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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.

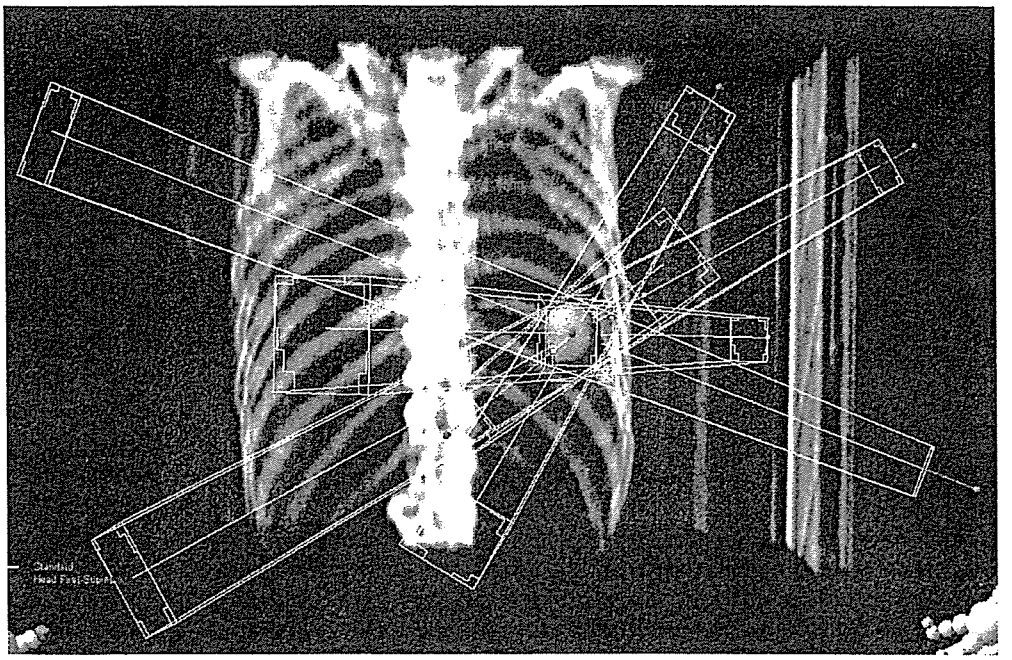

Fig. 1. Stereotactic body radiotherapy (SBRT) for lung cancer. In this image for treatment planning for left lung cancer, five beams are focused on the target

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

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

used, where i and j are indices of the categories being used, and I 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.

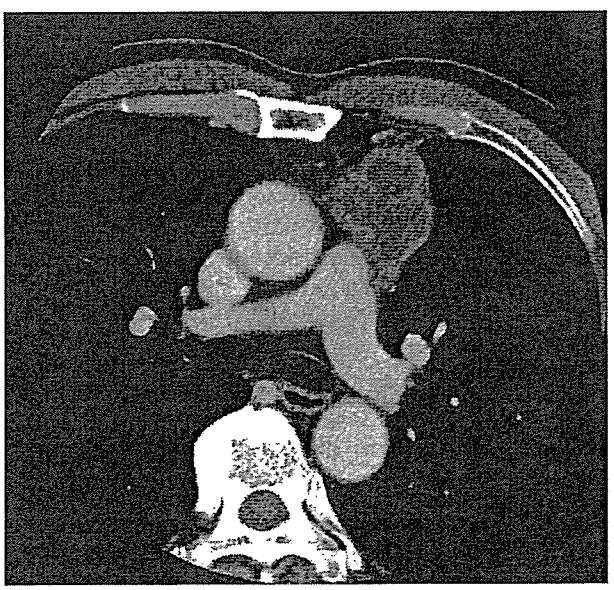

Figure 1 CT images from a patient with a false-negative diagnosis of thymic epithelial tumour by CT-guided PCNB. Enhanced transaxial CT image showing a heterogeneous attenuation with a peripheral irregularly enhancing wall in the left anterior mediastinum. Histological examination revealed thymoma B1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

Although the success rate of open surgical biopsy for establishing the diagnosis of a thymic epithelial tumour is approximately 90%, it requires general anaesthesia and is associated with a higher morbidity and cost than CT-guided PCNB. No cases of seeding of the percutaneous needle tract or PCNB site have ever been reported. Moreover, there may be no overall survival benefit of incomplete resection over biopsy, when complete resection cannot be achieved.[25,27]

The results of the present study suggested that 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.

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56 支持療法

1 化学療法薬物有害反応の対策

1．血管外漏出

多くの抗がん剤は，血管外漏出を起こすと周囲組織に障害を引き起こすため，予防と対策が必要である．抗がん剤と血管外漏出に伴う皮膚軟部組織の反応性の分類を示す．vesicant drugは，DNAと結合するしないに関わらず周囲組織の壊死，潰瘍を形成する薬剤であり，irritant drugは局所炎症にとどまる薬剤である．血管外漏出時の対処方法は，①抗がん剤投与を中止し，漏出残存している薬液を吸引除去，②薬剤の種類に応じて局所冷却（アントラサイクリン，タキサン系）または保温（ビンカアルカロイド）を開始，③解毒剤（DMSO，hyaluronidaseなど）の投与，④経過観察し形成外科処置が必要かの判断，である．本邦ではこれら解毒剤使用が困難であり，一般的に，ステロイドと局所麻酔薬を漏出部周囲に皮下注射する方法がとられているが，確立した方法ではない．抗がん剤希釈濃度によっても周囲軟部組織の障害程度は異なり，漏出予防が大切であり，①適切な静脈の選択（脆弱，硬化，細い血管を避ける），②適切な位置の選択（放射線治療部，上大静脈症候群，リンパ浮腫，血管炎部位を避ける．位置は固定しやすい前腕が最適である），③点滴技術と管理の向上（点滴針が血管内に留置されたかの確認，抗がん剤投与中の定期的観察，患者教育），を徹底すべきである．

2．悪心，嘔吐

悪心嘔吐は，がん化学療法の有害反応のなかでも患者にとって最も苦痛であり，適切にコントロールするべき症状である．悪心嘔吐は発現時期から3つに分類できる．急性の悪心嘔吐は抗がん剤投与後24時間以内に出現し，セロトニン受容体拮抗薬に感受性が高い時期といわれている．遅延性の悪心嘔吐は抗がん剤投与後24時間以降に出現し，予測性悪心嘔吐は，抗がん剤投与前から出現し，過去の化学療法時に経験した悪心嘔吐に対する心因性反応である．予測性悪心嘔吐を予防するためにも，初回治療から急性，遅延性悪心嘔吐を確実に予防することが大切である．抗がん剤の催吐頻度による分類を表1に示した．

嘔吐は延髄の嘔吐中枢が刺激されることで引き起こされる．嘔吐中枢の刺激経路としては，①化学受容体引き金帯（chemoreceptor trigger zone：CTZ）を介するもの，②消化管-自律神経を介するもの，③大脳皮質を介するもの，に分類できる．2006年NCCN（National Comprehensive Cancer Network）の制吐剤使用ガイドラインを示す．海外ではニューロキニン1受容体拮抗薬であるaprepitantが用いられ，嘔吐発現率30％以上の抗がん剤投与時の急性悪心嘔吐予防には，aprepitant，セロトニン受容体拮抗薬，dexamethasoneの併用，遅延性に対してはaprepitantとdexamethasone，その他の制吐剤の単独投与が推奨されている．また，嘔吐発現率10～30％の抗がん剤

表1 催吐性を有する抗悪性腫瘍薬　　単位 mg/m²

危険群	高 (high)	中 (moderate)	低 (low)	最小 (minimal)
嘔吐発現率	>90%	90～30%	30～10%	<10%
抗悪性腫瘍薬	cisplatin ≧ 50 dacarbazine cyclophosphamide >1,500 procarbazine	cisplatin < 50 busulfan>4mg/b carboplatin cyclophosphamide ≦1,500, 内服 cytarabine > 1,000 doxorubicin procarbazine (内服) daunorubicin doxorubicin epirubicin etoposide (経口) idarubicin ifosfamide imatinib (内服) irinotecan methotrexate 250～1,000 melphalan>50 oxaliplatin >75	capecitabine cytarabine 100～200 docetaxel etoposide 5-FU gemcitabine methotrexate 50～250 mitomycin mitoxantrone paclitaxel trastuzumab	bleomycin busulfan cladribine fludarabine methotrexate ≦50 vinblastine vincristine hydroxyurea vinorelbine melphalan imatinib gefitinib rituximab

(www.nccn.org 一部改変)

投与では，急性悪心嘔吐予防として metoclopramide，dexamethasone の単剤投与，遅延性に対しては，予防的投与は施行されない．本邦では aprepitant は認可されていないため，セロトニン受容体拮抗薬と dexamethasone の併用となる．予測性嘔吐に対しては，治療に対する悪いイメージを変えることが必要である．医師患者間の信頼関係を大切にし，不安や緊張に由来する身体症状を，抗不安薬や精神療法などで対処する．

3. 好中球減少症，感染症

がん化学療法時，好中球が減少し発熱することは多く経験される．適切な治療が施行されないと細菌性ショックに至ることもあるため，菌の同定を待たずに抗菌薬投与が必要になる．米国感染症学会では，発熱性好中球減少症 (febrile neutropenia：FN) に対し 1990 年ガイドラインを発表し，2002 年に改訂している．1998 年わが国でもガイドラインが発表された．本稿では 2003 年改訂された本邦のガイドライン[3] の概略を説明する．FN の定義は，好中球数が 1,000 未満で 500 未満になる可能性がある状況下で，1 回の腋窩検温≧37.5℃ (または 1 回の口腔内検温≧38℃) の発熱が生じ，薬剤熱，腫瘍熱，膠原病，アレルギーなど，原因がはっきり分かっているものを除外できる場合とする．発熱の時点で病歴，診察，血液検査，画像検査，培養など治療前評価を行うと同時に，患者が重症化する可能性を予測するため，スコアリングインデックスで判定する．臨床症状の経過が良好：無症状，症状が軽度 (5 点)，症状が中程度 (3 点)，低血圧がないこと (5 点)，慢性閉塞性肺疾患がないこと (4 点)，固形腫瘍や血液疾患で真菌感染既往なし (4 点)，脱水症状なし (3 点)，発熱時外来 (3 点)，年齢＜60 歳 (2 点)，であり，合計 21 点以上が低危険群，20 点以下は高危険群である．

図 1 に FN の初期治療を示す．高リスク群はカルバペネム系抗菌薬，第 4 世代セフェム系薬か，アミノグリコシドとの併用を行う．低リスク群は経口 ciprofloxacin または levofloxacin を投与する．3～5 日投与しても解熱が得られない場合は再評価し，単剤治療施行例ではアミノグリコシドの追加，アミノグリコシドを併用している例では β ラクタム薬の変更を考慮し，また，他のアミノグリコシドか ciprofloxacin 静注薬への変更を考慮する．48 時間経過しても改善が認められない場合は，抗真菌薬の追加，グラム陽性菌が培養されたときはグリコペプチド系抗菌薬を追加する．グリコペプチド系抗菌薬は，血液あるいは感染の可能性のある部位から MRSA が分離された場合に使用すべきで，初期治療としては行うべきではない．重症感染症時にはガンマグロブリン投与を考慮する．顆粒球コロニー刺激因子 (granulocyte colony

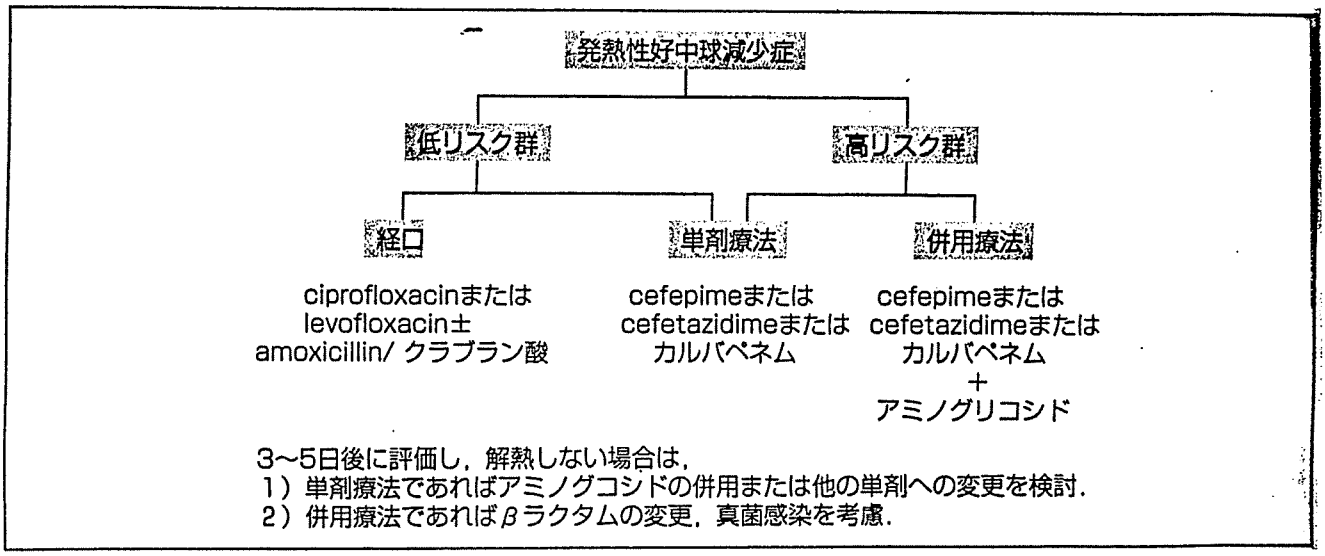

図1　発熱性好中球減少時の抗生剤使用ガイドライン（初期治療）

stimulating factor：G-CSF）使用については，本邦でのG-CSF適正使用ガイドライン[4]では，発熱があり，好中球減少をきたしている場合には，抗菌薬との併用の有効性が明確に証明されてはいないが，感染症の悪化の可能性の高い症例について使用が勧められている．ASCOのガイドライン[5]でも，20％以上のFNの可能性のある場合の予防投与，高危険群に相当する危険因子（10日を超える好中球減少の長期化と100/μl未満の重症化，原疾患のコントロール不能，肺炎，低血圧，多臓器不全，侵襲性の真菌感染症など）が存在する場合は，G-CSFの使用が考慮されている．これらガイドラインをもとに，個々の患者に配慮した治療を施行することが大切である．

4．貧血

がん患者における貧血の原因は，がん化学療法や放射線治療による骨髄抑制のほかに，がん進行による骨髄浸潤，出血，播種性血管内凝固症候群による溶血など，あるいは鉄利用障害，赤芽球系前駆細胞の抑制，エリスロポエチンの産生低下，エリスロポエチンの骨髄反応性の低下など，様々な原因が考えられる．近年，がん化学療法は投与量増加，併用療法が進み，より骨髄抑制の強い治療法へと変遷している．また，がん化学療法の臨床試験では貧血を伴いやすい高齢者，PSの悪い患者は対象にならないことが多く，軽度の貧血がQOLに及ぼす影響が評価されにくい背景があった．functional assessment of cancer therapy-anemia scoreを使用したがん患者の貧血調査では，Hb＜12g/dl群はHb＞12g/dlと比較しQOLが低下することが報告された．欧米では，がん化学療法による貧血に対してエリスロポエチン投与しQOLの改善をみる大規模試験が施行され，Hb 11～12でQOLの改善が認められた．海外では，ガイドライン[6]に基づき，がん化学療法による貧血Hb≦10g/dlの患者を対象にエリスロポエチンが使用されている．一般的に本邦では，重篤な貧血Hb 7g/dl以下に対して赤血球輸血が施行されている．輸血はウイルス感染，容量負荷，輸注反応などの副作用があるため，本邦でもそれにかわるエリスロポエチン治療が期待され，臨床試験が進んでいる．一方，エリスロポエチン適応拡大に伴う医療経済的な問題もあり，本邦におけるガイドライン作成が望まれる．

5．血小板減少症

貧血と同様，がん患者における血小板減少症の原因も，がん化学療法のみに限局することが困難な場合がある．治療による重篤な血小板減少症は，

通常は，血液疾患のがん化学療法やあるいは造血幹細胞移植時に出現する．血小板減少が用量規制因子となっているがん化学療法薬としては，carboplatin, nedaplatin, gemcitabine, mitomycin Cなどがあげられるが，実際には臨床では多剤併用化学療法が用いられており，有害反応としての血小板減少症の発現頻度は高いと思われる．血小板減少症時に気を付けることは，出血の予防であり，薬剤の皮下注射や筋肉内注射，抗凝固薬投与，観血的検査，手技をできるだけ避けることが大切である．米国のガイドライン[7]では，血小板数1万/μl以下が予防的血小板輸血の基準とされているが，本邦では，血小板濃厚液適正使用の指針として血小板数1～2万/μlで時に重篤な出血をみることがあり，血小板輸血が必要になることがある，と記載されている．実際は，がん種や出血傾向，発熱，感染，凝固異常などの状態で維持すべき血小板数を検討すべきであろう．血小板造血因子であるトロンボポエチンの開発は進んでいるものの，まだ一般臨床では用いられていない．

赤血球，血小板輸血に関しては次項輸血を参照されたい．

6. 粘膜炎

がん薬物療法時，粘膜炎は口腔内から肛門，気管に認められることがあり，患者のQOLを低下させ，がん治療継続が困難となるとともに，重症感染の要因にもなりうる．したがって，その予防対策が重要になる．ここでは，口内炎と下痢について説明する．

口内炎の発症は，抗がん剤の直接作用として，投与後2～10日目に出現するフリーラジカルやサイトカイン放出による粘膜上皮基底細胞障害と，間接作用として，投与後10～14日目に出現する好中球低下による口腔内感染，が影響していると考えられる[8]．

口内炎を起こしやすい抗がん剤は，fluorouracil, methotrexate, cytarabine, doxorubicin, cisplatin, cyclophosphamide, etoposide, タキサン系があげられる．特にfluorouracilやmethotrexateは口内炎が用量規制因子となっている．口内炎の予防としては，①口腔内，歯科領域の感染源の除去（歯周病，う歯，義歯の調整），②口腔内衛生管理指導（口腔内のブラッシング，プラークコントロール）が大切であり，口内炎発症時は，①食事の工夫，②含嗽薬の使用，③鎮痛薬の使用が必要になる．

含漱薬としては，ヨウ素の酸化力によって殺菌効果を持つポビドンヨード，抗炎症作用・創傷治癒促進作用を持つアズレン酸，線維素融解酵素剤のエレース，抗真菌薬が用いられている．鎮痛薬としては局所麻酔薬入り含漱水，acetaminophen内服，非麻薬，麻薬鎮痛薬が投与される．予防法としては，fluorouracil静脈注射時のクライオテラピー，methotrexate投与時のロイコボリンレスキューがあげられる[9]．

下痢の発症機序は，抗がん剤投与直後に出現する早期性下痢と，抗がん剤投与後24時間以上経過し出現する遅発性下痢に分類される．前者は抗がん剤によるコリン作動性により，消化管の副交感神経が刺激され腸管の蠕動運動が亢進するためであり，持続時間は比較的短期間である．一方，後者は抗がん剤や代謝物が腸粘膜上皮の絨毛を萎縮・脱落させる腸管の粘膜障害であり，腸内細菌叢の変化，偽膜性腸炎なども関与している．下痢を起こしやすい抗がん剤は，irinotecan, fluorouracil, methotrexate, cytarabine, doxorubicin, cisplatin, etoposide, actinomycin D, gefitinibなどがあげられる．便の性状とともに，脱水，腹痛，食欲不振，悪心・嘔吐などの随伴症状の観察が大切である．安静や食事療法，止痢薬，整腸薬などの薬物療法，水分や電解質補正のための輸液療法，皮膚障害，感染予防のため肛門周囲の清潔化が必要になる．止痢薬として，腸管運動抑制薬としてアヘンアルカロイド関連薬剤[10]（loperamide, codeine phosphate），副交感神経遮断薬(抗コリン薬)としてscopolamine butylbromide, mepenzolate bromide，収斂薬としてalbumin tannate，ビスマス製剤，吸着薬としてnatural aluminum silicate，乳酸菌製剤が投与される．下痢が持続する場合は偽膜性大腸炎など感染症を鑑別する必要がある．

表2 肺毒性を引き起こす薬剤

抗腫瘍性抗生物質	アルキル化剤	分子標的治療薬
bleomycin*	busulfan*	imatinib
mitomycin*	cyclophosphamide*	gefitinib*
actinomycin	ifosfamide	erlotinib
	chlorambucil	bevacizumab
代謝拮抗薬	melphalan	cetuximab
methotrexate*	carmustine*	
cytarabine	procarbazine	その他
fludarabine		インターロイキン-2
gemcitabine*	トポイソメラーゼ阻害薬	bortezomib
hydroxyurea	irinotecan	L-asparaginase
微小管阻害薬		
paclitaxel		
docetaxel		
ビンカアルカロイド		

*は特に注意すべき薬剤

7. 肺毒性

がん化学療法による肺毒性の症状は，進行する呼吸困難，肺浸潤影，発熱などであり，感染，悪性腫瘍の浸潤，肺出血，心血管障害と区別することが困難である．肺毒性は発症時期により早発性（early-onset）と遅発性（late-onset）に分類できる[11]．早発性は，抗がん剤投与後2ヵ月以内に出現する病態で炎症性間質性肺炎，肺浮腫，気管攣縮，胸水が認められ，遅発性は投与後2ヵ月以降に認められ肺線維症が主たる病態である．ステロイド投与が常に有効であるとは限らず，致死的な場合もある．多くの抗がん剤が肺毒性を合併する可能性があるため（表2），肺毒性の起こる頻度と時期，臨床症状，危険因子，対処方法を常に念頭において抗がん剤を投与すべきである．特に注意すべき薬剤はbleomycin，mitomycin C，busulfan，gemcitabineなどであるが，分子標的治療薬であるimatinibやgefitinibにおいても重篤な肺毒性が問題になっている．

8. 心毒性

がん化学療法における心毒性は，軽度不整脈から心筋障害，致死的な心筋出血など様々な病態を呈する（表3）．また，心筋は再生しないため，抗がん剤の蓄積毒性も重要な問題である．特に様々ながん治療で重要な役割を担っているアントラサイクリン系を投与する場合は，左室駆出機能をエコー，シンチで定期的に測定し，アントラサイクリン総投与量300 mg/m^{2}以上の場合は，欧米では心筋保護剤であるdexrazoxaneの投与が推奨されている．残念ながら本邦では認可されておらず定期的な心機能検査を行い，駆出率が低下した場合薬剤を中止することが大切である．アントラサイクリン総投与量550 mg/m^{2}以上の場合は，10%で心不全が出現し[12]，アントラサイクリン系と分子標的治療薬であるtrastuzumabを併用すると16%にclass ⅢからⅣ度の心不全が出現するとの報告[13]がある．がん化学療法の成績の向上に伴い，多剤併用療法が必要な小児がんや，術後補助療法として長期に抗がん剤治療を受ける乳がん患者にとっては，常に気を配らなくてはならない有害反応である．

9. 脱毛

抗がん剤治療を受ける患者にとって，脱毛はボルフイメージとQOLの点から重大な問題となる．多くの薬剤が脱毛の原因となり（表4），患者にとっては，がん告知あるいは乳房切除より抗が

表3 心毒性を引き起こす薬剤と主な症状

抗悪性腫瘍抗生剤	アルキル化剤	モノクローナル
アントラサイクリン(CM,MP,SVT,VE)	cyclophosphamide	trastuzumab (CM,Cardiac failure)
(doxorubicin>400mg/㎡)	(AT,CHF,HM>120～170mg/kg)	rituximab (AT)
mitoxantrone	ifosfamide	bevacizumab (MI,CVA)
(CHF,AT>160mg/㎡)	(AE,AT,CHF>6.25～10g/㎡)	
mitomycin (CHF>30mg/㎡)	cisplatin (AT,CHF,MI)	その他
bleomycin (MP,MI)	busulfan (Endocardial fibrosis)	砒素(Prolonged QT, Trosades de pointes)
トポイソメラーゼ阻害薬	微小管阻害薬	インターロイキン-2(CHF,AT,MI)
etoposide (Vasospasm,MI)	ビンカアルカロイド(MI)	インターフェロン(AT,CHF,MI)
	タキサン(MI,AT,CHF)	
代謝拮抗薬		
fluorouracil (CF,Atrial+VE,MI)		
methotrexate (AT,MI)		
fludarabine (Hypotension,Angina)		
cytarabine (PE,Angina)		

AE：atrial ectopy, AT：arrhythmia, CF：cardiac failure, CHF：congestive heart failure, CM：cardiomyopathy, CVA：cerebrovascular accident, HM：hemorrhagic myopericarditis, MI：myocardial ischemia/infarction, MP：myopericarditis, PE：pericardial effusion, SVT：superficial venous thronbosis, VE：ventricular ectopy,

( ) 内数字は心毒性が高頻度となる薬剤総投与量

表4 脱毛発現率が高い薬剤

抗悪性腫瘍抗生剤	アルキル化剤
doxorubicin (61.6)	cyclophosphamide (24.3)
epirubicin (24.6)	ifosfamide (5%以上)
idarubicin (54.8)	
amrubicin (70.4)	微小管阻害薬
actinomycin D (33.7)	タキサン系
	paclitaxel (27.8)
トポイソメラーゼ阻害薬	docetaxel (77.5)
etoposide	ビンカアルカロイド
(44.4%：注射, 59.1%：21日間内服)	vincristine (21.9)
irinotecan (50)	vinorelbine (24.9)
nogitecan (28.5)	vindesine (25.6)

( ) 内は添付文書記載の脱毛の頻度（%）

剤の脱毛のほうが受け入れにくいという報告もある．古くから行われていた脱毛予防法としての頭部冷却法は，頭部の血管を収縮させ，毛根部への抗がん剤の分布を減少させる方法であるが，頭部転移の危険性があるといわれている．現在，抗がん剤による脱毛に対する予防薬が開発中であるが，臨床段階にはいたっていない[14]．命が助かるのだから脱毛ぐらいがまんしなさいとの安易な発言は慎み，患者の気持ちを受け入れ，脱毛は治療終了後，6ヵ月ほどで回復すること，かつら，スカーフ，帽子など患者のセルフイメージとQOLを保つための情報提供が必要になろう．

10. 神経障害

がん化学療法の神経毒性は，①中枢神経障害，②末梢神経障害，③自律神経障害，④聴覚などの感覚器障害に分類される．各薬剤の1回投与量，総投与量，投与間隔に注意する．cisplatinは総投与量300mg/m²以上で高率に神経障害が出現し，神経毒性が投与量規制因子であるvincristineは1回投与量は2mgに制限されている．タキサン系，白金製剤，ビンカアルカロイド系は末梢神経障害を起こしやすいが，エビデンスのある予防，治療

は現時点ではなく，患者の訴えを丁寧に聞き，症状を把握し，原因薬剤の減量，中止を検討することが大切である．oxaliplatin は寒冷刺激によって末梢神経障害（感覚異常）が誘発されるため，手袋など防寒とともに，冷たい飲み物を避ける工夫が必要である．

11．生殖機能障害（生殖細胞の凍結保存を含む）

がん化学療法の治療成績向上により，若年患者の長期生存に伴う妊孕能の問題が重要視されるようになった．放射線治療を含めたがん治療は，一過性，あるいは永久的妊孕能の低下を起こすが，その程度はがん種，治療時年齢，性腺機能，抗がん剤の種類，治療プロトコールに左右される．抗がん剤の種類ではアルキル化剤による胚細胞障害が最も強い．自然妊娠率はがん化学療法治療開始年齢が20歳未満では28%，20歳以上では5%との報告[14]もあるが，正確に予測することは困難である．

妊孕能温存療法として，男性の精子凍結法，女性の配偶者との体外受精で得られた受精卵凍結法が可能である．小児期，未婚女性が対象の未受精卵凍結法，卵巣組織凍結法では妊娠成功例は少なく臨床レベルにいたっていない．生殖医療技術は年々進歩を遂げており，現在，日本では認められていない第3者からの卵子や受精卵の提供も将来的に認められる可能性もある．不妊治療専門医と連携し最新の情報を患者に提供できることが望ましい．日本生殖医学会では，悪性腫瘍の治療などによって造精機能の低下をきたす可能性のある場合の精子凍結保存は可能であるとし，説明同意文書がホームページに記載されている（http://www.jsfs.or.jp）．

12．二次がん

がん化学療法，放射線治療成績の向上により，治癒を含めた長期生存患者が増加するにつれ，治療関連二次発がんの問題が検討されるようになった．患者自身のがんになりやすい素因，環境要因もあり，がん化学療法後の二次発がんの危険性を正確に評価することは難しい．欧米でのHodgkinリンパ腫の長期追跡例では，二次発がんが死因の1位であり，特に重要視されている．Hodgkinリンパ腫の二次発がん[16]としては，非Hodgkinリンパ腫，喫煙歴のある患者の肺がん，35歳以前にマントル照射を受けた患者の乳がん，腹部，骨盤照射を受けた患者の消化器がん，化学療法に関連した白血病（急性骨髄性白血病）があり，若年者の限局型Hodgkin病治療ではできるだけ放射線治療を避ける傾向となっている．乳がん患者においては，tamoxifenによる子宮内膜がん，胸部放射線治療による軟部肉腫，乳房切除と放射線併用による肺がん，高用量の抗がん剤と放射線治療併用に関連した白血病の危険性が指摘されている．自家造血幹細胞移植後の治療関連白血病では，アルキル化薬使用とetoposideの総投与量，全身放射線治療に関連するといわれ，標準的治療に抵抗性を示す．新規抗がん剤の登場，治療法の変更でこれら二次発がんの頻度は変化する可能性があり，初回治療時に二次発がんの可能性を説明し，原病が治癒した後も，禁煙の指導，定期的ながん検診が重要である．

13．その他（腎毒性，肝障害，過敏反応，血管毒性）

抗がん剤は上記に述べた以外にも，多くの有害反応を有する．主要臓器障害としては，腎，肝毒性があり，抗がん剤の種類によって肝障害[17]，腎障害[18]時には抗がん剤投与量の減量が必要になる．B型肝炎，C型肝炎あるいはこれら肝炎ウイルスキャリアという患者の因子にも気を配る必要がある．B型肝炎の場合にはlamivudine投与を検討し，ステロイド投与時は劇症肝炎の問題があり，注意が必要である．cisplatin投与時には腎障害を予防するためクロールを含む十分量の補液を行う．アナフィラキシーショックは，どの抗がん剤でも出現するという意識が大切であり，タキサン系などはアレルギーに対する前投与薬が必要である．

dacarbazine 投与時は血管痛を軽減するため投与直前の溶解と遮光が大切である．紙面の都合で全ての薬物有害反応に言及できないが，抗がん剤投与前には必ず薬剤添付文書を読み，知識の再確認を行うことが重要である．また，抗がん剤の投与方法，気を付けるべき点を整理し，医療チーム間でのレベルアップを図るとともに，患者教育にも力をいれるべきである．このような，地道な努力が薬物有害反応の予防，早期発見，治療につながるものと考える．

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