Fig. 6. Actuarial local control rates for the patients who received 60 Gy/8 Fr/2 weeks (line) and for those who received 48 Gy/8 Fr/2 weeks (dotted line).

It is apparent that the possibility of radiation pneumonitis may be increased by increasing the irradiated lung volume (27–29). Several authors have reported the results of pulmonary function tests after conventional radiotherapy for lung cancer (28, 29). Sunyach *et al.* reported that three-dimensional conformal radiotherapy for NSCLC significantly decreased the total lung capacity by 6.5% of the predictive value, but there was no significant change in DL_{CO} and $FEV_{1.0}$ (29). In another study, Abratt *et al.* reported that a conventional anteroposterior parallel opposed field significantly decreased DL_{CO} by 14% and total lung capacity by 6% at 6 months (30). The risk of radiation pneumonitis is known to be high if the total lung volume receiving 20 Gy (V_{20}) or 30 Gy (V_{30}) is larger than the threshold (27, 31). A small target volume is beneficial in that it can reduce the volume that is irradiated with greater than the threshold dose, so that radiation pneumonitis can be expected to occur less frequently. In preparatory studies, we found that small-volume IGRT can decrease the volume that receives 20–50% of the prescribed dose for PTV less than $6 \times 6 \times 6$ cm^3 (20, 21). As expected, symptomatic radiation pneumonitis resulting from small-volume IGRT did not occur in this study. Furthermore, the respiratory function test was not significantly declined. Our results suggest that small-volume IGRT is feasible for patients with poor respiratory function. The parallel structure of lung parenchyma may explain why there was no incidence of pulmonary functional deterioration or large volume effect in pulmonary function. The maximum treatment volume for which the symptomatic radiation pneumonitis does not occur cannot have been determined with our protocol.

Table 2. Patients with local failure

Metastasis or primary	Time to failure (months)	Histology	Maximum tumor size (cm)	Prescribed dose	Number of beams	Mean PTV dose	Maximum PTV dose	Minimum PTV dose
Primary	25	SCC	5.5	48 Gy/8 Fr	8	48.3 Gy	37.1 Gy	53.0 Gy
Primary	20	SCC	4	48 Gy/8 Fr	9	48.0 Gy	51.3 Gy	44.9 Gy
Primary	16	SCC	0.8	48 Gy/8 Fr	9	47.4 Gy	28.0 Gy	49.9 Gy
Primary	6	SCC	3	48 Gy/8 Fr	9	50.1 Gy	46.4 Gy	53.5 Gy
Primary	3	Adeno	3.5	48 Gy/8 Fr	9	47.8 Gy	40.9 Gy	51.8 Gy
Metastasis	10	SCC	1	48 Gy/8 Fr	9	48.1 Gy	39.1 Gy	52.5 Gy
Metastasis	9	SCC	1	48 Gy/8 Fr	9	48.9 Gy	35.7 Gy	54.9 Gy

Abbreviations: SCC = squamous cell carcinoma; Adeno = adenocarcinoma.

Careful dose escalation study with different bins for different treatment volumes will be required for this purpose (15).

Organ movement is an important issue as a source of uncertainty in our study. Systematic or preparatory error resulting from organ motion can significantly increase or decrease the dose distribution for the critical organs in general (32). Intrafractional organ motion can affect dose distribution considerably for lung tissues. Breath-holding, gating, and respiratory synchronization have been used to reduce the uncertainty resulting from respiratory movement (33–37). We have used a three-phase CT scan to determine the ITV and have not seen symptomatic radiation pneumonitis, probably because of the small size of the PTV. Technical developments may effectively reduce the safety margin for internal motion, but their clinical importance should be compared carefully with the technique introduced in the current study because our method does not require investment in new equipment.

We concluded that the optimal dose constraints for esophagus using our technique were lower than we had hypothesized. Forty-eight Gy in eight fractions at the isocenter can exceed the MTD of esophagus with our technique. In the past, we have had no dose constraints for chest wall. Sixty Gy in eight fractions cannot be recommended when a significant area of the chest wall receives 90% of the prescribed dose. Perhaps other serial structures such as coronary arteries and intercostal nerves should be also included in the dose constraints. Because of this, we have halted this Phase I/II study and are planning to rearrange the protocol setting accordingly.

The reproducibility and stability of the patients during our treatment may not have been optimal, because we have not taken a linacography from the second day nor used stereotactic devices. There is a great possibility that a greater dose than we estimated was delivered to the esophagus in the patient with Grade 5 esophageal complication as a result of the uncertainty in setup. We had considered that the level of accuracy required for IGRT of the lung might be rather modest because of the parallel structural nature of lung tissues—as long as small tumors are the targets of IGRT. However, this study suggested that immobilization is important to reduce error to the at-risk extrapulmonary serial organs, even when small tumors are treated. Negoro et al. have found that a correction to a patient's setup was required in 25% (20/80) cases with the absolute errors from 4 to 8 mm (mean 4.9 mm) by using a stereotactic body frame and daily film verification (38). By using this technique, they have not seen any serious complications after giving 40–48 Gy in 4 fractions for 37 patients with one or two lung tumors during the follow-up period of 3–29

months (median 18 months) (39). The risk of esophageal complication may be lower in their setup technique. Uematsu et al. have used CT scanning in the treatment room for verification before irradiation of lung tumor every treatment day (5). In the 50 patients with a median follow-up of 36 months, they have not seen any major radiation injury. CT must be more efficient than portal film as the verification method to reduce the risk of giving dose higher than tolerable dose of soft-tissue critical organs.

In this study, the local tumor control rate for all tumors was 80.4% ± 7.1%. The 2-year regional control rate in patients with Stage I primary lung cancer was 85.2% ± 9.8%. The 2-year local tumor control rate was 65% in Kaskowitz et al.'s series, in which Stage I NSCLC was treated with conventional radiotherapy using the median prescribed dose of 63 Gy (11). Cheung et al. reported that 49% of T1–3 NSCLC patients (30/61) experienced a local relapse within 2 years (8). Compared with these studies, the use of small-volume IGRT to treat lung tumors in our protocol setting provided better outcomes in terms of local control, although a simple comparison is misleading because of the heterogeneity of the patients in our series. There were more recurrences in patients who received 48 Gy in eight fractions than in those who received 60 Gy in eight fractions. Because the patients who received 48 Gy had larger tumors by stratification, this difference cannot be simply attributable to the difference in the dose, but it is not suitable for multivariate analysis. However, the good local control rates reported by other investigators are achieved with a dose biologically more similar to 60 Gy in eight fractions than to 48 Gy in eight fractions (5, 17, 18). Our results may suggest a dose–response relationship in tumor control between the two dose schedules. Caution must be used in the nonhomogeneous dose distribution in small-volume IGRT; in this study, the periphery of the tumor received about 80% of the prescribed dose.

In conclusion, the organs at risk in small-volume IGRT with a high-dose hypofractionated schedule are extrapleural organs such as the esophagus and internal chest wall/parietal pleura rather than the pulmonary parenchyma in the present protocol setting. Small-volume IGRT using 60 Gy in eight fractions is highly effective for local control of lung tumors, but MTD has not been determined in this study. The prospective study of small-volume, hypofractionated radiotherapy for lung tumors requires dose constraints not only for the spinal cord, large bronchus, esophagus, and brachial plexus, but also for internal chest wall, and probably for other organs with serial structures. Consideration of uncertainty in the contouring of normal structures is critically important in the setup of patients and internal organ in high-dose hypofractionated IGRT.

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Radiation Therapy in the Treatment of Lung Cancer

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Abstract: Although non-small cell lung cancer (NSCLC) has the potential for cure with surgical resection, unfortunately, less than 15% of all patients and less than 25% of those who present with intrathoracic localized disease are candidates for curative surgical resection. Elderly patients, even if they have resectable disease, often have medical contraindications to surgery, such as cardiovascular diseases and pulmonary dysfunction. For inoperable or unresectable NSCLC, radiation therapy (RT) is widely used as either curative or palliative treatment. There is increasing evidence that RT may improve the survival rate for patients with locally advanced unresectable NSCLC when combined with cisplatin-based chemotherapy or administered by altered fractionation. In limited-stage small cell lung cancer, the addition of thoracic RT and prophylactic cranial irradiation to systemic chemotherapy has also improved disease control. In patients with more advanced disease, RT has provided relief of symptoms. Newer radiotherapeutic methods are promising for increasing the dose targeted to the tumor while sparing healthy tissue. In addition, heavy ion charged particle therapy, brachytherapy, stereotactic irradiation, and multi-daily fractionation have shown promise in the treatment of lung cancer. Furthermore, there have been advances in the technology for treatment delivery, especially three-dimensional treatment planning systems, patient fixation tools, and respiratory synchronous system for RT.

Key words: Lung cancer; Radiotherapy; Chemotherapy

Introduction

Radiotherapy for lung cancer has been practiced as (1) curative treatment for unresectable non-small cell lung cancer (NSCLC); (2) preoperative and postoperative irradiation; (3) thoracic irradiation for small cell lung cancer (SCLC); (4) prophylactic cranial irradiation (PCI) for brain metastasis of SCLC; and (5) palliative treatment for respiratory symptoms,

superior vena cava syndrome, and bone and brain metastases.[1,2] Although the treatment outcome is still poor, survival rates have been improved gradually through the development of radiotherapy techniques, as well as the advancement of combined chemoradiotherapy. This article discusses the role of radiotherapy in the treatment of lung cancer and reviews recent advances of radiotherapy, including combined therapies.

Curative Radiotherapy for Non-Small Cell Lung Cancer (NSCLC)

Curative radiotherapy is indicated for locally advanced NSCLC patients in the clinical stage of Bulky N2 IIIA and IIIB excluding the cases with malignant pleural effusion, as well as early-stage NSCLC in patients who are considered too old to be operable or who have other complications such as cardiopulmonary dysfunction.

1. Tumor size and local control

Because radiotherapy induces stochastic death of cancer cells according to the dose of radiation, the possibility of tumor control depends on the amount of cancer cells. In addition, larger tumors have higher proportions of hypoxic cells, which are less sensitive to radiation. Thus, patients with smaller tumors have a better chance of cure. It is generally considered that curative radiotherapy is indicated for tumors of sizes up to about 5 cm.[1,2] Using the standard fractionated irradiation of 2 Gy once daily, the dose needed for tumor control is 40 to 50 Gy for microscopic tumors and over 60 Gy for macroscopic residual tumors. The tumor control probability is 80% for T1 tumors at the dose level of 70 to 75 Gy, and 50% to 70% for T2 tumors with diameters of 5 cm or less at 75 Gy or more.[3]

2. Histological types and irradiation to nodal metastasis

Different histological types of lung cancer

show different trends in lymph node metastasis. Observation in surgical cases indicates that squamous cell carcinoma metastasizes continuously from the pulmonary hilum to the mediastinum, while adenocarcinoma tends to spread discontinuously.[3] Some cases of squamous cell carcinoma have no distant metastasis even when there are mediastinal lymph node metastasis. On the other hand, mediastinal lymph node metastasis of adenocarcinoma and large cell carcinoma often accompanies distant metastasis. As a result, long-term survivors treated with radiotherapy include a high percentage of cases with squamous cell carcinoma, in which local control of disease has improved long-term survival. If the primary tumor is located in the upper lobe or the superior segment of the lower lobe, both the primary tumor and nodal metastasis can be irradiated within a relatively small field of irradiation. Better long-term survival can be expected in these cases as compared with cases having primary sites in other locations.

3. Combination with chemotherapy (chemoradiotherapy)

The standard treatment for unresectable locally advanced NSCLC now consists of combinations of radiotherapy and chemotherapy intended to control microscopic metastases and enhance the local effect of radiation.[4] The timing of the combined use of these therapies is crucially important in chemoradiotherapy. There are 3 different timings of the combined use: (1) sequential chemoradiotherapy in which neoadjuvant (induction) chemotherapy is followed by radiotherapy, (2) alternating chemoradiotherapy in which the two therapies are performed, and (3) concurrent chemoradiotherapy in which antineoplastic agents are used during radiotherapy. Sequential chemoradiotherapy is the least toxic and used widely in routine clinical practice. However, it has been reported that sequential chemoradiotherapy did not show clear benefit in the survival of patients with squamous cell carcinoma, although

it was effective in non-squamous cell carcinoma,[5] and it does not improve the overall rate of local relapse. For these reasons, the preference is moving towards concurrent chemoradiotherapy aiming at the improvement of local control rate.[4] Alternating chemoradiotherapy is not commonly used, since this protocol involves split course of radiotherapy. Chemoradiotherapy for elderly patients is still controversial because of the problems of toxicity.[5]

4. Advancement of radiotherapy techniques

The basic principle of radiotherapy is to improve the local control rate through administration of as large doses as possible to target lesions while limiting the effect on surrounding normal tissues within the limit of tolerance. Several irradiation methods have been developed to maximize dose concentration to lesions, including 3-dimensional conformal radiotherapy,[6] heavy ion (charged particle) therapy, stereotactic irradiation, and brachytherapy. Apart from brachytherapy, external radiotherapy methods are further reinforced by the development of techniques such as respiration synchronous irradiation and dynamic tracking systems, which counteract the respiratory movement of tumors. These techniques have been reported to achieve good local control of inoperable peripheral lung cancer in the early stage. While early-stage squamous cell carcinoma in the pulmonary hilum region is showing a tendency to increase, the most effective therapy for this cancer is endobronchial brachytherapy. This treatment is reported to achieve a cure rate of over 80%.[7]

While standard radiotherapy uses once daily fractionated irradiation at 1.8–2 Gy, 5 times per week, multi-daily fractionation may be performed for the purpose of expanding the difference between the effect on normal tissues and the therapeutic effect on tumors. The benefit of increasing doses in multi-daily fractionation is reported to be more marked in cases with squamous cell carcinoma.

Combination with Surgery

Because surgery and radiotherapy are both local therapies, a combination of these two modalities can be used only to a limited extent. The timing of combined use can be preoperative irradiation intended to improve resectability and prevent intraoperative metastasis and postoperative irradiation for the main purpose of controlling residual tumors and microscopic mediastinal lymph node metastasis. While the effectiveness of preoperative irradiation has not been reported except for the reports on Pancoast tumor, recent progress of chemotherapy has promoted clinical studies on the use of preoperative chemoradiotherapy. On the other hand, postoperative irradiation is generally considered to offer no benefit in survival, although it contributes to the improvement of the local control rate. However, radiotherapy after non-curative resection has been reported to achieve a 5-year survival rate of over 40%,[1] suggesting the significance of postoperative irradiation in cases with residual tumors. Future study is needed to evaluate postoperative mediastinal irradiation in patients with pN 2 to 3 tumors intended for control microscopic residual tumors.[8]

Radiotherapy for Small Cell Lung Cancer (SCLC)

1. Thoracic radiotherapy

While SCLC is more sensitive than NSCLC to both radiation and many antineoplastic

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Note: LD refers to the lesions that are limited to the hemi-thorax, including the ipsilateral pulmonary hilum, the bilateral mediastinal lymph nodes and supraclavicular fossa (or ipsilateral pleural effusion). Advanced cases beyond the above-mentioned limits are referred to as ED (ipsilateral malignant pleural effusion is usually included in ED).

agents, it proliferates aggressively and the majority of patients show locally advanced disease or distant metastasis at the time of diagnosis. For this reason, clinical stages are generally classified into limited disease (LD) and extensive disease (ED).[Note] Although SCLC is treated mainly with chemotherapy, standard therapy for LD disease includes the addition of thoracic irradiation to systemic chemotherapy, because it reduces local progression rate. The timing of radiotherapy is best when it is used concurrently with chemotherapy early after the beginning of treatment, and a 5-year survival rate of about 20% has been reported for LD cases.[9] Recommended dose and fractionation is 45 Gy delivered as twice daily 1.5 Gy fractions over 3 weeks (accelerated hyperfractionation).

2. Prophylactic cranial irradiation (PCI)

Central nervous tissues are not sufficiently sensitive to the effect of chemotherapy because of the presence of the blood-brain barrier. Hence, prophylactic cranial irradiation PCI has long been used for the purpose of controlling microscopic brain metastases in the treatment of SCLC. Although PCI reduced the relapse rate of brain metastasis, few reports had documented the improvement of survival rate, and the propriety of this procedure is controversial. Recent results of meta-analysis, however, demonstrated that PCI also improves survival rate in patients showing clinically complete remission (CR) after initial treatment. As a result, PCI is gradually being incorporated into the standard therapy for patients showing CR after initial treatment. Recommended doses for PCI are 25 to 30 Gy in 10 to 15 fractions.[10]

Palliative Radiotherapy

Even if extensively advanced stage of cancer prohibits the expectation of cure, patients with advanced cancer have multiple symptoms that impair function and quality of life. Various symptoms of lung cancer can be palliated by a slight reduction of the tumor volume in the infiltration sites causing symptoms. Hence, radiotherapy is also widely used as palliative treatment. Indications for palliative irradiation include (1) cancer pain, (2) symptoms due to tumor compression on organs, and (3) hemorrhage from tumors.[2] More specifically, such treatment is considered for symptoms such as pain from chest wall infiltration and bone metastasis, disturbance of motor function and consciousness due to brain metastasis, superior vena cava syndrome, airway obstruction, and hemoptysis. All these symptoms are improved by irradiation in 80 to 95% of the patients. Doses of 20 Gy or less are sufficient for the purpose of relieving subjective symptoms. Unlike narcotics, irradiation for pain can achieve not only pain relief but also the control of metastatic foci. The ability of radiotherapy to facilitate rehabilitation of patients is an important advantage.

Adverse Events Associated with Radiotherapy and Precautions[2]

Because the effect of radiation on normal tissues is limited to the irradiated volume, radiotherapy usually does not cause significant systemic adverse reactions such as leukopenia, vomiting, and immunodeficiency, unless anticancer drugs are used concurrently. One of the acute reactions observed frequently during thoracic radiotherapy is radiation esophagitis associated with mediastinal irradiation. In some patients treated with multi-daily irradiation or the concurrent use of chemotherapy, radiation esophagitis may cause severe swallowing difficulty that would require interruption of treatment. In most patients, however, esophagitis is transient and resolves naturally after a few weeks from the completion of treatment. Alcohol ingestion during radiotherapy must be strictly prohibited.

Adverse reactions occurring after treatment include radiation pneumonitis and pulmonary fibrosis. Lung tissues receiving irradiation de-

velop inflammatory changes a few months after treatment and might eventually develop fibrosis. Although this condition is usually limited to the field of irradiation, serious pneumonitis extending beyond the radiation field may occur occasionally after chemoradiotherapy.

Among delayed adverse reactions after radiotherapy, the most important one that requires the greatest caution is the effect on the spinal cord. However, radiation myelopathy can be avoided if sufficient precautions are taken in the treatment plannings.

Conclusion

Radiotherapy plays important roles in the local control of lung cancer. Radiotherapy for inoperable or unresectable NSCLC provides a greater chance of cure when the tumor is smaller in diameter. The success of the treatment for locally advanced NSCLC depends on the locations of primary tumors and lymph node metastases. Recent advances of therapeutic techniques have enabled us to deliver large doses to the targets and improve local control rate. An important theme for future study is development of optimal regimens for the combined use of chemotherapy and radiotherapy aiming to improve local control rate and prevent distant metastases.

While clinical results of the treatment for SCLC has been improved substantially by the introduction of platinum agents, thoracic radiotherapy also plays a major role and PCI has been gradually incorporated into the standard therapy.

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肺癌に対する放射線治療

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Radiation Therapy in the Treatment of Lung Cancer

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Although non-small cell lung cancer(NSCLC)has the potential for cure with surgical resection, unfortunately less than 15% of all patients and less than 25% of those who present with intrathoracic localized disease are candidates for curative surgical resection. Elderly patients, even if they have resectable disease, often have medical contraindications to surgery, such as cardiovascular disease or pulmonary dysfunction. Radiation therapy(RT)for lung cancer has been practiced as(1)curative thoracic irradiation for inoperable or unresectable NSCLC,(2)preoperative and postoperative irradiation,(3)thoracic irradiation for limited-stage small cell lung cancer(SCLC), (4) prophylactic cranial irradiation(PCI) for SCLC, and(5)palliative irradiation for more advanced disease. Recent evidence indicates that RT with high equivalent doses of 60 Gy or more using conventional once daily fractionation may improve the survival rate for patients with locally advanced unresectable NSCLC when combined with cisplatin-based chemotherapy or administered by altered fractionation. In limited-stage SCLC, the additions of thoracic RT and prophylactic cranial irradiation to systemic chemotherapy have also improved disease control. In patients with more advanced disease, RT has provided relief of symptoms. Newer radiotherapeutic methods are expected to hold promise in increasing the dose to tumor while sparing normal tissue. Recently, heavy ion charged particle therapy, brachytherapy, stereotactic irradiation, and multi-daily fractionation have shown promise in the treatment of lung cancer. Furthermore, there have been advances in the technology for treatment delivery, especially three-dimensional treatment planning systems, patient fixation tools, and respiration synchronous systems for RT.

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はじめに

　肺癌は，わが国の全悪性腫瘍による死因の第一位を占め，年々死亡数が増加している疾患である．肺癌全体の治癒率が低い理由として，症例の多くが，診断時すでに切除不能の進行癌となっていることが挙げられる．また，人口の高齢化に伴い，高齢者肺癌の増加も治療を難しくしている要因となっている．このような状況の中で，肺癌治療に占める放射線治療の役割は益々重要となっている．

　肺癌の放射線治療には，① 切除不能非小細胞肺癌の根治的放射線治療，② 術前・術後照射，③ 小細胞肺癌の胸部照射，④ 小細胞肺癌の脳転移に対する予防的全脳照射(PCI)，⑤ 広範囲な腫瘍進展や遠隔転移に伴う症状の緩和を目的とした対症的照射などがある[1]．また，根治的放射線治療を行う場合，肺癌に特有な配慮すべき項目が非常に多く，このことが放射線治療を難しくしている要因にもなっている．治療計画に関わる主な項目として，① 個々の腫瘍の生物学的特長(組織学的・生物学的多様性，遠隔転移のリスク)，② 放射線物理学的問題点(線質と腫瘍内吸収線量，肺不均質補正の有無，呼吸性移動への対応)，③ 放射線生物学的問題点(腫瘍の放射線感受性・反応性，放射線肺臓炎・肺線維症，脊髄症，気管支狭窄などに関わる正常組織の耐容線量と線量－容積関係)，④ 併用療法による照射効果の修飾(化学療法，手術，増感剤，防護剤，温熱療法)，などが挙げられる．

　本稿では，主として最近の肺癌の集学的治療に占める根治的放射線療法の役割と治療法の進歩について述べる．

非小細胞肺癌の根治的放射線療法

　根治的放射線療法の適応となるのは，臨床病期Bulky N2-IIIAおよび悪性胸水，対側肺門リンパ節転移を除くIIIB期の局所進行癌と，高齢や合併症のために医学的に手術不能と判断されるI/II期症例である[1]-[3]．局所進行癌の放射線療法では高齢者やPS不良例を除けば化学療法を併用するのが標準的治療法である[4]-[6]．手術との境界領域にある局所進行癌に対する術前あるいは術後照射の意義は明らかではない[7]．

放射線治療で腫瘍制御が望めるための条件としては，①腫瘍の存在範囲を照射野内に完全に含めうること，②放射線による正常組織反応が許容される照射線量の範囲内で腫瘍制御が可能なこと，が必要となる．したがって，放射線療法では，①腫瘍の放射線感受性や発育・進展様式などの生物学的特性，②腫瘍の大きさ，③腫瘍の占拠部位などが治療の成否を制約する重要な因子となる．その他の予後因子としては，臨床病期，全身状態(PS，体重減少)などが重要である．

1. 腫瘍サイズと局所制御

放射線治療では線量に応じて確率的に腫瘍細胞量が減少していくために，放射線治療による腫瘍制御の可能性は腫瘍細胞量に依存する．また，腫瘍サイズが大きくなると放射線感受性の低い低酸素細胞の割合も高くなる．したがって，腫瘍サイズが大きいほど大線量が必要となる(Fig. 1)[8]．

2. 線量と照射野

腫瘍制御に要する線量は，顕微鏡的な腫瘍細胞量に対しては1回2Gyの通常分割で40〜50Gyでよいが，肉眼的に残存する腫瘍には60Gy以上の線量が必要となる．さらに，末梢発生のT1腫瘍では70〜75Gyの照射で80％，T2は腫瘍径5cm以下であれば75Gy以上の照射で50〜70％の制御の可能性が報告されている[1),9)]．しかし，肺門部への80Gy以上の照射は過照射の危険性がある[10]．

一般的に照射野が小さいほど正常組織の耐容線量は高くなるため大線量投与が可能となる．逆に照射野が広いと肺臓炎の発症のリスクが高くなるため，肺癌の放射線治療に関わる臨床試験のプロトコールでは，照射野について肺野1/2規定が設けられているものが多い．これは，X線シミュレータ写真上で照射野が片側肺の1/2(右上葉または左上区原発の場合には2/3)を超えないように治療計画することを規定したものである．最近では3次元治療計画が普及し，grade 2(RTOG)以上の放射線肺臓炎発症のリスクを低下させるためには，20Gy以上照射される正常肺の体積V_{20}が重要であるとされている．すなわち，放射線単独の場合には，V_{20}が正常肺全体の体積の40％を超えないよう(できるだけ35％以下になるよう)に，化学療法併用時には25％を超えないように計画することが推奨されている[11-12]．原発巣が肺末梢部にある症例では，照射野の縮小時に原発巣と転移リンパ節を別々の照射野で照射する方法も考慮すべきである．とくに，高齢者や低肺機能患者では可能な限り縦隔・肺門への照射は避け，肉眼的腫瘍体積(GTV)に限局した照射野を設定する．

3. リンパ節転移に対する照射

リンパ節転移の特徴を組織型別にみると，扁平上皮癌は肺門から縦隔へと順次性に転移していくのに対して，腺癌では非順次性に進展する(スキップ転移)傾向が認められる(Table 1)[13]．また，扁平上皮癌では，縦隔リンパ節転移が
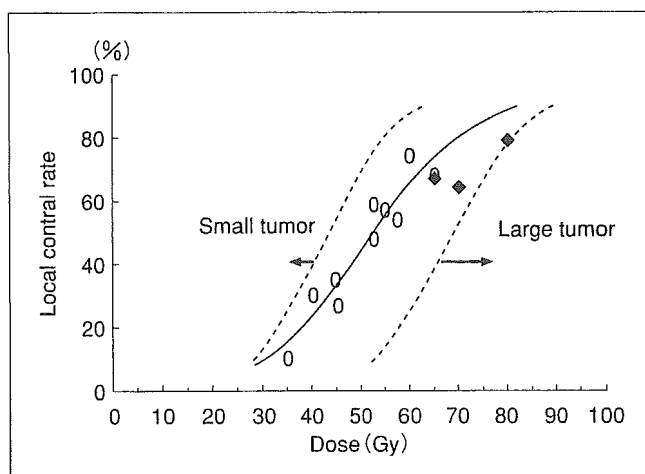

Fig. 1　Correlation between dose and local control for non-small cell lung cancer(modified data[33)]published by Vijayakumar S, et al.)

存在しても遠隔転移を伴わない症例が少なからず認められるのに対し，腺癌の縦隔リンパ節転移例では遠隔転移の頻度は高くなる．したがって，所属リンパ節への予防照射は扁平上皮癌で意義があるものと考えられる[14]．また，III期N2症例では原発部位が上葉あるいは下葉上区の症例の方が他部位原発例にくらべ予後良好である[1),3),15)]．これは，原発部位が上葉あるいは下葉上区であれば肺門・縦隔あるいは鎖骨上窩までを一緒に照射しても照射野が比較的小さくできるので，正常肺組織への照射の影響が少なくてすむためである(Fig. 2)．リンパ節転移部位では気管分岐部や対側縦隔まで転移があると予後は不良である[15]．また，両側肺門部を含む照射は肺機能に大きな影響を及ぼすばかりでなく，重篤な肺臓炎のリスクも高くなる．鎖骨上窩リンパ節転移例は，上葉原発で同側の鎖骨上窩転移であれば照射野も小さくでき(Fig. 2)，長期生存の可能性がある．

一方，末梢型I期例では，原発巣に限局した照射でも縦隔リンパ節のみの再発は少なく[16),17)]，対象症例が高齢や低肺機能であることなどを考慮すると，原発巣のみの照射でよいと考えられている．また，肺内腫瘍への局所照射では10MVよりも6MV X線が望ましいとする意見がある．

4. 組織型と治療成績

放射線療法主体の治療成績について組織型別にみると，扁平上皮癌に長期生存例が多く認められ，その治療成績には分化度による差異は認められない[18]．一方，腺癌では分化度が高いと，扁平上皮癌と同等の5年生存率がえられるが，担癌生存例も含まれ，予後の良否は腫瘍の自然史に依存していると考えられる．低分化な腺癌や大細胞癌は，増殖旺盛で早くから血行性転移をきたすため，長期生存例は例外的に認められる程度である．また，扁平上皮癌症例では治療後2年時に非担癌状態であれば，そのまま5年生存することが多く[18]，局所制御がそのまま長期生存に結びつく可能性の高い疾患であると考えられる．これらのことか

ら，非小細胞肺癌は少なくとも扁平上皮癌と非扁平上皮癌とに大別すべきと考えられる．

放射線治療効果を高める工夫

放射線治療による局所制御を高める方法としては，①空間的線量分布の改善，②時間的線量配分の工夫，③化学薬剤や温熱などを用いた放射線の効果の修飾，とに大きく分けられる．

1．空間的線量分布の改善

放射線治療の基本は，病巣周囲の正常組織への影響を許容範囲内にとどめて，病巣にできるだけ大量の線量を投与することにより局所制御率の向上を図ることである．この目的のために注目されている治療法に3次元原体放射線治療（3-D conformal radiotherapy）[19]，定位放射線照射[20]がある．とくに局所進行癌に対する化学放射線療法でも3次元原体照射による線量増加試験が行われている．

小腫瘍に対して行われる定位的放射線照射は，照射範囲が小さいため照射回数を1ないし数回とすることも可能である．線量分割法では，48Gy/4回，45Gy/3回，60Gy/5回などの照射法が用いられている[20]．なお，病巣の呼吸性移

動への対処法として，腹部圧迫による腹式呼吸抑制法が簡便であるが，呼吸同期や動態追跡などの照射技術も開発されている．

最近注目されている陽子線や重イオン線を用いた照射は

Table 1　Frequency of Nodal Metastases by Location and Cell Type

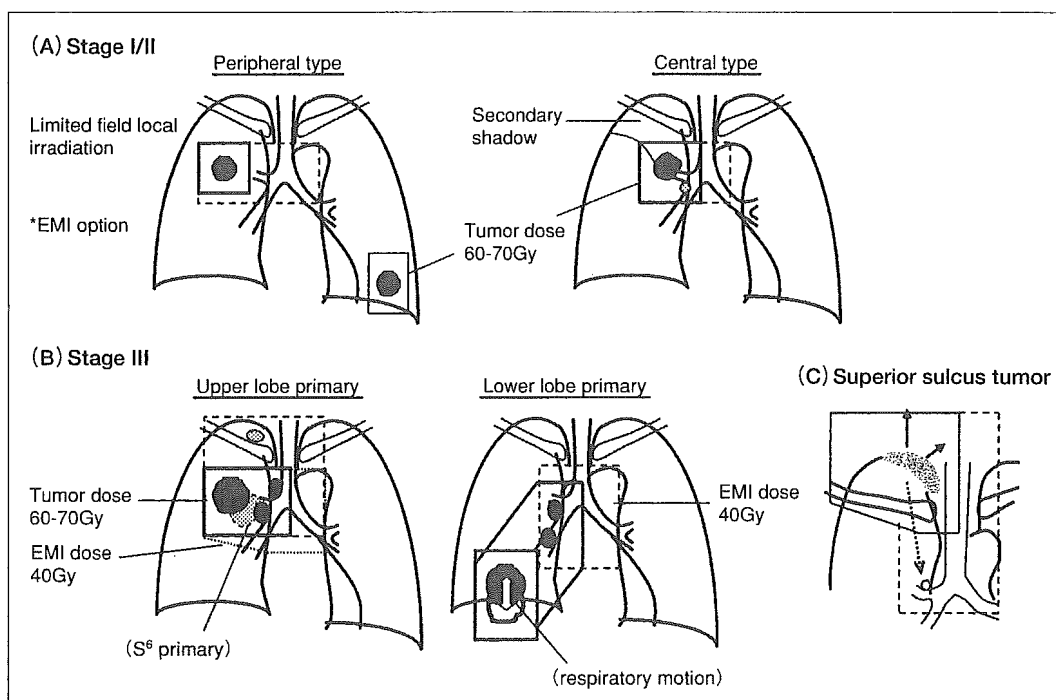| Location and Nodal Status	Adenocarcinoma (%)	Squamous cell carcinoma (%)
Central cancers		
N0	8 (47)	13 (41)
N1	3 (18)	10 (31)
N1+N2	4 (24)	9 (28)
N2 only	2 (12)	0
Total	17 (100)	32 (100)
Peripheral cancers		
N0	35 (61)	31 (78)
N1	6 (11)	6 (15)
N1+N2	8 (14)	3 (8)
N2only	8 (14)	0
Total	57 (100)	40 (100)

Data[13] from Libshitz HI, et al.

Fig. 2　Radiation field for non-small cell lung cancer according to clinical stage and tumor location[34]
A: For peripherally located stage I tumors, isolated regional recurrence was uncommon, and therefore elective mediastinal irradiation (EMI) may be omitted. On the other hand, centrally located stage I and II tumors, especially squamous cell carcinoma, have a high probability to involve the regional nodes. Elective regional irradiation is recommended because the radiation field is not too large to encompass the primary tumor and regional nodes.
B: For stage III-N2 disease, tumors located in the upper lobe or superior segment of the lower lobe make it easy to encompass the tumor and all regional nodes including the supraclavicular nodes with smaller fields than those at any other sites.
C: Superior sulcus tumors extensively invade the apex of thoracic wall, but less commonly have hilar or paratracheal nodal metastases. For clinical N0 superior sulcus tumors, high-dose irradiation with limited local field may be recommended.

線量分布が良好なことからConformal Radiotherapyに適しており，わが国でも陽子線治療施設の設置が進められている．さらに，放射線医学総合研究所で行われている高LET炭素線治療は，殺細胞効果に優れており，末梢型非小細胞癌に対するI/II相試験では良好な治療結果が得られている[21]．それによると，腫瘍の大きさがT2でも通常の光子に換算して86.4Gy/18回あるいは72Gy/9回以上の照射を行えば90-95％局所制御可能であり，正常肺組織への影響も軽微であることがわかってきた．これらのデータは今後の陽子線治療やConformal Radiotherapyの発展に大いに寄与することが期待されている．

密封小線源治療は，理想的に病巣への高線量投与が可能であり，肺癌では[192]Ir密封小線源を用いた気管支腔内照射がある．わが国では，肺門部早期扁平上皮癌の根治的治療法として行われており，低線量率[192]Ir線源による治療では85％前後の局所制御率がえられている[22]．最近では高線量率[192]Ir後充填式治療装置の普及に伴い，高線量率[192]Irによる治療が行われているが，有効性の検証と今後の至適照射法の確立が期待されている．

2．時間的線量配分の工夫

通常の放射線治療では1日1回2Gyを週5回照射する単純分割照射法が標準的に用いられている．これは，正常組織と腫瘍組織との間で放射線感受性や照射後の回復に差がみられることを利用して確立された照射法である．したがって，肺癌でも個々の腫瘍に対する至適分割照射法が存在するはずである．近年，注目されている多分割照射法では，照射間隔は正常組織が照射後の亜致死障害から回復する時間間隔である4～6時間あけるため，日常臨床では時間的制約から1日2回が一般的である．RTOGでは非小細胞肺癌に対し1回1.2Gy1日2回の多分割照射による線量増加試験を行い，総線量69.6Gyの照射群が単純分割照射60Gy群に比し有意に生存率が向上したと報告している[23]．しかし，それ以上線量を増加しても予後の改善は明らかではなかったとの結果も認められている．これは1回1.2Gy程度の多分割照射法では，総線量の増加も可能となるが，治療期間も延長するため，治療期間中の腫瘍の再増殖が影響しているとも考えられる．また，照射野が大きい場合には，線量増加にも限界があることを示しているものと考えられる．そこで，治療期間の延長を避けるために，Medical Research Councilでは，1回線量は1.5Gyで1日3回の照射を週末も休まず12日間連続で照射するContinuous hyperfractionated accelerated radiotherapy（CHART）と呼ばれる照射法の臨床試験が行われた[24]．その結果，CHARTは局所制御率に優れ，とくに生存率でみると扁平上皮癌で大きな利益があると報告されている[24]．すなわち，前述したように扁平上皮癌は局所制御の向上がそのまま予後改善に結びつく疾患であると考えられる．

3．温熱療法との併用

腫瘍細胞に対する温熱の効果は照射効果と相補的関係にあることから，併用による局所制御率の向上が期待されている．温熱療法では肺内腫瘤に対する加温は困難であるが，胸壁に接している腫瘍の加温はむしろ容易であることから，胸壁浸潤型の大きな腫瘍に対して併用効果が期待される．著者らは胸壁浸潤型肺癌に対して温熱併用放射線治療を行い，良好な局所効果を認めている[25]．

局所進行非小細胞肺癌に対する化学放射線療法の現状

進行非小細胞肺癌に対する放射線療法に抗癌剤を併用する目的としては，①潜在性の微小遠隔転移を制御するため，②腫瘍の照射効果を増強するため，とに大別される．

1．化学放射線療法の適応

手術不能な局所進行非小細胞肺癌（Bulky N2IIIA/IIIB期）にはシスプラチンを含む化学放射線療法を行うことが標準的治療法であり，鎖骨上窩リンパ節転移例も化学放射線療法の適応になりうると考えられている．メタアナリシスの結果[4-5]では，化学療法併用による利益は2年生存率で4％程度であり，併用の利益は未だ十分とはいえない状況にある．化学放射線療法の良い対象は，全身状態が良好（PS：0，1）な症例であるが，70歳以上の高齢者では化学療法併用の利益は明らかではない[6]．化学療法を併用しても通常分割照射法での必要な推奨線量は最低60Gy/6～7週である[26]．化学療法との同時併用では，急性障害の軽減のためにスプリットコース照射法としても，照射休止期間の生存に対する不利益は明らかではない[27]．

化学放射線療法の治療成績を組織型別にみると，順次併用療法は非扁平上皮癌に利益が大きい[6]が，同時併用療法では組織型による差は明らかではない．

2．薬剤との相性と有害事象の防護

化学放射線療法と放射線単独療法との臨床比較試験のメタアナリシスの結果[4]-[5]，シスプラチンを含む化学療法に限定すれば，放射線と化学療法併用の利益が認められている．シスプラチンは化学放射線療法のkey drugであり，プラチナ製剤あるいはエトポシドは放射線との同時併用でも安全に施行しうる薬剤である．新規抗癌剤との併用にも期待が寄せられているが，明らかに予後を改善したとする薬剤の組み合わせは未だ報告されていない．逆に有害事象には注意が必要で，イリノテカンとの同時併用では，肺臓炎や食道炎などの非血液毒性のリスクが高く[1]，わが国ではゲムシタビンと放射線との同時併用は禁忌である．

ところで，化学放射線療法の毒性を軽減する方法として放射線防護剤であるAmifostine（WR-2721）の併用が注目されている．このAmifostineの併用効果に関するRTOGのランダム化比較試験の中間解析では，Amifostineの防護効果は明らかである[28]．しかし，わが国では本剤を使用できない

制約がある.

小細胞癌

　小細胞肺癌の限局型に対しては胸部照射を行うことにより局所再発率が有意に低下することから，限局型小細胞癌では全身化学療法と胸部照射との併用療法が標準的治療法となった[29]. 化学療法に用いる抗癌剤は，CDDPとエトポシド(VP-16)の併用が標準的組み合わせとなっている. 胸部照射では，① 併用時期，② 分割照射法，③ 線量，④ 照射野について議論されている. 治療成績を向上させるためには，化学療法・放射線療法の併用時期が重要で，胸部照射の併用時期は治療開始から早い時期に化学療法と同時に行うことが望ましいとされている. ErridgeとMurray[30]は，治療開始から放射線治療終了までの期間を化学放射線療法のpackageと定義すると，代表的臨床試験の中で生存期間中央値・2年生存率が優れているのは，このpackage期間が6週以内の治療群であるとしている(Fig. 3).
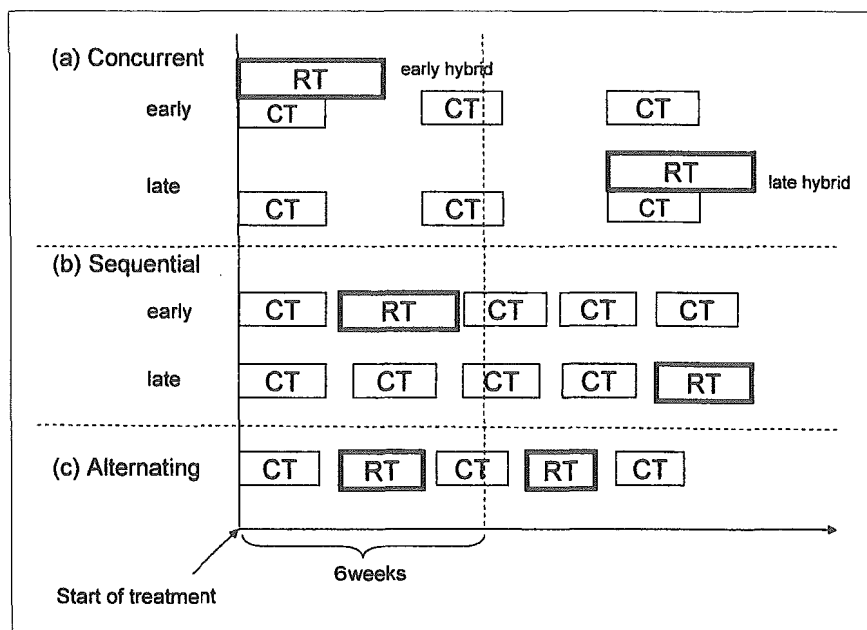

Fig. 3　Sequencing and timing of the chemotherapy and radiotherapy for limited stage small cell lung cancer
The duration of the chemoradiation package for limited stage small cell lung cancer trials may be difiend as the time elapsed from the first therapeutic intervention until the completion of the radiotherapy. Generally, the best median and 2-year survival outcomes are associated with a chemoradiation package duration of 6 weeks or less[30].

　線量は単純分割照射法で55Gy以上は必要と考えられているが，最近では1回1.5Gy1日2回の加速過分割照射法がよいとする臨床試験の結果が報告され[31]，米国では加速過分割照射法が標準的照射法になりつつある.

　しばしば論争されてきたのは小細胞肺癌の脳転移に対する予防的全脳照射の是非である. 大規模なメタアナリシスの結果，PCIはComplete Response(CR)例に限れば脳転移再発の頻度を著しく低下させるばかりでなく，有意に生存率を向上させることが明らかとなった[32]. また，PCIの中枢神経機能への影響は明らかではなく，これらの結果から，PCIは小細胞癌のCRあるいはCRに近い効果がえられた症例の標準治療として行われつつある. PCIの線量については25Gy/10回以上の線量が推奨されているが，PCIの至適線量，施行時期について，さらに検討が進められている. ただし，PCIによる有害反応の軽減には1回線量2.5Gy以下が望ましい. また，化学療法との同時併用は精神神経症状の増強をもたらす可能性があることから，PCI施行前後の1週間は化学療法を控えるべきとされている[29].

まとめ

　非小細胞肺癌の放射線治療では，腫瘍径の小さいものほど根治性は高い. 進行例では原発部位やリンパ節転移部位が治療の成否に関わり，組織型では扁平上皮癌が最もよい適応と考えられる. 最近では治療機器の進歩により局所への大線量投与が可能となり，局所制御率も向上しつつある. 今後，局所制御率の向上は扁平上皮癌の治療成績向上に大きく貢献するものと期待されるが，非扁平上皮癌の治療成績向上には化学療法の併用も重要な課題である.

　小細胞肺癌の治療成績はプラチナ製剤の登場により著しく向上したが，局所制御に果たす放射線治療の役割は大きく，照射方法にはまだ議論の余地がある.

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Segmental multileaf collimator （SMLC)-IMRTにおける
線量照合と評価
—第一報：線量分布—

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DOSIMETRIC VERIFICATION AND EVALUATION OF SEGMENTAL MULTILEAF COLLIMATOR (SMLC)-IMRT FOR QUALITY ASSURANCE
—THE FIRST REPORT: DOSE DISTRIBUTIONS—

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Abstract: Intensity-modulated radiation therapy (IMRT) was developed to irradiate the target are more conformally, sparing organs at risk (OARs). Since the beams are sequentially delivered by many, small, irregular, and off-center fields in IMRT, dosimetric quality assurance (QA) is an extremely important issue. QA is performed by verification of both the dose distribution and doses at some arbitrary points. This paper reports verification of dose distribution in our hospital for Segmental multileaf collimator (SMLC)-IMRT

The calculated dose distribution was compared with that acquired by film measurements. In film dosimetry, we used two kinds of the radiographic film (Kodak X-OmatV and EDR2) and Tough Water (Kyoto Kagaku Co. Ltd) as a water equivalent phantom and the dose distribution calculated of any plane by using a FOCUS (CMS Co. Ltd) Radiation Treatment Planning System (RTP). In general, film dosimetry is a method for obtaining the relative dose distribution, because the film sensitivity changes variably with the distribution of photon energy corresponding to the field size and set-up depth of the film in a phantom.
We studied the physical characteristics and properties of these two different films. X-OmatV film showed higher dose values as the irradiated volume increased in a phantom but EDR2 film was seldom affected by scattering volume. Therefore we decided to use EDR2 for verification of dose distributions for intensity-modulated beams rather than X-OmatV.

The film method is not widely accepted for absolute dosimetry, but we thought that it might be able to be used for absolute point-dose verification with EDR2. To verify three-dimensional (transverse, coronal, sagital) dose distributions, some radiographic films put between layers of Tough Water were irradiated and the corresponding calculated dose distributions were obtained with RTP with using CT images of the same phantom. The two-set isodose curves on the dose distribution keep almost the same shape and they had good agreement in high regions of the dose gradients. In low regions of the dose gradients of the phantom, the doses differences were within about 3%.

This difference between the paired set-dose profiles were about 20 cGy on and the deviation distance was about 1.5 mm. The discrepancy in high regions of the dose gradients may be affected by the geometrical accuracy of the MLC leaves movements. If errors of MLC leaves position are about 1.5 mm, the according output change is within about ±0.1%. We supposed that dose distributions were not significantly influenced by the deviation of output due to the accuracy of the MLC leaves positions.

Key words: Intensity-modulated radiation therapy, Dosimetry, Quality assurance, Film dosimetry

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はじめに

現在の放射線治療技術には急速な進歩がみられている．特に，外部照射法においては二次元的な病巣の広がりに対応した固定照射技術に対して，高橋ら[1]によるMulti Leaf Collimator（以下，MLC）を用いた原体照射法は三次元的な腫瘍に線量を集中することを可能にした．その後，高度先進技術の発展によりMLCはコンピュータ制御となり，原体照射法や不整形照射野の形成が容易になった．さらに，可動絞りの位置におけるモニタ単位をコンピュータ制御し一次元における線量の強度変調技術（dynamic wedge）が臨床へと応用された[2)-4)]．

しかしながら，脊髄で代表されるリスク臓器（Organ at risk：以下，OAR）を取り囲む腫瘍に対して，これを避けながら腫瘍に充分な線量を投与することは困難であった．このような状況で，MLCなどを用いた二次元における強度変調技術を可能にする強度変調放射線治療（intensity modulated radiation therapy：以下，IMRT）が開発され[5)-8)]，腫瘍へ一層の線量集中と腫瘍周辺のOARや正常組織の温存を図れるようになった．

MLCを用いたIMRTはSegmental multileaf collimator（step and shoot）[7]とDynamicl multileaf collimator（Sliding Window）IMRT[8]がある．Segmental multileaf collimator（SMLC）-IMRTは治療計画装置（Radiation Treatment planning system：以下，RTP）で計算されるIntensity Mapを任意に設定するIntensity Levelで分割[9), 10)]し，これにより得られた複数の不整形照射野（segments：以下，セグメント）を連続的に照射して最適な線量分布を得る方法である．一方，Dynamic multileaf collimator（DMLC）-IMRTはMLCを連続的に動作させる方法でIntensity Mapの再現に理想的であるが，MLCの高い動作精度が求められる[11), 12)]．いずれの方法も腫瘍に高線量を集中させOARには最小線量となるように不整形照射野を連続して照射するため，放射線治療の品質保証（Quality Assurance：以下，QA)[11)-16)]の重要性が強く言われるようになってきている．

IMRTのQAは直線加速器やMLCなどの機器的なQA[12), 16)]と線量の検証に関わるQA[11)-13), 15)]などがある．線量の検証は線量分布や任意の点での絶対線量の検証などがある．

フィルム法での線量分布の測定はフィルムの高原子番号の物質（臭化銀）のため光電効果領域の光子に対してエネルギー依存性が大きい．従って，照射される体積（散乱領域）が大きいほど線量が高く評価される[17)-20)]．一般的に用いられるX-OmatVフィルム（Kodak社）において4 MV X線，照射野サイズ25×25 cm²でファントムの深さ5 cmに対する深さ15 cmにおけるフィルムの感度は4％増加すると報告されている[13), 17), 19)]．しかしBurchら[18]は12％の増加を報告して発表者による相違が認められる．また，Danciuら[19]とTsaiら[13]もSykesらとほぼ同様の結果を示している．

X-OmatVフィルムを用いたIMRTの検証でJuら[20]はフィルムによる線量が電離箱に対し約15％増加するが，Burchら[18]

の方法を用い約3％以下にしている．線量分布の検証においてLoSassoら[15]はRTPとフィルムの線量分布で約10％の相違を報告しているがWangら[11]は2％以下で検証が可能であると言っている．

当院では下段絞り兼用のMLCを搭載した直線加速器を用いたSegmental multileaf collimator（SMLC）-IMRTを行っており本研究では我々が行っている線量分布の検証について検討を加え報告する．

方　法

人体に照射される線量を直接的に測定する事は現実的に困難である．Wangら[11]やLoSassoら[15]は不均質が小さければ，人体におけるRTPの計算値と実測値の比率は密度の均質なファントムにおける両者の比率と同じであると仮定して線量検証を行っている．我々も同様にRTPを使用した治療計画の結果で得られたIMRTビームを用い，人体を固体ファントムに置き換え，照射およびRTPにおいて計算することで線量におけるQAを行っている．Fig. 1に線量におけ
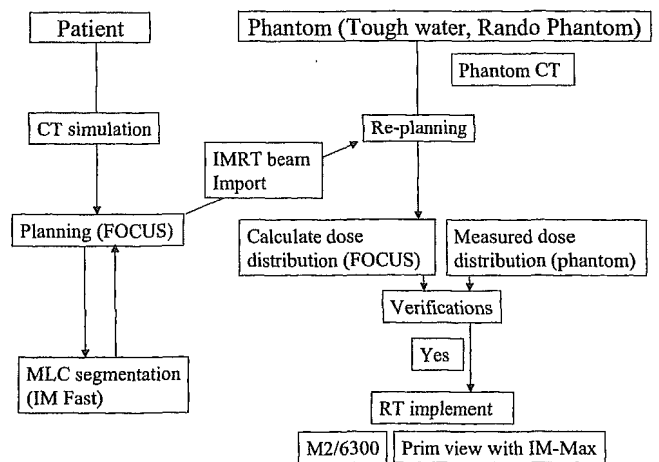

Fig. 1　Flow chart of dosimetric verification Segmental mulileaf collimator-IMRT.
Radiation treatment planning is performed by inverse planning using the CT image of a patient with a FOCUS Radiation Treatment Planning system (RTP). Intensity maps are calculated from the RTP. These maps are imported to IM-FAST™, segmented to many fields and monitor units accordingly. The segments are export to the RTP and the dose calculated.
The CT images of a water equivalent phantom (Tough Water phantom) using quality assurance are transferred to the RTP. The dose distribution (or dose) for the patient derived from radiographic film (or ionization chamber)-exposed in Tough Water phantoms to IMRT beams, is compared with the dose distribution (or dose) for the same beams calculated at the same position in the Tough Water phantoms in the RTP.
The verification is compared with the measured dose and the calculated dose.
IMRT is implemented as results of the verifications of the absolute dose and dose distribution.

るQAの手順を示す．患者のCT画像をRTPに転送しinverse planning（2-1.で後述）を行う．計算されたintensity mapをMLC segmentationアルゴリズム（IM-Fast™，2-2.で後述）にインポートし，再現可能な複数の照射野（segments）に対するモニター単位に分割する．これらのデータをRTPにエクスポートし線量計算を行う．QAに使用するファントムのCT画像をRTPに転送する．患者のIMRTのビームデータをファントムに置き換えて線量計算する．次に，直線加速器（M2/6300，1.で後述），各セグメントを自動的に照合・照射するPrim-viewおよびこれを高速化するためのIM-MAXを使用し，ファントムのビームデータをRTPと同じ幾何学配置でファントムに照射し実測値を得る．RTPと実測値の線量および線量分布を検証し治療を実施する．

1. 使用器材

直線加速器は4 MV X線を発生するSiemens社製M2/6300でMLCと下段絞り（X方向：X絞り）が兼用である．このMLCは対向する29対のLeaf構成（X1（1）からX1（29），X2（1）からX2（29），（　）内はLeaf番号）で各Leaf番号はYの正方向に増加する．コリメータ回転中心軸に存在す

るLeaf番号は15番（X1（15）とX2（15））である．架台回転中心面での各Leaf幅はLeaf番号が1番（X1（1），X2（1））と29番（X1（29），X2（29））は6.5 cm，それ以外は1cmである．X1（X2）の可動範囲はX軸上で-10 cmから+20 cm，Y1（Y2）はY軸上で-7 cmから+7 cmで最大照射野は40×40 cm²である．ただし，MLCで照射野を作成する際は閉じている最外縁のLeafまで上段絞りは自動的に絞られる（auto coverage）．RTPはFOCUS（version3.1，CMS社製）を用い，線量計算アルゴリズムはSuperposition法を使用した．

線量分布照合はファントムとして均質な固体ファントム（Tough Water，京都科学社製）を用いた．フィルムは報告が多いX-OmatV（Kodak社製）とEDR2（Kodak社製）を用いた．フィルムスキャナーはVXR-16（Vidar Systems社製）とフィルム解析ソフトはRIT113（version1.3，Radiological Imaging Technology社製）を使用した．絶対線量の測定には電位計にIonex Dose Master 2590B（NE Technology社製），電離箱はFarmer型電離箱（NE2581 0.6 cc，NE Technology社製）と電離容積の小さい電離箱（PinPoint 0.015 cc，PTW社製：以下，PinPoint電離箱）を使用した．
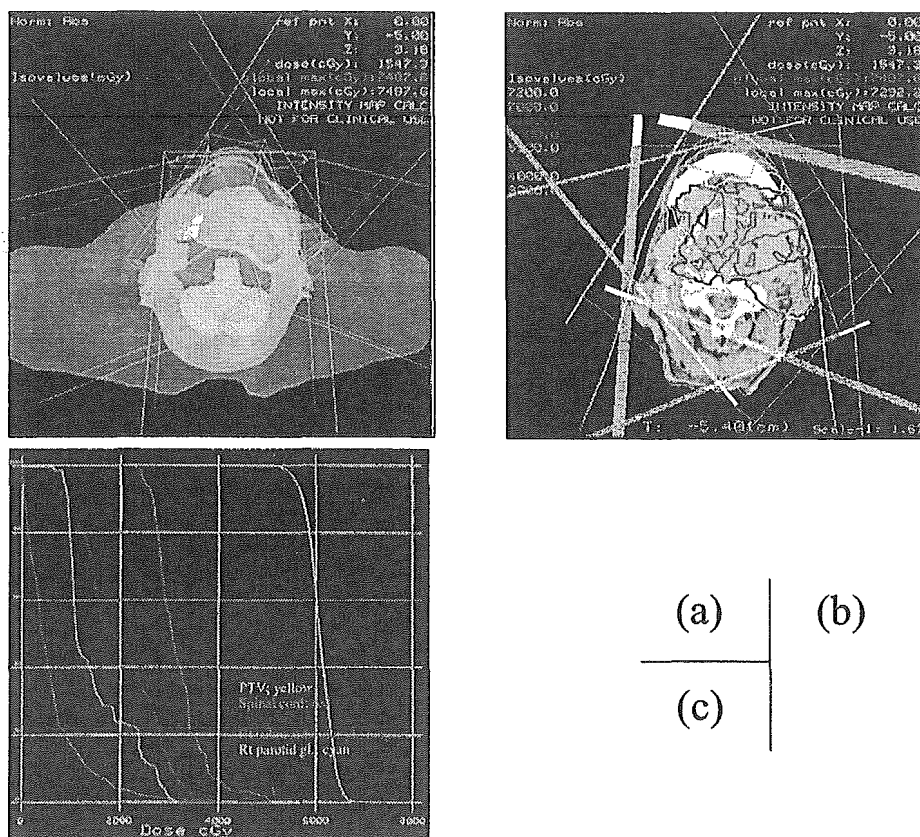

Fig. 2　(a) Tumor and organs at risk (OARs) of mesopharyngeal tumor.
Tumor is red, brain and submaxillary salivary gland on the right are yellow, the submaxillary salivary gland is blue and Planning Target Volume (PTV) is white.
The gantry angles of IMRT beams for five directions are 0, 72, 144, 216, and 288 degrees, respectively.
Dose distributions (b) and dose volume histograms (c) for tumors and OARs were calculated according to intensity maps.

2. IMRTの治療計画

2-1. inverse planning

IMRTの治療計画はBrahme[21]によって提唱された inverse planningを用いた.

まず，予め決定した標的，PTVとOARに対し最低線量 （minimum dose）と最高線量（maximum dose）およびそ れぞれの許容容積の割合（または重要度，importance weight）を入力する．次にビームの門数とその入射方向 を入力する．目的とする線量分布と最適化で計算される 線量分布の違いを最低線量，最高線量と許容容積の割合 を示す目的関数にて評価する．RTPは目的関数に基づき 繰り返し（Iteration）を行う．最適化アルゴリズムは繰 り返しバックプロジェクション法[22]，シュミレイテッド アニーリング法[23]および，グラディエント サーチ法[24]な どがある．

今回使用したRTPは繰り返しグラディエント サーチ法 を採用している．inverse planningの結果，空間上の線量 強度が最適化され各々のビームにおけるintensity mapが 作成される．最適化されたintensity mapに基づく一次光 子の線量分布とDose Volume Histogram（以下，DVH）を 検証する．Fig. 2に中咽頭腫瘍に対する治療計画例を示 す．5門のIMRTビームの架台角度はビーム1から5でそれ ぞれ0，72，144，216および288度である．この症例にお けるinverse planningにおける最適化条件（Dose constraints） はPTVに対し0.5 cmの三次元的なマージン領域（PTV+0.5 cm）およびGTVに対し最小線量60 Gy，最大線量64 Gyお よびゴール線量64 Gyを設定した．また，脊髄に対し0.3 cmの三次元的なマージン領域（Spinal cord+0.3 cm），左 右の耳下腺および右顎下腺は最大線量30 Gy，患者に対し ては最大線量40 Gyを設定した（Table 1）．

Table 1　Optimimal conditions in the inverse plan of the RTP (FOCUS).

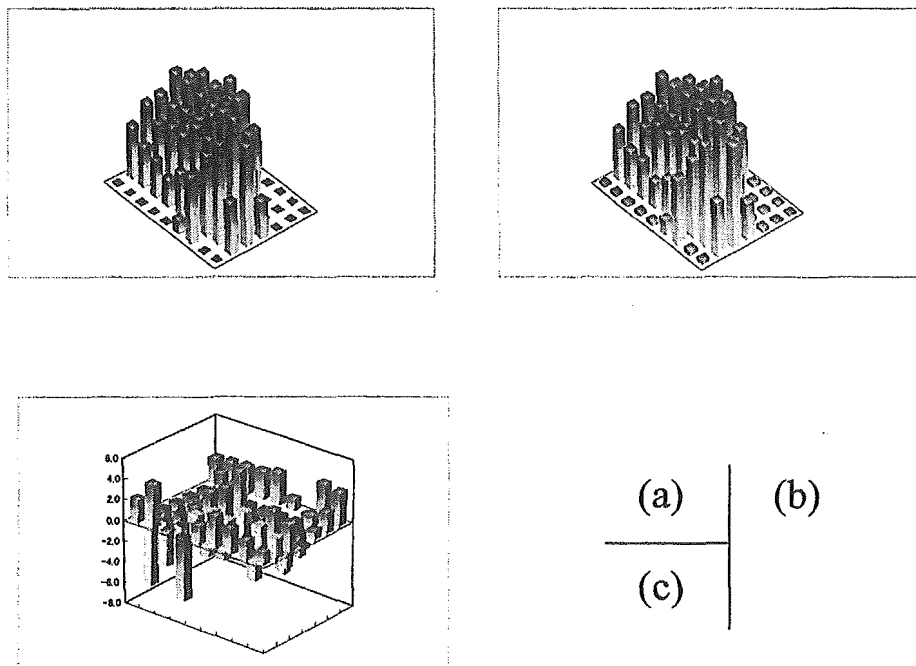| Structure	minimum dose	maximum dose	goal dos	important weight
PTV+0.5 cm	60 Gy	64 Gy	64 Gy	100
GTV	60 Gy	64 Gy	64 Gy	100
Spinal cord+0.3 cm	-	30 Gy	-	95
Lt. parotid gl.	-	30 Gy	-	80
Rt. parotid gl.	-	30 Gy	-	90
Rt. submandibular gl.	-	30 Gy	-	90
Patient	-	40 Gy	-	5

Fig. 3　Intensity maps were derived from RTPs (a) and IM-FAST™ (b). (c) is the deference between (a) and (b).
The algorithms of IM-FAST™ were used optimal with a standard including correction of fluence. Intensity level was 10.

2-2. MLC segmentation

Segmantal multileaf collimator IMRTはRTPで最適化されたIntensity MapをMLC segmentationアルゴリズム[9], [10]を用いて再現可能な複数の形状の照射野に分割する．我々は専用装置のIM-Fast™（Version1.04，Siemens社製）を使用している．RTPで最適化されたIntensity MapをIM-Fast™に転送し，任意に強度レベル（intensity level）を設定すると自動的にsegmentationがなされる．

IM-Fast™は標準法，スライス法，プラットフォーム法，標準+最適法とプラットフォーム+最適法の5つの基本となるsegmentationアルゴリズムがある．さらに，MLCやフラットニングフィルタからのX線の発生などの特性を考慮してのTongue and Grove，Match Line，Single ApertureとFluenceの4つの補正が可能である．RTPで発生させたIntensity Mapとsegmentation後のIntensity Mapを比較し適切なものを採用する．2-1.の臨床例における両者の比較をFig. 3に示す．ただし，IM-FastTMのアルゴリズムは標準+最適法を用いた．補正はFluenceを使用し，Intensity levelは10を用いた．全てのアルゴリズムおよび補正の組み合わせでsegmentationを行ったが，本症例では標準+最適法でsegmentation前後のIntensity Map間の相違がほぼ最小になった．これはPotterら[10]の結果とほぼ同様である．

また，分割されたセグメントとMUをRTPに転送し実際に使用する最終的な線量分布の再計算を行う．Fig. 4に最終的な線量分布およびDVHを示す．

3. 線量分布の照合

線量の検証は2-2.で決定したIMRTビームを固体ファントムに照射し，実際に測定することで行った．

フィルムを挟んだRTP上の固体ファントムのCT画像を用いて再計算する．実際の照射はフィルムで測定できる最高線量を越えないようX-OmatVは約1 Gy，EDR2は約4 GyとしRTPで得た同じMUを比例的に減少させ固体ファントムに照射する．

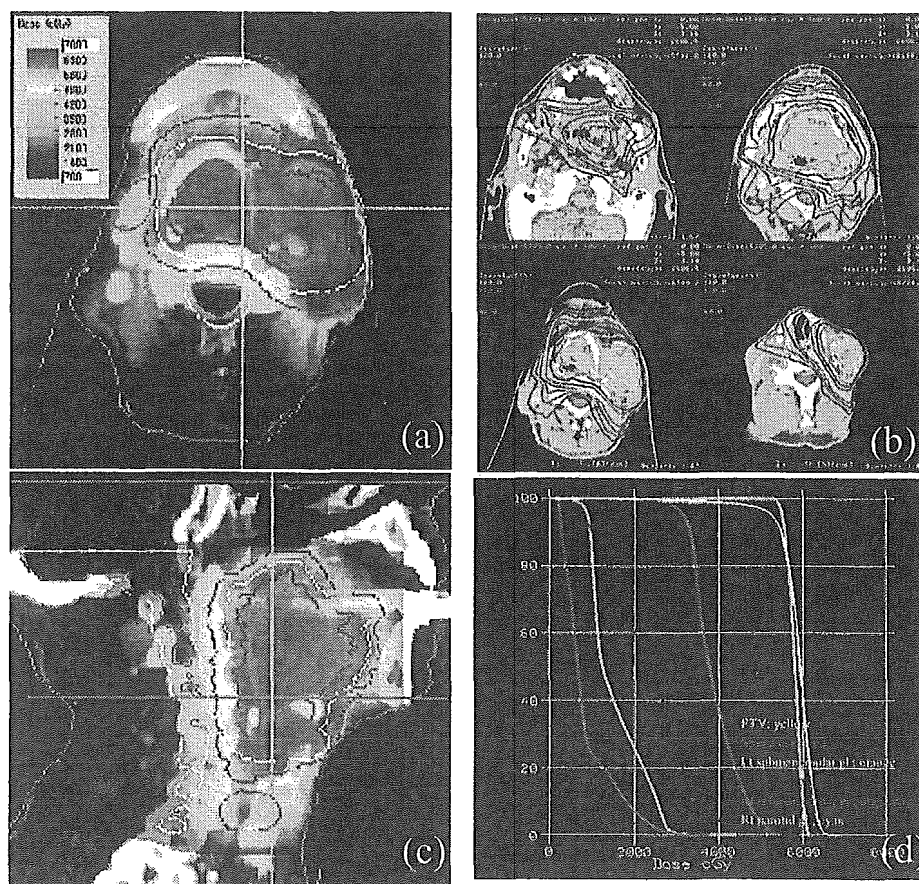フィルムはエネルギー依存性があり照射野が大きい場合やファントムの深部領域などの照射容積が多くなる場合は低エネルギー散乱線が多く含まれ，測定される線量が高く

Fig. 4 (a,b,c) The dose distributions and (d) dose volume histograms (DVH) of a mesopharyngeal tumor treated by IMRT.
The dose distribution shows that the doses for the spinal cord and the salivary gland could be decreased.
The index for implementation of IMRT at our hospital. The ratio of the dose at the 90% of the DVH to the dose at 5% of the DVH of the PTV is less than 20%.

評価されることが予想される[17)-20)]. そこで, 照射容積の変化に対する線量をフィルムとPinPoint電離箱で測定した. 照射野サイズは1×1 cm²から10×10 cm²まで任意に設定した. さらに, IMRTビームのフィルムへの照射はRTPで得たMUを比例的に小さくするためMUと線量の直線性を測定した. フィルムおよびFarmer型電離箱を用い, 照射野サイズ10×10 cm², MUは1 MUから100 MUまで任意に変化して行った. ただし, フィルム（電離箱）の測定は固体ファントムを用い線源フィルム（検出器）間距離100 cm, フィルム（電離箱）はX線ビームに対し垂直に最大線量深（1.0 cm）に配置し, ビーム中心軸を測定点とした.

フィルムの特性曲線の作成は従来の方法[18)]の一枚のフィルムに任意の照射野で照射して得られた黒化度と電離箱で得られた線量で作成している. しかし, 特性曲線の作成と線量の検証で照射したフィルムは同一の現像処理の必要がある[25)]. 従って, 従来の方法では非常に時間を必要とする. そこで, 我々は, 直線加速器の自動照合・照射機能を使用し, 照射野サイズをY2=15 cm, X=30 cmと一定にし, Y1を15 cm, 10 cm, 5 cm, 0 cm, -5 cmおよび-10 cmの計6個の照射野に対して任意のMUを設定し, 一枚のフィルムに照射した. また同様にFarmer型電離箱で線量を測定した. ただし, 固体ファントムを用い線源フィルム（電離箱）間距離100 cm, フィルム（電離箱）はX線ビームに対し垂直に最大線量深（1.0 cm）に配置した. 測定点はY1が15 cm, 10 cm, 5 cm, 0 cm, -5 cmおよび-10 cmの計6個の照射野に対しY軸上でそれぞれ12.5 cm, 8.5 cm, 2.5 cm, -2.5 cmおよび-8.5 cmとした. また, 電離箱による測定は各照射野の照射が完了するまで行った.

IMRTは三次元の強度変調があるため三次元的な線量分布の検証が必要である. そこで, 固体ファントムは任意の厚さを用い全体で30×30×30 cm³の大きさを作成し, その中心を架台回転中心とした. フィルムはIMRTビームに対して平行にY：0 cm, Y±0.5 cm, Y±1 cm, Y±2 cmとY±3 cmの位置に計9枚挟み, 9つの横断面の線量分布を取得した（Fig. 5）. また, 架台角度が0度に対して垂直にフィルムをファントム中心に配置して照射し, 体軸を直交する冠状面の線量分布も検証した. 設定MUはフィルムで測定できる最高線量を越えないようX-OmatVとEDR2でそれぞれ, 1/80, は1/20と比例的に減少させた.

さらに, 各5門のIMRTビームの線量分布と線量プロファイルを検証するために, 各々のIMRTビームを架台角度0度に変更し固体ファントムに照射した. ただし, フィルムはIMRTビームに垂直に深さ5 cmに配置した. 線源フィルム間距離100 cmである. 設定MUはX-OmatVとEDR2でそれぞれ, 1/10, は1/3と比例的に減少させた.

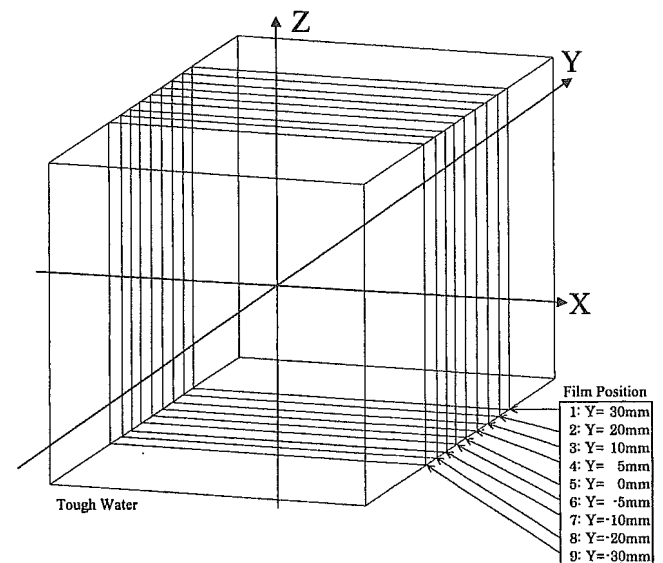また, 特性曲線の作成と線量の検証で照射したフィルムは同一の現像処理を行った. フィルムの黒化度のデジタル

Fig. 5 (a,b,c) The dose distributions and (d) dose volume histograms (DVH) of a mesopharyngeal tumor treated by IMRT.
The dose distribution shows that the doses for the spinal cord and the salivary gland could be decreased.
The index for implementation of IMRT at our hospital. The ratio of the dose at the 90% of the DVH to the dose at 5% of the DVH of the PTV is less than 20%.

Table 2　The doses derived from a PinPoint ionization chamber and radiographic films (X-OmatV and EDR2) in irradiated 1×1 cm² to 10×10 cm² fields. The deviation is for the dose of radiographic film (X-OmatV and EDR2) to the PinPoint ionization chamber. The measurement depth was the maximum depth (1.0 cm).

Side of square field (cm)	PinPoint (cGy)	X-OmatV (cGy)	Dev. (%) (X-OmatV)	EDR2 (cGy)	Dev. (%) (EDR2)
1	64.55	59.76	7.42	63.50	1.62
2	85.83	76.89	10.41	84.50	1.55
3	90.24	80.50	10.79	88.71	1.69
4	92.00	84.07	8.62	91.09	0.98
5	93.67	87.41	6.69	93.10	0.61
6	95.12	90.46	4.89	94.32	0.84
8	97.79	93.90	3.97	97.66	0.12
10	99.82	96.53	3.30	99.85	-0.03