stage, and the results showed that the cisplatin-based adjuvant chemotherapy improved survival in patients with completely resected stage II and stage III NSCLC (Table 1). Japanese adjuvant trials showed that a survival benefit was obtained with adjuvant chemotherapy using uracil-tegafur (UFT) in stage I adenocarcinoma.[7] Meta-analysis revealed that the benefit was limited to those with a tumor size of 2 cm or more.[8] This suggests that the indications of adjuvant chemotherapy might extend from pathological stage I to stage III, which means that most operated NSCLC cases should be recommended to receive postoperative chemotherapy after surgery.

However, it is a sad scenario when many patients receive toxic agents with few benefits; therefore the

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Table 1. Results of representative adjuvant trials

	ALPI	IALT	JBR.10	ANITA01	BLT
Publication year	2003	2004	2005	2006	2004
Stage	I–IIIA	I–IIIA	IB, II	IB–IIIA	I–IIIA
No. of cases	1,209	1,867	482	840	381
Regimen	CDDP + VDS + MMC	CDDP + ETP CDDP + VLB/ VDS/VNR	CDDP + VNR	CDDP + VNR	CDDP + MMC + IFO/VLB CDDP + VDS/ VNR
HR (95% CI)	0.96 (0.81–1.13)	0.86 (0.76–0.98)	0.69 (0.52–0.91)	0.80 (0.66–0.96)	1.02 (0.77–1.35)
P value	0.589	<0.03	0.009	0.017	0.90
Survival benefit at 5 years (%)	3	4.1	15	8.6	–
TRD (%)	0.5	0.8	0.8	1.7	3.1

ALPI, Adjuvant Lung Project Italy; IALT, International Adjuvant Lung Cancer Trial; ANITA, Adjuvant Navelbine International Trialist Association; BLT, Big Lung Trial; HR, hazard ratio; 95% CI, 95% confidence interval; TRD, total radiation dose; CDDP, cisplatin; VDS, vindesin; MMC, mitomycin C; ETP, etoposide; VLB, vinblastine; VNR, vinorelbine; IFO, ifosfamide.

pursuit to identify patients who would really benefit from specific regimens is important. To classify them and to apply the optimal therapy to each subgroup would provide a breakthrough in lung cancer management. The ability to identify responder patients with particular drugs or regimens is a challenge that requires the application of translational research to clinical practice.[9,10] The strong relationship between epidermal growth factor receptor (EGFR) mutation and high response to gefitinib[11,12] is a typical example of the individualized treatment of lung cancer.

A resection of NSCLC usually yields large amounts of tissue for molecular analysis. Rapid advances in technology have led to advanced assays to measure changes in deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and proteins, which help to identify potential molecular biomarkers of clinical outcome. Translational research performed using specimens obtained in some of the adjuvant trials mentioned above has provided some information about biomarkers and identification of the subsets of patients who would benefit from adjuvant chemotherapy. Many biomarkers have been evaluated in the context of the largest positive adjuvant NSCLC trials, such as gene expression signatures, p53 expression, and K-*ras* mutations;[13] DNA-repaired genes;[14] and class III β-tubulin (βTubIII) expression status.[15] The individualized treatment for the determination of adjuvant chemotherapy is extensively discussed in this manuscript.

Excision Repair Cross-Complementation Group 1[14]

The excision repair cross-complementation group 1 (ERCC1) enzyme plays a role in the nucleotide excision repair pathway that recognizes and removes cisplatin-induced DNA adducts.[16] IALT demonstrated a 5% survival benefit in overall 5-year survival among 1,867 NSCLC patients who received adjuvant cisplatin-based chemotherapy after curative surgery.[4]

ERCC1 expression was evaluated by immunohistochemistry in a total of 761 consecutive tumor samples from IALT. It was found to be positive in 335 (44%) and negative in 426 (56%). Cisplatin-based adjuvant chemotherapy significantly prolonged the survival in ERCC1 negative cases (HR: 0.65; 95% CI: 0.50–0.86), but not in ERCC1 positive cases (HR: 1.14; 95% CI: 0.84–1.55). Among patients who received no adjuvant chemotherapy, those with ERCC1 – positive tumors survived longer than those with ERCC1 – negative tumors (HR: 0.66; 95% CI: 0.49–0.90). The result showed that completely resected ERCC1 – negative NSCLC cases could benefit from cisplatin-based adjuvant chemotherapy (Table 2). The evaluation of ERCC1 expression in NSCLC before chemotherapy predicts the effect of cisplatin-based adjuvant chemotherapy, and this is therefore our promising biomarker for individualized treatment.

Table 2. Results of IALT and ERCC1

Group	All patients	Chemotherapy group	Control group	Hazard ratio for death (95% CI)	P value
Patients with ERCC1 – negative tumors				0.65 (0.50–0.86)	0.002
Deaths – no./total no. of patients	218/426	105/224	113/202		
Rate of survival at 5 yr – % (95% CI)	44 (38–49)	47 (40–55)	39 (32–47)		
Median survival – months	48	56	42		
Patients with ERCC1 – positive tumors				1.14 (0.84–1.55)	0.40
Deaths – no./total no. of patients	172/335	92/165	80/170		
Rate of survival at 5 yr – % (95% CI)	43 (37–49)	40 (32–49)	46 (37–55)		
Median survival – months	52	50	55		

ERCC1, excision repair cross-complementation group 1; 95% CI, 95% confidence interval; yr, year.

Table 3. Results of JBR.10 and β-tubulin III expression

	RFS	OS
Low expression (132 cases)		
Observation (60)	1	1
Chemotherapy (72)	0.78 95% CI: 0.44–1.37 (p = 0.4)	1.00 95% CI: 0.57–1.75 (p = 0.99)
High expression (133 cases)		
Observation (65)	1	1
Chemotherapy (68)	0.45 95% CI: 0.27–0.75 (p = 0.002)	0.64 95% CI: 0.39–1.04 (p = 0.007)

RFS, relapse-free survival; OS, overall survival; 95% CI, 95% confidence interval.

Class III β-Tubulin[15]

Tubulins constitute a family of globular proteins that make up microtubules in cells; they are vital for cell structure, movement, mitosis, and metabolism (vesicular transport). High expression βTubIII in advanced NSCLC is known to correlate with both reduced response rates and inferior survival following treatment with antimicrotubule agents.

Winton et al. published the results of a randomized trial of adjuvant vinorelbine and cisplatin compared with observation in completely resected stage IB and stage II NSCLC (National Cancer Institute of Canada Clinical Trials Group [NCIC] JBR.10).[5] A total of 482 patients were randomly assigned to either an adjuvant group (cisplatin/vinorelbine) or an observation group. The adjuvant group had a statistically significant longer survival than the observation group (69% vs. 54% at 5 years; p = 0.002).[5] Tumor tissues of resected specimens were collected from 265 out of 482 patients. Immunohistochemical staining was performed to evaluate the expression of βTubIII. High βTubIII expression is a sign of poor relapse-free survival (RFS) (HR: 1.52; 95% CI: 1.05–2.22; p = 0.03), and a similar trend was observed in overall survival (OS) (HR: 1.39; 95% CI: 0.96–2.01; p = 0.08). However, the high βTubIII expression group (n = 133) cases in the adjuvant group had more significantly favorable RFS (HR: 0.45; 95% CI: 0.27–0.75; p = 0.002) than in the observation group, and similar results were observed in OS (HR: 0.64; 95% CI: 0.39–1.04; p = 0.007). These results showed that adjuvant chemotherapy might prolong the RFS and OS in the high-tubulin expression patients, but the effect was unclear for the low-tubulin expression cases (Table 3).

KRAS and p53[13]

Protein expression of p53 and gene mutation of p53 and RAS were retrospectively evaluated using NSCLC samples obtained in the NCIC JBR.10 study. A total of 132 out of 253 cases showed p53 protein overexpression. And

Table 4. Results of JBR.10 and p53, RAS expression

Marker	No. of patients	Overall survival			
		Median	Hazard ratio	95% CI	P
p53 wild type					
Observation	136	6.2	1		0.04
Chemotherapy	137	7.8	0.67	0.46 to 0.98	
p53 mutant					
Observation	64	5.4	1		0.35
Chemotherapy	60	NR	0.78	0.46 to 1.32	
RAS wild type					
Observation	169	6.2	1		0.03
Chemotherapy	164	NR	0.69	0.49 to 0.97	
RAS mutant					
Observation	42	6.5	1		0.70
Chemotherapy	46	6.2	0.91	0.47 to 1.78	

95% CI, 95% confidence interval; NR, not reported.

though patients with p53-positive tumors had an overall significantly shorter survival than those with p53-negative tumors (HR: 1.89; 95% CI: 1.07–3.34; p = 0.03), p53-positive tumors did show significant benefits from adjuvant chemotherapy (HR: 0.54; 95% CI: 0.32–0.92; p = 0.02). Patients with p53-negative tumors, however, had no survival benefit from adjuvant chemotherapy (HR: 1.40; 95% CI: 0.78–2.52; p = 0.26).

In 333 patients with wild-type RAS, survival was significantly prolonged by adjuvant chemotherapy, compared with observation-only cases (HR: 0.69; 95% CI: 0.49–0.97; p = 0.03). But no survival benefit for adjuvant chemotherapy was recognized in patients with RAS mutant tumor (HR: 0.91; 95% CI: 0.47–1.78; p = 0.70) (Table 4).

Comments

Evidence-based medicine has been increasingly emphasized in medical practice in recent years, and standardized treatment methods have been developed mainly by multicenter randomized control trials. However, since the biological nature of tumors varies with each patient and their physical constitution, individualized treatment that takes both of these aspects into consideration could provide ideal optimal care for each cancer patient. Scientists have made enormous efforts to discover powerful biomarkers to help evaluate the biological behavior of cancer, and this strategy should be beneficial in selecting the most suitable therapy for each patient. Several biomarkers were evaluated using samples obtained in large adjuvant chemotherapy trials of lung cancer (Table 5), and some hold promise. The increased interest in identifying biomarkers with implications for personalized treatment is reflected in a recent decision by the Food and Drug Administration (FDA) to allow, under certain conditions, retrospective analyses of biomarkers from completed trials.[17] The relationship between the histological type of lung cancer and the sensitivity of pemetrexed has been reported in inoperable lung cancer cases.[18] Pemetrexed is currently approved in the United States in combination with cisplatin for the treatment of malignant mesothelioma and for second-line treatment of advanced NSCLC. A recent phase III trial compared cisplatin and gemcitabine with cisplatin and pemetrexed for the treatment of advanced NSCLC. This noninferiority phase III randomized study compared OS between two groups. The OS for cisplatin/pemetrexed was noninferior to cisplatin/gemcitabine. Statistically, OS was significantly superior for cisplatin/pemetrexed than cisplatin/gemcitabine was in adenocarcinoma patients and large cell carcinoma patients (12.6 vs 10.9 months, 10.4 vs 6.7 months, respectively).[18] Because pemetrexed is an antifolate that inhibits multiple enzymes involved in purine and pyrimidine synthesis, thymidylate synthase (TS) is its main target. Preclinical data indicate that overexpression of TS correlates with lower sensitivity to pemetrexed. The baseline expression of TS gene and TS protein was significantly higher in patients with squamous cell carcinoma than in those with adenocarcinoma. This might be

Table 5. Drug sensitivity, prognosis, and biomarkers

Biomarker		ERCC1		RRM1		BRCA1		Class III β-tubulin		KRAS	
Expression		High	Low	High	Low	High	Low	High	Low	Wild	Mutant
Prognosis		Good		Good		Poor		Poor			
Sensitivity	CDDP		○				○				○
	Taxane					○		○			○
	VNR							○			○
	GEM				○						○

ERCC1, excision repair cross-complementation group 1; RRM1, ribonucleotide reductase subunit M1; BRCA1, breast cancer 1, early onset; CDDP, cisplatin; VNR, vinorelbine; GEM, gemcitabine.

part of the explanation for the higher response of adenocarcinoma to pemetrexed. Further analysis of the relationship between the chemotherapy regimen and TS will be performed in a prospective manner; patients with stage II and stage III completely resected NSCLC are being treated with standard adjuvant chemotherapy or an individualized regimen determined by TS and ERCC1 expression (International Tailored Chemotherapy Adjuvant [ITACA] trial).[19]

Here is another approach to determine a suitable biomarker using proteomics. Maeda et al. performed a comprehensive protein analysis using surgically resected specimens of stage I adenocarcinoma by liquid chromatography tandem mass spectrometry, followed by bioinformatical investigations to identify protein molecules.[16] Two kinds of molecules (myosin IIA and vimentin) were identified as being related to prognosis and also to the responsiveness to adjuvant chemotherapy. Patients lacking expression of both myosin IIA and vimentin showed a significantly better outcome, regardless of postoperative adjuvant chemotherapy using UFT.

The nonrelapse survival of these patients at 5 years was 100%, which is better than that of patients positive for both myosin IIA and vimentin. Also, cases lacking expressions of both the two proteins had a good prognosis, irrespective of whether the patients had undergone adjuvant chemotherapy. In cases showing a positive expression of both myosin IIA and vimentin, the 5-year survival benefit was approximately 19% by adjuvant chemotherapy using UFT. Therefore these two proteins appear to be potentially useful biomarkers for the selection of adjuvant chemotherapy.[16]

The current retrospective data are by no means sufficient to support the routine use of molecular markers to guide adjuvant therapy for NSCLC outside of a clinical trial.

Before a molecular test can be adopted for routine practice, valid and standardized laboratory techniques must be established. The establishment of the feasibility of molecularly tailored adjuvant therapy for patients with resected NSCLC requires a prospective phase II trial. It is also important not only to select a suitable regimen, but also to develop innovative treatments, such as gene and molecular-targeted therapy.

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医療機器開発推進研究事業

（活動領域拡張医療機器開発研究事業）

高度医療技術の効率化及び標準化の開発に関する研究

平成２１年度　総括・分担研究報告書

研究代表者　廣橋　説雄

平成２２（２０１０）年３月３１日

２／２冊

原　著

市立堺病院放射線治療部門での2008年の医学物理業務

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キーワード
放射線治療，医学物理，品質保証，精度，治療計画

要　旨

目的：2008年4月1日より行ってきた市立堺病院の医学物理業務内容と放射線治療の精度に関与した重要な結果について報告する。

方法：はじめに，これまでに行われてきた治療装置(リニアック)および治療計画装置の品質保証(QA)記録を調査したうえで，新たにQAプログラムを作成した。それに基づき，治療装置の線量および幾何学的精度を継続的に検証した。治療計画装置のQAとしては，2種類の線量計算アルゴリズムの計算精度をファントムを用いて電離箱線量計またはフィルムによって実測し，徹底的に検証した。また，医学物理的観点から，全症例の治療計画チェックを行った。さらに，一部の症例の治療計画立案を行った。

結果：過去のQA記録から，QAの実施状況は米国医学物理学会(AAPM)や日本放射線腫瘍学会，日本医学物理学会のQAガイドラインと比較すると不十分であった。リニアックおよび治療計画装置に対するQAプロトコールを立案し，放射線治療担当技師とともに定期的に実施した。リニアックの線量および幾何学精度はほぼAAPMの提唱する許容範囲内であった。しかし，ビーム平坦度・対称性やコリメータ表示，レティクル取り付け精度は許容値を超えていた。それらについて院内または業者により調整を行い，線量および幾何学的精度を向上させた。治療計画装置のQAでは市立堺病院で2008年10月まで線量計算に使用していたClarkson法と実測値の間に最大10%の誤差があることが判明した。一方，Convolution法で計算することで，精度が最大10%程度改善した。そのため，Convolution法を臨床へ導入した。治療計画のチェックでは20症例の線量分布の改善方法を提案し，放射線腫瘍医との議論のうえ，再計画または計画修正を行った。また，約20症例のCTを用いた治療計画を行い，典型的な照射野よりも良好な線量分布(腫瘍の線量均一性，リスク臓器の線量低減)を達成した。

結論：市立堺病院の医学物理業務により，治療装置と線量計算精度および，計画手法が改善され，放射線治療の質が向上した。

Ⅰ．はじめに

放射線治療ビームは強力であり，その場所と量の精度は常に保証されなければならない。しかも放射線は目に見えないので，保証するためには測定や計算が必要となり，時間と専門知識が必要となる。米国ではその役割を果たす「医学物理士」が約5,000名，病院で勤務している。彼らの臨床業務内容は放射線治療装置や治療計画装置などの品質保証(Quality Assurance：QA)だけでなく，治療計画立案とチェック，放射線腫瘍医の物理的コンサルテーション，教育，新しい治療法の研究・開発をも行い，物理面で責任を持つ立場にある[1)]

一方，わが国では病院で医学物理士業務を専ら行っている者は希少である。また，その必要性が認識されたのも最近のことである。そのきっかけは，ここ約10年間に多発した放射線治療事故[2)-5)]であった。それら

の多くは治療計画装置に関するものであり，初期導入時のパラメータの誤入力や誤使用などが主な原因であった。これらは品質管理を適切に行えば防止できていた[2)3)5)]。また，治療(計画)装置は複雑化し，相当の物理工学的知識も要求されるようになってきた。

2008年4月1日より市立堺病院の非常勤医学物理士として，装置の品質保証と治療計画立案，またはチェックなどの医学物理業務を行ってきた。本稿では2008年4月から12月までに行ってきた医学物理業務を紹介し，それによって得られた重要な結果の一部を報告する。

Ⅱ．方　法

2．1．放射線治療装置(リニアック)の品質保証

はじめに2008年3月までに行われていたリニアックのQA項目を調査した。また，米国医学物理学会(AAPM)[1)6)~8)]やヨーロッパ放射線腫瘍学会(ESTRO)[8)]，日本放射線腫瘍学会(JASTRO)[10)]，日本医学物理学会のガイドライン[11)]に基づき網羅的にQAを実施した。さらに市立堺病院のシステムで必要なQA項目の洗い出しおよびQA項目を決定しプロトコールを作成した。表1に市立堺病院のQA項目を頻度別に示す。それに基づき定期的にQAを放射線技師とともに行い，問題があれば，それに対する対応を行った。

2．2．放射線治療装置(XiO)の品質保証

治療計画装置の線量分布は自施設での測定データを登録することで得られる。過去にその時点での誤登録による事故が頻発していることから[2)~4)]，はじめにその登録データの妥当性を確認した。また，4MV X線でClarkson法と呼ばれる線量計算アルゴリズムを使用した場合に，実測値と10%を超える誤差があることが判明した。これを契機に，詳細に，かつ実臨床に即して複数のアルゴリズムの線量計算精度を表2の条件

表1　市立堺病院の月QAプログラム(2008年12月版)

1ヶ月
X線モニタ線量計の校正
X線線量プロファイル対称性，平坦度
X線の線質(TPR20，10)
X線照射野，光照射野および数値との一致
Jawの対称性
照射野の表示
レーザーアラインメント
ガントリ角度表示
ガントリ回転中心精度
コリメータ角度表示
コリメータ回転中心精度
カウチ位置の表示
距離計の表示(実寸との比較)
クロスヘアの中心
トレイ&レティクルの取り付けとあそび
ウェッジの取り付け
電子線線量プロファイル対称性，平坦度
電子線モニタ線量計校正
【インターロック】
カウチの緊急停止ボタンの作動
壁の緊急停止ボタンの作動
計画と異なったウェッジを挿入した場合のインターロック
計画と異なった電子線アプリケータを挿入した場合のインターロック

3ヶ月
MLC位置精度
MLC位置精度再現性
1年以内に一度
X線線量モニタシステム再現性
X線線量モニタシステム直線性
電子線線量モニタシステム再現性
電子線線量モニタシステム直線性
X線線量モニタシステム架台角度依存性
電子線線量モニタシステム架台角度依存性
X線線量モニタシステム運動照射中の安定性
X線線量モニタシステム運動照射の終了位置
X線PDD(3次元水ファントム)
電子線PDD(3次元水ファントム)
X線OCR(3次元水ファントム)
電子線OCR(3次元水ファントム)
X線出力係数
ウェッジ係数
コリメータ回転の平行性，直角性
アイソセンタからのビーム軸の変位
カウチ回転中心精度
カウチのしなり
テーブルの垂直方向への動き
ハーフビームマッチングライン線量変化

*略語：TPR：Tissue Phantom Ratio，MLC：Multileaf collimator，PDD：Percent Depth Dose，OCR：Off Center Ratio

で検証した(表2)。

(1)絶対線量検証

水ファントムを用い，電離箱線量計により測定し，XiOの計算値と比較した。

表2　検証内容

Open正方形照射野(深さ：dmax，5cm，10cm，20cm)
ウェッジ正方形照射野(深さ：dmax，5cm，10cm，20cm)
Open矩形照射野(深さ：dmax，5cm，10cm，20cm)
ウェッジ矩形照射野(深さ：dmax，5cm，10cm，20cm)
非対称照射野(深さ：10cm)
側方散乱体欠損照射野(深さ：20cm)

(2)側方散乱体欠損照射野の線量検証

乳房接線照射を想定し，水等価固体ファントムで電離箱線量計により実測し，XiOの計算値と比較した(図1)。すなわち，アイソセンターを空気・ファントム境界からファントム内部へ移動して測定し，散乱線の増減による線量計算精度を検証した。

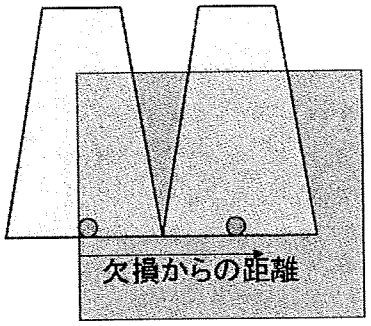

図1　側方散乱欠損照射野の線量検証ジオメトリ

(3)Open照射野およびウェッジ照射野の線量分布

固体ファントムを用い，Filmにより線量分布を測定し，XiOの計算値と比較した。

(4)実臨床例でのアルゴリズムによる比較

市立堺病院で乳房接線照射を行った11症例の22門を対象に，Clarkson法とConvolution法のMU値の変化を検討した。

2．3．治療計画の物理的チェック

2008年4月1日から12月26日に照射された全症例治療計画のチェックを行った。チェックは線量計算パラメータ，MU値の独立検証，照射野の妥当性について行った。さらに，線量分布が改善されると見込まれた症例，または典型的な照射野と大きく逸脱した症例に関しては医師と議論の上，計画修正または再計画を行った。

2．4．治療計画立案

一部の症例の治療計画立案の支援を行った。図2にCTを用いた治療計画の医学物理士の役割を示す。すなわち，医師は標的のContouring，医学物理士はリスク臓器のContouringと最適なビームセットアップおよび線量評価を行った。腫瘍の線量カバーは最大限に，リスク臓器は最小限の線量が投与されるように複数の候補計画を立案した。最終的には担当医と直接，またはメールで議論し，承認を得た計画で治療が行われた。

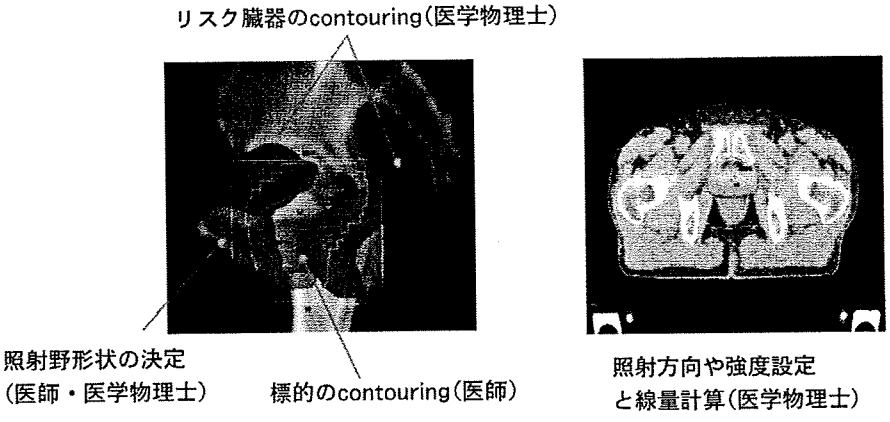

図2　治療計画に対する医学物理士の役割

表3　直近のリニアックの精度

試　験　項　目	直　近 点 検 日	結果(精度) (worstdata)	AAPM or JASTRO 許容値	備　　考
1．ビーム特性				
出力	2008/11/18	0.30%	2％	
出力直線性	2008/10/21	0.80%	2％	
出力再現性	2008/10/21	0.10%	2％	
＊X線対称性(10×10)	2008/11/27	3.5%	3％	2008/9/5業者調整後
＊X線平坦度(10×10)	2008/11/27	4.7%	3％	2008/9/5業者調整後
＊電子線対称性(10×10)	2008/11/27	4.2%	3％	12MeVInlineは要調整
ウェッジ係数変動	2008/6/3	0.90%	2％	
出力係数変動	2008/5/29	0.80%	2％	
エネルギー安定性(TPR20，10)	2008/11/18	0.99%	2％	
2．幾何学特性				
照射野デジタル表示	2008/12/2	＜1㎜	2㎜	
カウチ移動距離表示	2008/9/25	＜1㎜	2㎜	
光学系表示精度	2008/9/25	2㎜	2㎜	
＊コリメータ角度の表示	2008/12/9	1度以内	2度	12/18日　業者調整
＊ガントリ角度の表示	2008/9/25	0.6度	2度	
＊光照射野と放射線照射野の一致	2008/12/2	2.2㎜	2㎜	
Jawの対称性	2008/12/2	1.4㎜	2㎜	
MLC位置精度	2008/11/4	1㎜以内	1㎜(IMRT)	
MLC位置の再現性	2008/11/4	1㎜以内	1㎜(IMRT)	
ガントリ回転中心精度	2008/9/25	0.8㎜	2㎜	
コリメータ回転中心精度	2008/12/2	0.9㎜	2㎜	
カウチ回転精度	2008/12/2	約0.5㎜	2㎜	
＊トレイ＆レティクルの遊び	2008/11/11	1㎜	2㎜	市立堺病院調整後データ
ウェッジの遊び	2008/11/11	なし	2%	
電子線アプリケータ取り付け	2008/11/11	異常なし	異常なし	
緊急停止ボタン	2008/11/11	異常なし	異常なし	
ウェッジインターロック	2008/11/11	異常なし	異常なし	
アイソセンターからのビーム軸の変位	2008/4/15	＜2㎜	2㎜	

略語：TPR：Tissue Phantom Ratio，MLC：Multileaf collimator，IMRT：Intensity Modulated Radiotherapy

3．結果と考察

ここでは特に重要な結果を抜粋して述べる。

3．1．リニアックの品質保証

表3に直近のリニアックの精度を示す。ビーム特性，幾何学精度ともに，ほとんどがAAPMまたはJASTROガイドラインの定める許容範囲内であった。第1欄の＊は不具合または精度不良により調整を行った項目である。以下に詳細を述べる。

3．1．1．X線の平坦度と対称性

X線ビームには照射野の中心付近は平坦かつ対称であり，辺縁では対称に線量が減少する特性がある(図3)。この平坦度と対称性は治療精度に大きく影響するので，月間QAとして行ってきた。平坦度F(%)は