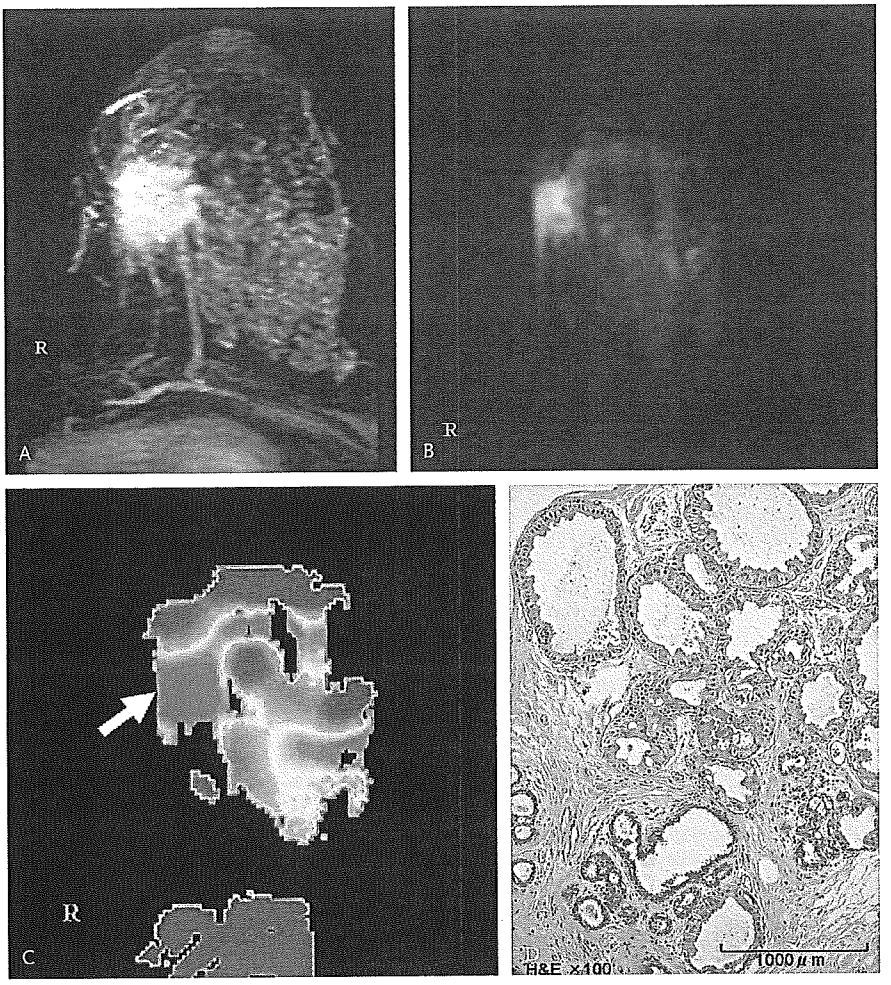

FIGURE 3. A case of solid tubular carcinoma that showed a low ADC area around the mass lesion. A, Maximum intensity projection (MIP) image of subtraction image. An enhanced mass lesion is evident in the right area. There is diffuse nodular enhancement around the mass lesion. B, DWI in the axial plane. There is a high-intensity lesion on the right side that demonstrates the carcinoma lesion (b-value = 750 s/mm^2). C, Axial plane ADC map (b-value = 750 s/mm^2). The green area (arrow) indicates the low ADC area (ADC < 1.3). The area of low ADC value in the right side represents IDC (ADC value = 1.1 × 10^{-3} s/mm^2). In the surrounding green area, ADC value = 1.5 × 10^{-3} s/mm^2. D, Histologic appearance of the benign hyperplasia adjacent to carcinoma in concordance with the area of low ADC value (H&E, ×100). Marked apocrine metaplasia is seen.

In 78% of our cases, carcinoma spread was almost precisely detected by the ADC map. This result shows that DWI could be used for the preoperative examination of cancer extension.

In this study, the b-value was 750 s/mm^2, which is lower than recommended. By using a higher b-value, the ADC value would be less affected by perfusion, and the ADC discrepancy between malignant and benign lesions could be larger, as the perfusion effect would be much more in malignant lesions than benign lesions because of tumor angiogenesis.[2] However, a high b-value would require a long TE and would cause distortion of the image. Using new technology such as parallel imaging, DWI will provide higher sensitivity and detectability for breast cancer.[8] Because our study showed a high sensitivity for malignancy and cancer spread, a b-value of 750 s/mm^2 was sufficient to retain image quality and to obtain a high sensitivity for the diagnosis of breast cancer.

EPI has a magnetic susceptibility artifact. One of our false-negative cases and one underestimated case showed hemorrhage and hemosiderin deposition in the area where the ADC map did not show low ADC value despite the existence of a carcinoma compartment. It was considered that a blood component caused a magnetic susceptibility artifact and resulted in a high ADC value. This type of false-negative result will be predictable because T1-weighted images showed high-intensity lesions where the hemorrhagic component was present in these two cases (see Fig. 5); also, it is possible that bloody

TABLE 3. Histopathologic Detail of Groups 3 and 4

Case	Group	Group Description	Tumor Size (mm)	Pathology
1	3	Underestimate	20 × 10	Lobular Ca
2	3	Underestimate	20 × 20	Comedo-type DCIS with hemorrhage and necrosis
3	3	Underestimate	25 × 15	Lobular Ca
4	4	False-negative	20 × 20	Intracystic papillary Ca surrounded by comedo-type DCIS with hemosiderin deposition and hemorrhage

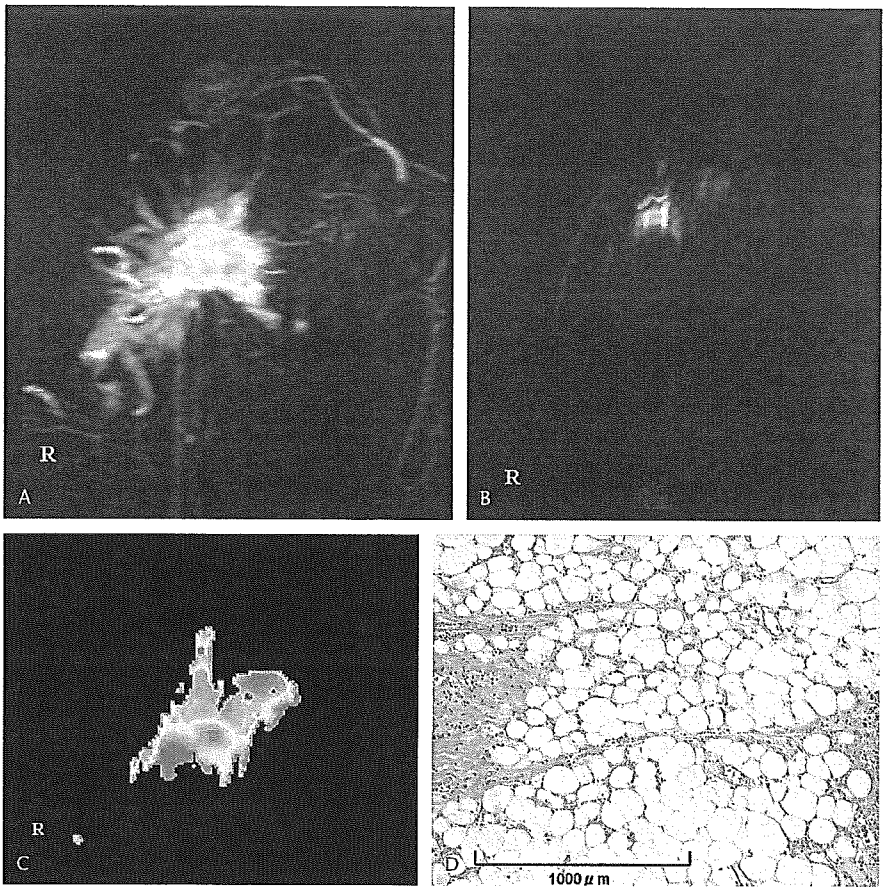

FIGURE 4. A case of lobular carcinoma with widespread carcinoma component over mammary gland and fatty tissue. A, MIP image of subtraction image. There is an enhanced tumor with segmental nodular enhancements around which is an extensively invasive component. B, DWI shows localized high-intensity lesion in Carea area (b-value = 750 s/mm^2). C, ADC map shows ADC decrease referring to the center of the tumor. Invasive compartment around the center of the tumor is not depicted on the ADC map. D, Histologic appearance of the area where the ADC map did not show ADC reduction (H&E, ×100). Sparse and scattered distribution of cancer cells is shown in the fat tissue.

secretion will be observed on physical examination in such cases. In addition, these two cases had necrotic compartment referring to comedo-type DCIS. Noguchi et al mentioned high ADC values of necrosis in brain tumors.[11] Conversely, brain abscess showed a low ADC value. They hypothesized that the reason for this discrepancy was viscosity differences: the viscosity is low in tumor necrosis but high in brain abscess because of the packing of molecules and leukocytes. In our cases, though a low ADC area in DCIS lesions would mainly be affected by susceptibility artifacts, necrosis may have had some influence on high ADC values.

Another factor that affects ADC values is the architecture of tumors. In our study, the ADC map did not detect the sparse distribution of lobular carcinoma in two cases. Guo et al reported that a 4-mm-diameter DCIS was not visualized on DWI.[16] The distribution of scattering small cores as in DCIS and the marginal lesions of lobular carcinoma will be difficult to be seen on an ADC map. Spatial resolution will be one of the factors to affect the resolution of the ADC map. Guo et al[16] and Sinha et al[22] showed that the ADC value has relevance to cell density: the mean ADC value was in inverse proportion to cell density. The disparity of the ADC value between IDC and NIDC originates from cell density as well.[20]

Our study revealed that the major factor of overestimation for cancer invasion is benign proliferative change. More than half of the overdiagnosed cases showed benign proliferative change in low ADC areas where no carcinoma existed. Distribution of low ADC values referring to benign proliferative change showed a segmental and spotty distribution, similar to the one of DCIS. Moreover, the ADC value of benign proliferative lesions overlaps with that of malignant tumor. The overlap range between breast cancer and benign proliferative lesions was 1.3 to 1.5 × 10^{-3} mm^2/ sec. Although the low ADC value of benign proliferative lesions may be due to high cellularity, leukocytes, and fibrosis because of inflammatory change, the cause is still uncertain.

Among the factors that will affect ADC values are magnetic susceptibility, cellularity, tumor size and distribution, and tissue component. In addition, spatial resolution and the signal-to-noise ratio of DWI will affect the sensitivity and specificity for breast malignant lesions. However, we expect that these issues will be improved with advances in imaging instruments and software.

This study showed that DWI has high sensitivity for breast malignant tumors and has the potential to be used to analyze cancer extension. Benign proliferative change is a major factor in false-positive results and overestimation of cancer extension on the ADC map. Magnetic susceptibility and the limit of spatial resolution cased false-negative results and underestimation of tumor extension. These issues may be

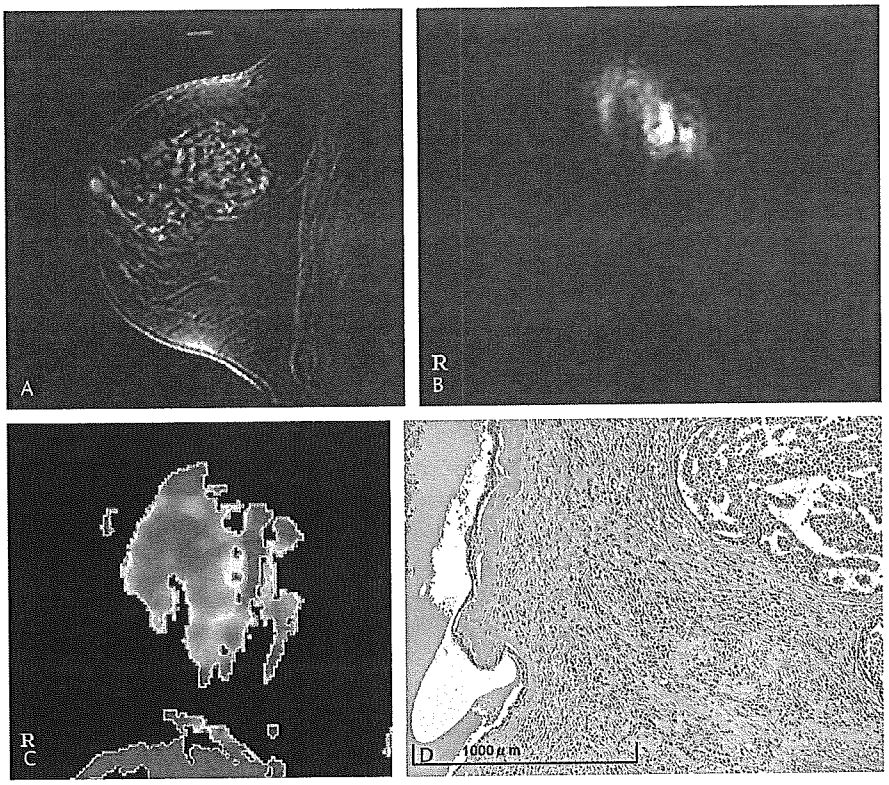

FIGURE 5. A case of intracystic papillary carcinoma with comedo-type DCIS surrounding it. A, 3D FSPGR before contrast enhancement. Note high-intensity lesion adjacent to the main tumor. It suggests a hemorrhagic lesion. B, DWI shows the main tumor as a high-intensity lesion (b-value = 750 s/mm^2). C, Axial plane ADC map shows no ADC decrease. D, Pathologic figure around the main tumor shows hemosiderin-laden macrophages adjacent to the carcinoma. There is also sporadic comedo-type DCIS distribution containing hemosiderin-laden macrophages and necrotic tissue (H&E, ×100).

solved by advances in MRI hardware and software. DWI could be one of the tools used for breast cancer diagnosis, evaluation of tumor extension, and screening because of its short scan time and high sensitivity.

REFERENCES

1. Tamaki Y, Akashi-Tanaka S, Ishida T, et al. 3D imaging of intraductal spread of breast cancer and its clinical application for navigation surgery. *Breast Cancer*. 2002;9:289–295.
2. Buadu LD, Murakami J, Murayama S, et al. Breast lesions: correlation of contrast medium enhancement patterns on MR images with histopathologic findings and tumor angiogenesis. *Radiology*. 1996;200:639–649.
3. Bone B, Aspelin P, Brouge L, et al. Sensitivity and specificity of MR mammography with histopathologic correlation in 250 breasts. *Acta Radiol*. 1996;37:208–213.
4. Schelfout K, Van Goethem M, Kersschot E, et al. Contrast-enhanced MR imaging of breast lesions and effect on treatment. *Eur J Surg Oncol*. 2004; 30:501–507.
5. Leach MO. Assessing response to treatment in breast cancer using magnetic resonance. *J Exp Clin Cancer Res*. 2002;21:39–45.
6. Rieber A, Brambs HJ, Gabelmann A, et al. Breast MRI for monitoring response of primary breast cancer to neo-adjuvant chemotherapy. *Eur Radiol*. 2002;12:1711–1719.
7. Kaiser WA, Mittelmeier O. MR mammography in patients at risk. [in German] *Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr*. 1992; 156:576–581.
8. Siegmann KC, Müller-Schimpfle M, Schick F, et al. MR imaging-detected breast lesions: histopathologic correlation of lesion characteristics and signal intensity data. *AJR Am J Roentgenol*. 2002;178:1403–1409.
9. Orel SG, Schnall MD, LiVosi VA, et al. Suspicious breast lesions: MR imaging with radiologic-pathologic correlation. *Radiology*. 1994;190: 485–493.
10. Warach S, Boska M, Welch MK. Pitfalls and potential of clinical diffusion-weighted MR imaging in acute stroke. *Stroke*. 1997;28:481–482.
11. Noguchi K, Watanabe N, Nagayoshi T, et al. Role of diffusion-weighted echo planar MRI in distinguishing between brain abscess and tumour: a preliminary report. *Neuroradiology*. 1999;41:171–174.
12. Kim T, Murakami T, Takahashi S, et al. Diffusion weighted single-shot echoplanar MR imaging for liver disease. *AJR Am J Roentgenol*. 1999; 173:393–398.
13. Namimoto T, Yamashita Y, Sumi S, et al. Focal liver masses: characterization with diffusion-weighted echo planar MR imaging. *Radiology*. 1997;04:739–744.
14. Kuroki S, Nasu S, Murakami K, et al. Pancreatic cancer on DWI. *Nippon Acta Radiol*. 2003;63:S184.
15. Englander SA, Ulug AM, Brem R, et al. Diffusion imaging of human breast. *NMR Biomed*. 1997;10:348–352.
16. Guo Y, Cai YQ, Cai ZL, et al. Differentiation of clinically benign and malignant breast lesions using diffusion-weighted imaging. *J Magn Reson Imaging*. 2002;16:172–178.
17. Lyng H, Haraldseth O, Rofstad K. Measurement of cell density and necrotic fraction in human melanoma xenografts by diffusion weighted magnetic resonance imaging. *Magn Reson Med*. 2000;43:828–836.
18. Sugahara T, Korogi Y, Kochi M, et al. Usefulness of diffusion weighted MRI with echo-planner technique in the evaluation of cellularity in gliomas. *J Magn Reson Imaging*. 1999;9:53–60.
19. Noguchi K, Watanabe N, Nagayoshi T, et al. Role of diffusion weighted echo-planner MRI in distinguishing between brain abscess and tumour: a preliminary report. *Neuroradiology*. 1999;41:171–174.
20. Kuroki Y, Katsushiro N, Kuroki S, et al. Diffusion-weighted imaging of breast cancer with the sensitivity encoding technique: analysis of apparent diffusion coefficient value. *MRMS*. 2004;3:79–85.
21. Bammer R. Basic principles of diffusion-weighted imaging. *Eur J Radiol*. 2002;45:169–184.
22. Sinha S, Lucas-Quesada FA, Sinha U, et al. In vivo diffusion-weighted MRI of the breast: potential for lesion characterization. *J Magn Reson Imaging*. 2002;15:693–704.

Successful Treatment of Concurrent Chemoradiotherapy for Stage I Nasal NK/T Cell Lymphoma: A Report of Two Cases

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Abstract. *Nasal natural killer/T cell (NK/T cell) lymphoma is a rare subtype of lymphomas, being a subtype of non-Hodgkin's lymphoma with a much worse prognosis than other subtypes. One reason for this worse prognosis is that nasal NK/T cell lymphoma is resistant to standard sequential chemoradiotherapy. Thus, we adopted concurrent chemoradiotherapy using a CHOP-like regimen for treating stage I nasal NK/T cell lymphoma. Case 1 was treated with concurrent chemoradiotherapy using 41-Gy irradiation with 12 cycles of the CHOP-like regimen (THP-CVP). Case 2 was treated with concurrent chemoradiotherapy using 50-Gy irradiation with 10 cycles of THP-CVP. In both Case 1 and Case 2, the tumors disappeared after chemoradiotherapy. The Case 1 patient is still alive with 45 months free of relapse. The Case 2 patient is also still alive with 39 months free of relapse. These results suggest that concurrent chemoradiotherapy using a CHOP-like regimen for stage I nasal NK/T cell lymphoma provided sufficient dose intensity and may be a useful treatment option.*

Nasal natural killer/T cell (NK/T cell) lymphoma is a rare subtype of lymphomas. However, in Asia and native populations of Mexico and Central and South America this subtype of lymphomas is more common than in the United States and Europe (1). In Japan, NK/T cell lymphoma comprised 1.85% of all non-Hodgkin's lymphomas (2), while in the United States or Europe, it was less than 1% of all non-Hodgkin's lymphomas (3). This subtype of non-Hodgkin's lymphoma has a much worse prognosis than other subtypes such as diffuse large B cell lymphoma. The 5-year overall survival rate of localized nasal NK/T cell lymphoma was reported to be 14-87% (4-8) and that of localized intermediate- or high-grade lymphoma was 70-82% (9, 10). One reason for the worse prognosis is that nasal NK/T cell lymphoma is resistant to the standard treatment of sequential chemoradiotherapy, such as 3-8 cycles of CHOP followed by involved radiation therapy of 30–55 Gy. Recently, concurrent chemoradiotherapy was reported to achieve a better initial response for localized nasal NK/T cell lymphoma (11). This treatment method employed an increased dose intensity.

We adopted concurrent chemoradiotherapy to treat stage I nasal NK/T cell lymphoma in November 2000. In this report, we present two consecutively diagnosed cases of stage I nasal NK/T cell lymphoma treated with concurrent chemoradiotherapy using a CHOP-like regimen. As a result of this treatment, the patients have achieved more than 3 years relapse-free survival.

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Key Words: Concurrent chemoradiotherapy, in NK/ T cell lymphoma.

Case Reports

Case 1. A 28-year old woman had sudden severe pain in her right nasal ala region on July 28, 2001. She was treated with antibiotics at a regional hospital, where she was diagnosed as having acute inflammation. Her symptom, however, did not improve and her cheek began to swell. When she was referred to Kitasato University Hospital, Japan, in early August, her right nasal cavity was filled with a tumorous mass. Subsequently, biopsy was performed. The lesion was diagnosed as NK/T cell lymphoma. The patient underwent a detailed systemic evaluation, with tests including physical examination, computed tomography, Ga-scintigraphy and bone marrow aspiration. No tumor was identified anywhere except in her right nasal and paranasal cavities (Figure 1). The disease was, therefore, classified as stage I by the Ann-Arbor classification. At this point, the patient's lactose dehydrogenase (LDH) level was 419 mg/dl. From August 16 to October 4, the patient received 31-Gy irradiation to the entire nasal, paranasal and neck regions and an

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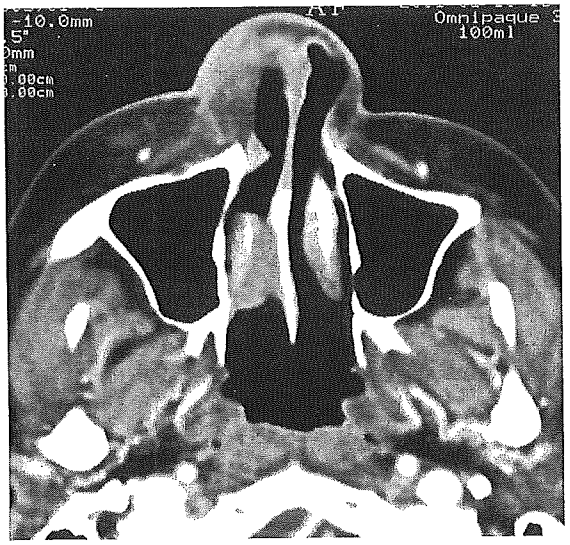

Figure 1. *Computed tomography taken before treatment of Case 1. The tumor can be detected in the patient's nasal cavities.*

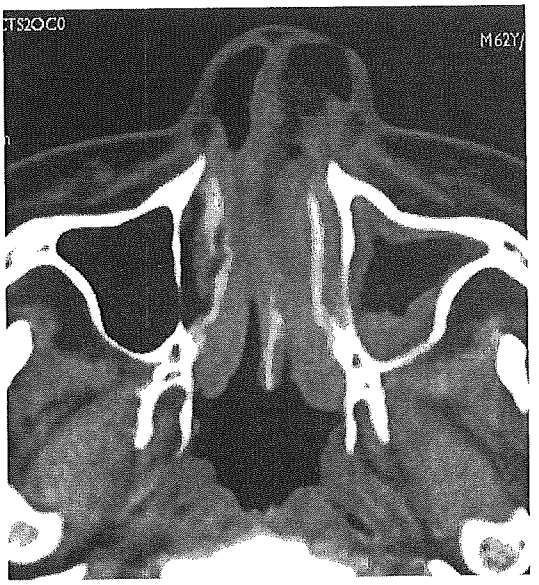

Figure 3. *Computed tomography taken before treatment of Case 2. The tumor can be detected in the patient's nasal and paranasal cavities.*

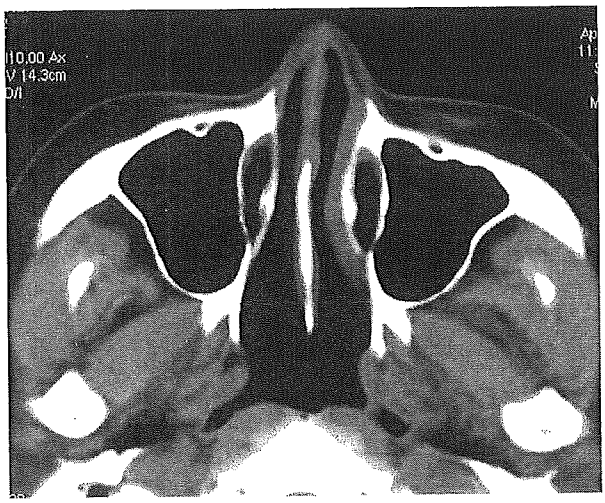

Figure 2. *Computed tomography taken after treatment (chemo-radiotherapy) of Case 1. The tumor disappeared from the patient's nasal and paranasal cavities.*

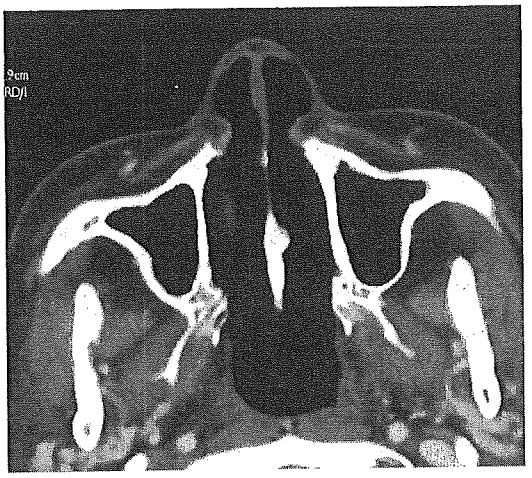

Figure 4. *Computed tomography taken after treatment (chemo-radiotherapy) of Case 2. The tumor disappeared from the patient's nasal and paranasal cavities.*

additional 10-Gy irradiation to the right nasal and paranasal regions. Concomitantly, beginning on August 17, the patient received the first course of CHOP-like chemotherapy (THP-CVP: therarubicin, 40 mg/body, Day 1; endoxan, 1000 mg/body, Day 1; firudecin, 3 mg/body, Day 1; predonine, 100 mg/body, Days 1-5). The tumor disappeared after 4 courses of chemotherapy. The LDH level at this time was 375 mg/dl. The patient received a total of 12 courses of chemotherapy. No severe morbidity was recognized during and after the treatment course. She is well and has achieved 45 months of relapse-free survival to date (Figure 2), and her LDH level has decreased to181 mg/dl.

Case 2. A 62-year-old man had been suffering from nasal obstruction for a few months. In July 2001, the nasal obstruction became exacerbated and the patient was admitted to a regional hospital. A deviated nasal septum was found

and, on November 6, the patient was referred to Kitasato University Hospital, where he underwent surgery of reptoplasty. At this point, only inflammation was noted in the pathological specimen of the inferior chonca. In January 2002, the patient's nasal obstruction rapidly worsened and the man was readmitted to our hospital. On admission, a tumorous swelling of the inferior chonca in his left nasal cavity was detected and biopsy was performed. The lesion was diagnosed as NK/T cell lymphoma. The patient underwent a detailed systemic evaluation. No tumor was found anywhere except in his nasal and paranasal cavities (Figure 3). The disease was classified as stage I. The patient's LDH level at the time of diagnosis was high, at 355 mg/dl. From February 13 to May 29, 2002, the patient received 30-Gy irradiation to the entire nasal, paranasal and neck regions and an additional 20-Gy irradiation to the left nasal cavity. Concomitantly, he received the first and second courses of THP-CVP chemotherapy (therarubicin, 40 mg/body, Day 1; endoxan, 1000 mg/body, Day 1; firudecin, 3 mg /body, Day 1; predonine, 100 mg/body, Days 1-5). The patient received a total of 10 cycles of chemotherapy. The tumor disappeared completely at the end of radiation therapy and 2 courses of chemotherapy. The patient's LDH level had decreased to 299 mg/dl at that time. No severe morbidity was recognized during or after the treatment course. The patient is well and has achieved 39 months of relapse-free survival to date (Figure 4), and his LDH level has decreased to 185 mg/dl.

Discussion

Treatment of NK/T cell lymphoma with standard therapy consisting of sequential chemoradiotherapy with a total radiation dose of 30-55 Gy has not been satisfactory. Ye *et al.* reported that the 5-year survival rate of stage I-II nasal NK/T cell lymphoma treated with chemotherapy followed by radiation therapy was 14% (4). Kwong *et al.* also reported that the 5-year survival rate of stage I CD56+ nasal lymphoma treated with chemotherapy followed by radiation therapy was 28% (5). On the other hand, Miller *et al.* reported that the 5-year survival rate of localized intermediate- or high-grade lymphoma, mainly consisting of diffuse large B cell lymphoma, treated by 3 cycles of CHOP followed by 40-55 Gy of radiation therapy was 82% (9). These results suggest that there is a need for a more intense treatment to improve the results in NK/T cell lymphoma. Thus, we began treating nasal NK/T cell lymphoma with concurrent chemoradiotherapy using THP-CVP. However, advanced stages of NK/T cell lymphoma are not considered to be curable by this regimen, because the radiation field can not cover all viable tumors, thus reducing the intensity. Therefore, our target was designed mainly to treat stage I-II nasal NK/T cell lymphomas. In the absence of a stage II case in which treatment had been completed, this report contains only cases of stage I nasal NK/T cell lymphoma.

Treatment based on this regimen was completed for both Case 1 and 2. Case 1 received 41-Gy irradiation with 12 cycles of THP-CVP as a concurrent (1st course) and adjuvant chemotherapy and achieved 45 months of relapse-free survival. On the other hand, Case 2 received 50-Gy irradiation with 10 cycles of THP-CVP as a concurrent (1st and 2nd course) and adjuvant chemotherapy and achieved 39 months of relapse-free survival. Yamaguchi *et al.* reported that concurrent chemoradiotherapy including DeVIC, which was usually used as salvage treatment, resulted in long-term relapse-free survival in 2 cases of localized nasal NK/T cell lymphoma (11). However, no studies have reported that concurrent chemoradiotherapy using a standard CHOP-like regimen including THP-CVP was effective and safe for treating localized nasal NK/T cell lymphoma. The reason why we adopted THP-CVP rather than standard CHOP is that the latter, including adriamycin and oncovin, could easily cause heart disorders and bone marrow suppression, respectively, and could exacerbate radiation toxicity in a concurrent regimen.

The 2 cases reported here achieved more than 3 years of relapse-free survival with acceptable toxicity. These results suggest that concurrent chemoradiotherapy using THP-CVP for treating stage I nasal NK/T cell lymphoma achieves a sufficient dose intensity and may be a useful treatment option.

References

1 Engelhard M, Brittinger G, Huhn D, Gerhartz HH, Meusers P, Siegert W, Thiel E, Wilmanns W, Aydemir U, Bierwolf S, Griesser H, Tiemann M and Lennert K: Subclassification of diffuse large B-cell lymphomas according to the Kiel classification: distinction of centroblastic and immunoblastic lymphomas is a significant prognostic risk factor. Blood *89*: 2291-2297, 1997.

2 Lymphoma Study Group of Japanese Pathologists: World Health Organization classification of malignant lymphomas in Japan: incidence of recently recognized entities. Pathol Int *50*: 692-702, 2000.

3 Armitage JO, Liang RHS, Sweetenham JW, Reyes F, Jaffe ES amd Paffeld M: Mature nodal and extranodal T-cell and non-Hodgkin's cell lymphomas (peripheral T-cell, angioimmunoblastic, nasal natural killer/T-cell, hepatosplenic T-cell, enteropathy-type T-cell, and subcutaneous panniculitis-like T-cell lymphomas). *In*: Mauch PM, Armitage JO, Coiffier B, Dalla-Favera R, Harris NL (eds.). Non-Hodgkin's Lymphomas. Lippincott Williams & Wilkins, Philadelphia, pp. 405-426, 2004.

4 Yu KH, Yu SC, Teo PM, Chan AT, Yeo W and Chow J: Nasal lymphoma: result of local radiotherapy with or without chemotherapy. Head Neck *19*: 251-259, 1997.

5 Kwong YL, Chan ACL, Liang R, Chiang AK, Chim CS, Chan TK, Todd D and Ho FC: CD56+ NK lymphomas: clinicopathological features and prognosis. Br J Haematol *97*: 821-829, 1997.

6 Nakamura K, Uehara S, Omagari J, Kunitake N, Kimura M, Makino Y, Murakami J, Jingu K and Masuda K: Primary non-Hodgkin's lymphoma of the sinonasal cavities: correlation of CT evaluation with clinical outcome. Radiology *204*: 431-435, 1997.

7 Kim GE, Cho JH, Yang WI, Chung EJ, Suh CO, Park KR, Hong WP, Park IY, Hahn JS, Roh JK and Kim BS: Angiocentric lymphoma of the head and neck: patterns of systemic failure after radiation treatment. J Clin Oncol *18*: 54-63, 2000.

8 Aviles A, Diaz NR, Neri N, Cleto S and Talavera A: Angiocentric nasal T/natural killer cell lymphoma: a single centre study of prognostic factors in 108 patients. Clin Lab Haematol *22*: 215-220, 2000.

9 Miller TP, Dahlberg S, Cassady JR, Adelstein DJ, Spier CM, Grogan TM, LeBlanc M, Carlin S, Chase E and Fisher RI: Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med *339*: 21-26, 1998.

10 Fillet G and Bonnet C: Radiotherapy is unnecessary in elderly patients with localized aggressive non-Hodgkin's lymphoma: results of the GELA LNH 93-4 study. Blood *100*: 92 a., 2002.

11 Yamaguchi M, Ogawa S, Nomoto Y, Oka K, Taniguchi M, Nakase K, Kobayashi T and Shiku H: Treatment outcome of nasal NK-cell lymphoma: a report of 12 consecutively-diagnosed cases and a review of the literature. J Clin Exp Haematopathol *41*: 93-99, 2001.

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Optimal dose for Stage IIIB adenocarcinoma of the uterine cervix on the basis of biological effective dose

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Summary

Purpose: Prognosis of uterine cervical adenocarcinoma in locally advanced stage treated with radiation therapy has been considered to be much worse than that of squamous cell carcinoma because the optimal dose for the former one has not been determined. Thus, the current study was performed to investigate the optimal dose for Stage IIIB, locally advanced stage, adenocarcinoma of the uterine cervix on the basis of the biological effective dose (BED).

Methods: One-hundred and seventy-nine patients with Stage IIIB carcinoma of the uterine cervix were treated with curative intended therapy at Kitasato University Hospital between 1976 and 2000. Out of them, 13 patients had an adenocarcinoma component in pathological findings. Nine patients were diagnosed with adenocarcinoma and four patients were diagnosed with adenosquamous cell carcinoma. All patients were treated with external radiation therapy combined with intracavitary radiation therapy. The total BED_{10} ($T\text{-}BED_{10}$) was caluculated from the BED of the external beam radiation therapy ($E\text{-}BED_{10}$) plus the BED of the intracavitary radiation therapy (A-BED).

Results: Overall survival rate was 51%. Stratified by $T\text{-}BED_{10}$, overall survival rate of the $T\text{-}BED_{10} \geq 100$ Gy group was 57% and that of the$T\text{-}BED_{10} < 100$ Gy group was 30%. There was a trend toward a better survival rate of the $T\text{-}BED_{10} \geq 100$ Gy group than the $T\text{-}BED_{10} < 100$ Gy group.

Conclusion: The current study suggested that the optimal dose for Stage IIIB adenocarcinoma of the uterine cervix might be $T\text{-}BED_{10} \geq 100$ Gy.

Key words: Radiation therapy; Adenocarcinoma of the uterine cervix; Biological effective dose.

Introduction

Early stage invasive adenocaricinoma of the uterine cervix has been reported to achieve almost the same treatment results of radiation therapy as early stage invasive squamous cell carcinoma of the uterine cervix. Nakano *et al.* reported that the 5-year overall survival rates of Stage I and II adenocarcninoma of the uterine cervix treated with radiation therapy were 85.7% and 66.7%, respectively [1]. On the other hand, Arai *et al.* reported that the 5-year overall survival rates of Stage I and II squamous cell carcinoma of the uterine cervix were reported to be 83% and 71%, respectively [2]. However, advanced invasive adenocarcnioma of the uterine cervix has had much poorer treatment results than advanced invasive squamous cell carcinoma of the uterine cervix. Stage III and IV squamous cell carcinoma of the uterine cervix achieved 52.2% and 24.1% of the 5-year overall survival, respectively [1], however, Stage III and IV adenocarcinoma of the uterine cervix achieved 32.3% and 9.1% of the 5-year overall survival, respectively [2]. These outcomes might have resulted because both the prescribed doses and treatment regimens, consisting of a combination of external beam irradiation and intracavitary irradiation for squamous cell carcinoma and adenocarcinoma of the uterine cervix, were the same in the previous studies. Thus, the optimal prescribed dose for advanced adenocarcinoma of the uterine cervix has not been established.

The purpose of the current retrospective analysis was to find the optimal dose for Stage IIIB, advanced stage, adenocarcinoma of the uterine cervix on the basis of the biological effective dose (BED).

Materials and Methods

Patients

One-hundred and seventy-nine patients with Stage IIIB carcinoma of the uterine cervix were treated with curative therapy at Kitasato University Hospital between 1976 and 2000. Out of them, 13 patients had an adenocarcinoma component in the pathological findings. Nine patients were diagnosed with adenocarcinoma and four patients were diagnosed with adenosquamous cell carcinoma. All 13 patients who were treated with radiation therapy, were investigated in the current study. The median age of these patients was 58 years (range; 39-83 years).

Radiation therapy schedule

The radiation therapy treatment schedule was as follows. All patients were treated with a combination of external beam radiation therapy and intracavitary radiation therapy. As for external beam irradiation, anterior-posterior parallel opposed fields were adopted with 1.7-2.0 Gy per fraction, five fractions per week using 4-10 MV X-rays and the total dose of 38-60 Gy was prescribed with central shielding after 27-30 Gy. As for intra-

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Fig. 1

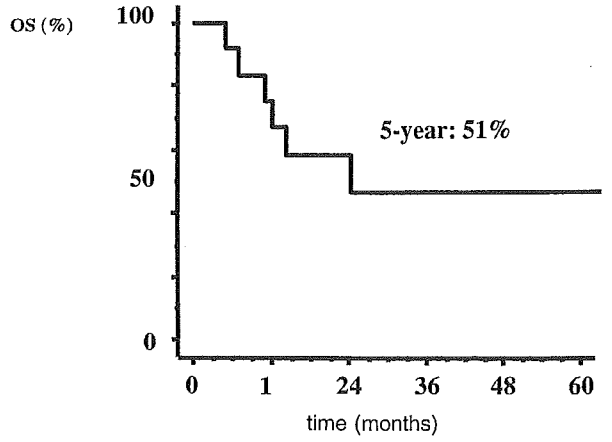

Fig.

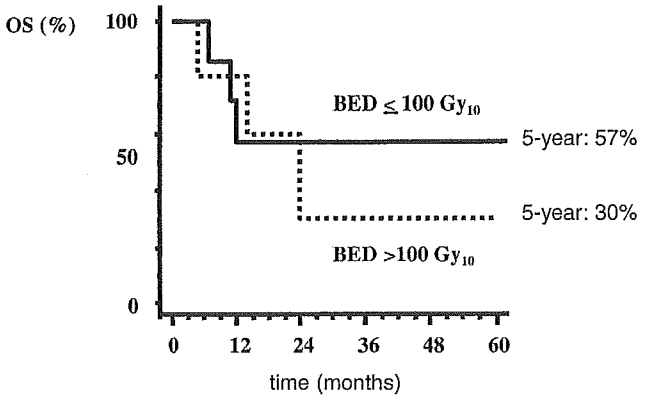

Figure 1. — Overall survival (OS) curve of Stage IIIB adenocarcinoma of the uterine cervix treated with radiation therapy.
Figure 2. — Overall survival (OS) curves of Stage IIIB adenocarcinoma of the uterine cervix treated with radiation therapy stratified by T-BED_{10}. The overall survival rate of the T-BED_{10} ≥ 100 Gy group was 57% and that of the T-BED_{10} < 100 Gy group 30%.

caviatary radiation therapy, all patients were treated with ^{60}Co high-dose rate remote after loading system. The point A dose per fraction was 3.5-6.0 Gy and the total dose to point A was 15-30 Gy. Intracavitary radiation therapy was performed once a week totaling four to six times. The radiation treatment scheduleis listed in Table 1.

Table 1. — *Radiation Therapy.*

External beam radiation therapy	
X-ray	4-10 MV X-ray
Technical	anterior-posterior parallel opposed ports
Fraction size	1.7 Gy-2.0 Gy
Total dose	38-60 Gy
Initiation dose of central shielding	27-30 Gy

Caluculation of biological effective dose (BED)

In the current study, calculation of the biological effective dose (BED) was performed to sum the dose of different fraction sizes. BED was calculated as the following formula.

BED = nd [1 + d/(α/β)] [3]

n = number of fractionation, d = dose per fraction, α/β = specific number

α/β was defined as 10 in most malignant tumor tissues and 2-5 in benign tumor or normal tissues. Thus, in the current study, α/β was defined as 10. This BED was referred to BED_{10} in as following this article.

Furthermore, we calculated BED_{10} separately in the cases of external beam radiation therapy and intracavitary radiation therapy. The former was defined as E-BED_{10} and the latter was defined as A-BED_{10}. E-BED_{10} was calculated from the dose to the following point. The half point between the isocenter of the anterior-posterior fields at the initiation of the treatment and the lateral side of the fields were used. A-BED_{10} was calculated from the dose to point A. Moreover, T-BED_{10} was defined as E-BED10 plus A-BED_{10}.

Statistics

Overall survival rate was calculated from the initiation of radiation therapy and overall survival curve was constructed by the Kaplan-Meier method.

Results

As for BED, E-BED_{10} ranged from 45 to 72 Gy. A-BED_{10} ranged from 22.5 to 48 Gy. T-BED_{10}, E-BED_{10} plus A-BED_{10}, ranged from 75 to 112 Gy.

The median follow-up time of all patients was 35 months (range; 2-170 months). Overall survival rate was 51% (Figure 1). Stratified by T-BED_{10}, overall survival rate of the T-BED_{10} ≥ 100 Gy group was 57% and that of the T-BED_{10} < 100 Gy group was 30% (Figure 2). There was a trend toward a better survival rate of the T-BED_{10} ≥ 100 Gy group vs than that of the T-BED_{10} < 100 Gy group.

Table 2 shows the late radiation morbidity. As for the small intestine, all four patients of the T-BED_{10} < BED 100 Gy group were grade 0. However, one patient experienced grade 3, one patient experienced grade 4, and the other seven patients experienced grade 0 in the T-BED ≥ 100 Gy group. As for the rectum, all four patients of the T-BED_{10} < BED 100 Gy group were grade 0. However, one patient experienced grade 2, one patient experienced grade 3, and the other seven patients experienced grade 0 in the T-BED_{10} ≥ 100 Gy. As for the bladder, all 13 patients of both the T-BED_{10} < 100 Gy group and T-BED_{10} ≥ 100 Gy group experienced grade 0.

Table 2. — *Late radiation morbidity.*

Organ		Grade				
		G0	G1	G2	G3	G4
Small intestine	T.BED > 100	4	0	0	0	0
	T.BED < 100	7	0	0	1	1
Rectum	T.BED > 100	4	0	0	0	0
	T.BED < 100	7	0	1	1	0
Bladder	T.BED > 100	4	0	0	0	0
	T.BED < 100	9	0	0	0	0

Based on NCI-CTC ver 2-0.

Discussion

BED is a useful tool to compare different treatments consisting of different fractionation schedules. In the case of advanced carcinoma of the uterine cervix, the combination of external radiation therapy and intracavitary radiation therapy is the standard method of radiation therapy. Actually, external radiation therapy usually adopts 1.8-2.0 Gy per fraction totaling 45-50 Gy and intracavitary radiation therapy usually adopts 5-6 Gy per fraction to point A totaling 15-30 Gy in advanced carcinoma of the uterine cervix. Thus, the calculation of BED to evaluate the optimal radiation therapy is very important. However, no previous studies have been performed to evaluate the optimal dose for adenocarcinoma of the uterine cervix on the basis of BED, although treatment results of advanced adenocarcinoma of the uterine cervix have not been satisfactory thus far. Nakano *et al.* reported that the 5-year survival rates of Stage III and IVA adenocarcinoma of the uterine cervix were 32.1 % and 9.1 %, respectively [2].

In the current study, a retrospective review was done of the treatment results of Stage IIIB adenocarcinoma of the uterine cervix by analyzing two recent reports in terms of BED [4, 5]. Toita *et al.* reported that the 5-year survival rate of Stage IIIB adenocarcioma of the uterine cervix was 0%. Their study adopted-median T-BED_{10} was 98.4 Gy (range: 98.4-132 Gy). Suzuki *et al.* reported that the 5-year survival rate of Stage IIIB adenocarcinoma of the uterine cervix was 43% using a median T-BED_{10} of 90.0 Gy (range: 88.5-98.4 Gy). On the other hand, the current study achieved 51% of the 5-year survival. The median T-BED10 of the current study was 105 Gy (range: 75-112). Furthermore, the T-$BED_{10} \geq 100$ Gy group achieved 57% of the 5-year survival. The previous two reports adopted a median T-$BED_{10} < 100$ and the current study adopted $\geq$ 100 Gy. The previous two studies adopted over 90 Gy of the median T-BED_{10}, which meant only about 10 Gy of T-BED_{10} more in the current study than the previous studies. However, this 10 Gy of T-BED_{10} had a much more significant impact on treatment results than the other 10 Gy of T.BED_{10} such as a range of 110-120 Gy because the dose-response consisted of a sigmoid curve.

As for radiation morbidity, only two patients experienced grade 3 or more late radiation morbidity of the small intestine. Only one patient experienced grade 3 late radiation morbidity of the rectum. No patients experienced grade 1 or more of the bladder. These results suggest that late radiation morbidity of the current radiation therapy of T-$BED_{10} \geq 100$ Gy is acceptable.

In conclusion, the current study suggests that the optimal dose for Stage IIIB adenocarcinoma of the uterine cervix might be T-$BED_{10} \geq 100$ Gy.

References

[1] Arai T., Nakano T., Morita S., Sakashita K., Nakamura Y.K., Fukuhisa K.: "High-dose-rate remote afterloading intracavitary radiation therapy for cancer of the cervix". *Cancer.*, 1992, *69*, 175.

[2] Nakano T., Arai T., Morita S., Oka K.: "Radiation therapy alone for adenocarcinoma of the uterine cervix". *Int. J. Radiat. Oncol. Biol. Phys.*, 1995, *32*, 1331.

[3] Perez C.A.: "Uterine cervix". In: Perez CA., Brady LW., Halperin EC., Schmidt-Ullrich RK. (eds.). Principles and Practice of Radiation Oncology, 4th edition; Philadelphia, Lippincott Williams & Wilkins, 2004, 1.

[4] Toita T., Takizawa Y., Nakano M., Sueyama H., Kushi A., Kakihana Y., Ogawa K. *et al.*: "Radical radiation therapy for adenocarcinoma of the uterine cervix". *Strahlenther. Oncol.*, 1994, *170*, 277.

[5] Suzuki Y., Nakano T., Arai T., Morita S., Tsujii H., Oka K.: "Progesterone receptor is a favorable prognostic factor of radiation therapy for adenocarcinoma of the uterine cervix". *Int. J. Radiat. Oncol. Biol. Phys.*, 2000, *47*, 1229.

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Original Article

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High-dose rate iridium-192 brachytherapy boost to external beam radiation therapy for prostate cancer in Japanese men

Abstract Introduction : This study evaluated treatment outcome of high-dose rate (HDR) brachytherapy and external beam irradiation therapy (EBRT) for patients with prostate cancer.

Materials and Methods : Between June 1999 and April 2003, 108 patients with clinically localized or locally extensive prostate carcinoma (T1N0M0-T3N0M0) were treated with HDR iridium-192 brachytherapy followed by EBRT.

Results : The median age of the 108 patients was 70.5 years (range 50-84 years). There were 20 low-risk patients, 30 intermediate-risk and 58 high-risk patients, with a median follow-up of 31.5 months (range : 12-58months). The overall actuarial biochemical control rate (bNED) was 78.7%. The actuarial bNED at 36 months for low-, intermediate-, and high-risk patients was 95.0%, 77.4% and 74.7%, respectively.

Conclusion : HDR brachytherapy and EBRT is an effective treatment modality for prostate cancer providing encouraging biochemical control rates after a median follow-up of 31.5 months.

Key words : prostate cancer, high-dose rate brachytherapy, outcome

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Introduction

Curative treatment options for localized prostate cancer include radical prostatectomy, external beam radiotherapy (EBRT) and interstitial brachytherapy. Afterloading brachytherapy is the sole interstitial radiotherapy modality currently available for treating prostate cancer in Japan. This technique has several advantages over permanent seed implantation, including absence of radiation protection and safety issues for patient, and dosimetry can be based on images obtained with the needles *in situ*, making it easy to optimize the dose. Currently several clinical trials reported that HDR brachytherapy is also appropriate for high-risk (unfavorable) prostate cancer. This study evaluated treatment outcome of Ir-192 HDR brachytherapy boost to EBRT for prostate cancer.

Patients and methods

Patients' characteristics

Between June 1999 and April 2003, 108 patients, aged 50-84years (median 70.5), were treated for prostate cancer with HDR brachytherapy followed by 30 Gy external beam radiotherapy. Clinical stage at the time of diagnosis was determined in accordance with the 1992 unified tumor node metastasis (TNM) system[1]. Stage T1 was found in 50, T2 in 38 and T3 in 20 patients. For the nine patients who were already under endocrine therapy at the time of referral, the clinical stage in the original report by the local urologist were utilized. Prostate-specific antigen (PSA) levels at diagnosis were measured at various laboratories using various techniques. These include Dainapack AxSYM PSA assay (Dinabot, Tokyo), Delfia PSA assay (Pharmacia and Upjohn, Tokyo) and Lumipulse PSA assay (Fujirebio, Tokyo). Results of these assays were not inter-converted, since the assays are considered virtually identical. Patients were considered candidates for combination radiotherapy if they presented with clinically organ-

confined or locally advanced prostate cancer but without distant metastasis (T1N0M0-T3N0M0).

Patients with clinical stage Tlc, T2a disease who also had a PSA level of 10 ng/ml or less and biopsy Gleason score of 2 to 6 were defined as the low-risk group[2]. Conversely, patients with clinical stage T2c disease or a PSA level of more than 20 ng/ml or a biopsy Gleason score of 8 or more were defined as the high-risk group. The remaining patients with PSA levels higher than 10 but below 20 ng/ml, a biopsy Gleason score of 7, or clinical stage T2b were defined as the intermediate-risk group.

In the high-risk group of patients, 18 patients were enrolled in HDR/EBRT monotherapy (without endocrine therapy) and 4 patients were given 3 months of neoadjuvant endocrine therapy prior to irradiation. After June 2000, the 36 high-risk patients since that date were prospectively enrolled into a study of 6 months' neoadjuvant endocrine therapy followed by 3 years of adjuvant endocrine following radiation therapy.

All patients were seen once every month for the first 3 months after completion of radiation therapy, quarterly for the first year and semiannually thereafter. Each follow-up visit required history, physical examination and serum PSA. The recommendations of the consensus panel of the American Society for Therapeutic Radiology and Oncology were followed for assessing biochemical failure[3]. Bone scanning was repeated annually.

Procedures for HDR brachytherapy and external beam radiotherapy

The complete details of these procedures have been described elsewhere[4]. Briefly, patients in the operating room were placed in a lithotomy position under epidural anesthesia and prostate volume was sonographically defined. Prostate volume was determined as prostate length × width × height × (π/6). Treatment was initiated using closed transperineal hollow needle placement under transrectal ultrasound guidance. Multiple 20-25 cm long, closed-end, 15G plastic hollow needles were inserted transperineally using a Syed-Neblett plastic template (Alpha-Omega Services, Bellflower, CA)[4]. Usually 18 needles were implanted. Flexible cystoscopy was conducted to ensure that the urethra had not been penetrated by the implanted tubes. The needle tips were left within the urinary bladder 1.5 cm above the sonographically and/or cystoscopically defined base of the prostate. Metallic marker seeds were placed transperineally into the base and apex[5]. Immediately following the implant, anterior/posterior and lateral pelvic radiographs were taken and a spinal CT scan was obtained. The contours of the planning target volume (PTV), defined as the whole prostate gland and the critical tissues were identified on all CT slices. Digitized representations were sent to the PLATO BPS planning workstation (Nucletron, Veenendaal, The Netherlands) for optimization in order to calculate the mean dose volume. The active dwell position was ascertained, with careful attention to ensure that all needles lay within the PTV so that 3D dose optimization could produce a homogeneous dose distribution. Reference points were generated at the surface as around the dorsal aspects of the prostatic gland. The reference dose was defined as 100%. The whole prostate and any tumor extension beyond the capsule were irradiated five times over 3 days using an HDR iridium-192 source with nominal activity of 370GBq (microSelectron-HDR, Veenendaal, The Netherlands). Each single dose was 5 Gy during the period from June 1999 through August 2000 and 7.5 Gy during the period from September 2000 through April 2003. Three days after the last HDR brachytherapy fraction, external beam radiation therapy (EBRT) was started (10 MV, MEVATRON, Siemens, Munich, Germany). A two-dimensional conventional technique was used until April 2000. Beginning in May 2000, a CT-based conformal 3D dose plan was created for each patient. The PTV was defined as the prostate gland plus the seminal vesicle with a surrounding margin of 0.5 cm. External beam irradiation was given using a fractionation of five times 3.0 Gy per week, specified at the isocenter, for 2 weeks. Thus, the total EBRT dose was 30.0 Gy[5].

Results

Biochemical and clinical outcome

The median follow-up period for the 108 patients was 31.5 months after complication of radiation therapy (range 12.0 - 58.0 months). The actuarial analysis of biochemical control for all 108 patients is shown in Fig. 1. Based on the ASTRO definition, the overall actuarial biochemical control rate was 89.8% at 12 months, 85.6% at 24 months and 78.7% at 36 months. The actuarial biochemical control rate at 36 months for the low-, intermediate-, and high-risk patient was 95.0%, 77.4% and 74.7%, respectively (Fig. 2). In the high-risk group, 16 patients received HDR/EBRT monotherapy (without endocrine therapy) and 38 patients received 6 months of neoadjuvant endocrine therapy followed by 3

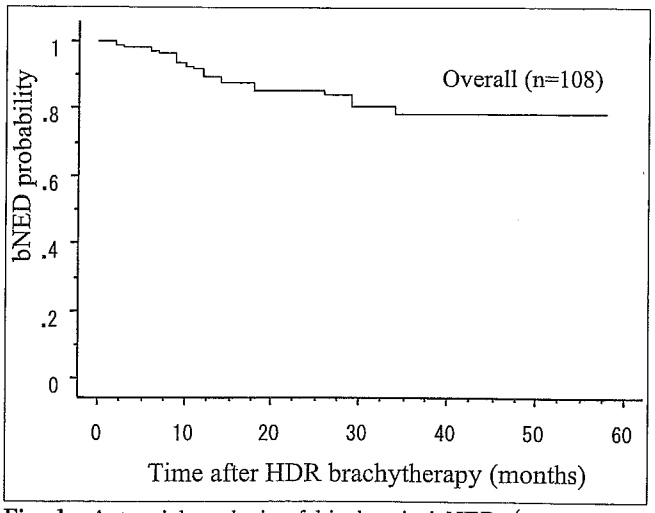

Fig. 1 Actuarial analysis of biochemical NED (no evidence of disease) for all 108 patients. Two- and 3-year bNED rates were 85.6%, and 78.7%, respectively.

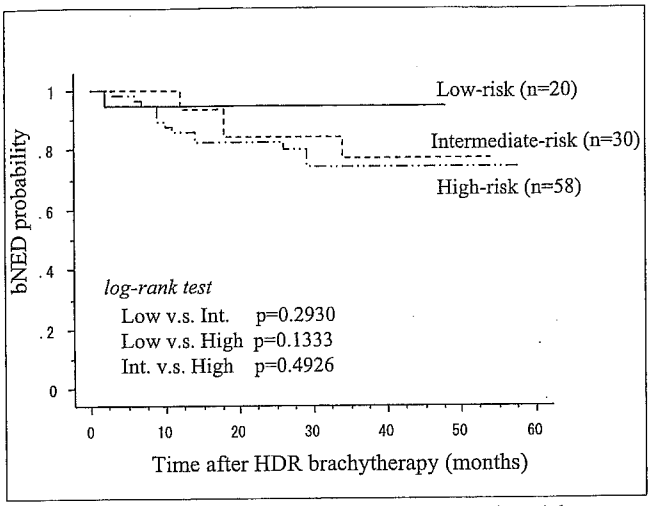

Fig. 2 Actuarial analysis of bNED stratified by risk group. Low-, intermediate-, and high-risk 3-year bNED rates were 95.0%, 77.4% and 74.7%, respectively.

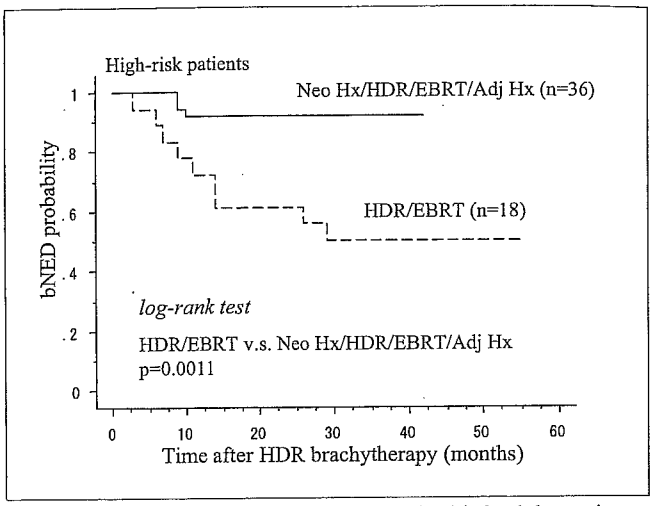

Fig. 3 Actuarial analysis of bNED in high-risk patients stratified by neoadjuvant/adjuvant hormone therapy (Neo Hx/Adj Hx) .

Table 1 Changes in RTOG scores in patients who underwent HDR brachytherapy combined with external beam radiotherapy

	No. pts	Genitourinary score					Significance of differences	Gastrointestinal score					Significance of differences
		Mean ± SD	No. pts				(v.s. post XRT 1M)	Mean ± SD	No. pts				(v.s. post XRT 1M)
		(range)	0	1	2	3	P value	(range)	0	1	2	3	P value
Post XRT 1M	101	0.9 ± 0.8 (0-3)	38	41	21	1	–	0.2 ± 0.5 (0-2)	82	14	5	0	–
Post XRT 3M	98	0.7 ± 0.8 (0-3)	50	32	15	1	N.S.	0.1 ± 0.3 (0-2)	90	7	1	0	0.0151
Post XRT 6M	96	0.5 ± 0.6 (0-2)	58	30	8	0	0.0014	0.1 ± 0.4 (0-3)	84	11	0	1	N.S.
Post XRT 9M	87	0.5 ± 0.7 (0-2)	50	29	8	0	0.0035	0.2 ± 0.5 (0-2)	71	12	4	0	N.S.
Post XRT 12M	102	0.4 ± 0.6 (0-2)	70	24	8	0	<0.0001	0.3 ± 0.7 (0-3)	79	14	8	1	N.S.
Post XRT 18M	95	0.5 ± 0.7 (0-3)	60	28	6	1	0.0030	0.3 ± 0.6 (0-2)	77	12	6	1	N.S.
Post XRT 24M	88	0.4 ± 0.6 (0-2)	63	18	7	0	0.0002	0.3 ± 0.5 (0-2)	63	22	3	0	N.S.
Post XRT 30M	74	0.3 ± 0.5 (0-2)	58	13	3	0	0.0001	0.3 ± 0.6 (0-2)	61	7	6	0	N.S.
Post XRT 36M	57	0.4 ± 0.6 (0-2)	38	16	3	0	0.0018	0.3 ± 0.6 (0-2)	44	10	3	0	N.S.
Post XRT 42M	44	0.2 ± 0.4 (0-2)	37	6	1	0	0.0001	0.3 ± 0.4 (0-1)	33	11	0	0	N.S.
Post XRT 48M	36	0.3 ± 0.7 (0-3)	27	7	1	1	0.0021	0.3 ± 0.5 (0-1)	26	10	0	0	N.S.

XRT, radiotherapy; M, month; SD, standard deviation; NS, not significant; No. pts, number of patients.

years of adjuvant endocrine following radiation therapy. The actuarial biochemical control rates were 50.0% and 91.7% at 36 months, respectively (Fig. 3). Nineteen patients developed biochemical failure at a median interval of 12.0 months (range 2.0 - 34.0 months) after completion of radiation treatment. Two patients died during follow-up period because of intercurrent disease and prostate cancer progression. The actuarial overall survival and disease-specific survival rates were 98.1% and 99.1% at 36 months, respectively.

Toxicity

Acute GU and GI morbidities G1-2 were seen in 57.4% (62/108) and 17.6% (19/108) of patients, respectively (Table 1). Urinary retention requiring catheterization as acute grade 3 morbidity occurred in 2 patients (1.9%). None of the patients developed acute grade 3 GI morbidity. Late grade 3 GU morbidities were seen in 1.9% (2/108). One patient developed urethral stricture requiring endoscopic urethrotomy 18 months after radiation and one patient developed urinary retention requiring catheterization 48 months after radiation. Late grade 3 GI morbidities were seen in 2.8% (3/108). These three patients developed rectal bleeding due to radiation proctitis and were hospitalization to undergo laser coagulation of the rectal mucosa.

Discussion

Surgical treatment of localized prostate cancer remains one of the most effective treatment options for organ confined disease. However, several disadvantages have been recognized such as postoperative incontinence and erectile dysfunction[6,7]. Afterloading brachytherapy is the sole interstitial radiotherapy modality currently available for treating prostate cancer in Japan. This treatment may be less invasive than surgical treatment and several clinical trials reported that HDR brachytherapy is also appropriate for high-risk (unfavorable) prostate cancer. There have been several

investigations of HDR brachytherapy using different regimens[8, 9, 10]. The total biological effect of the combined treatment is usually difficult to determine. A linear quadratic model is often used in an attempt to estimate the corresponding dose if the whole treatment had been given by a fractionation scheme of 2.0 Gy five times a week (NTD-2Gy : Normalized total dose at a fraction size of 2 Gy). It has recently been suggested that the α/β value for prostate cancer is much lower than that for other common tumors, in the range 1.2 to 2.5[11, 12]. In theory, according to the linear quadratic model, this implies an increased sensitivity of the tumor to large doses per fraction. Recognizing the uncertainties in our current understanding of the α/β value for prostate cancer, however, toxicity rates as well as clinical and biochemical outcomes should be evaluated to validate each treatment protocol. Using the linear quadratic model and an assumed α/β value of 1.5 Gy for prostate cancer, the total dose in this study reached values of 135.0 Gy. Assuming the α/β value of 3.0 Gy, the total dose to the rectum would be 69.8 Gy. Thus, these data suggest that the therapeutic ratio may be improved using hypofractionated ratio regimens, which would suggest that HDR brachytherapy could be ideal for the treatment of prostate cancer.

During the past decade, several institutions have published encouraging results using HDR brachytherapy and EBRT for patients with good to poor prognostic factors. Galalae et al. reported that in low-risk patients (PSA less than 10 ng/ml and Gleason score≤6 and clinical stage≤T2a), the actuarial 5-year bNED result was 96.0%[18]. In our series, the 5-year bNED result was 95.0%, which was in concordance with the literature. However, in high-risk patients, the actuarial 5-year bNED ranged from 38.0% to 84.0%[8-10]. This wide variation in results was partially due to the selection of different risk criteria and different biochemical failure definitions.

The most common related morbidity observed is genitourinary and rectal toxicities. Acute GU and GI morbidity G1-2 were seen in 57.4% (62/108) and 17.6% (19/108) of patients, and we observed 1.9% acute grade 3 morbidities in our series. These patients developed urinary retention requiring temporary catheterization, but all these patients had obstructive symptoms prior to radiation therapy because of benign prostate hyperplasia. However, unexpected, late urinary retention was seen in one patien (0.9%) who required catheterization 48 months after radiation. Zeitlin et al reviewed 212 patients with a minimum of 24 months of follow up (mean 33) for localized prostate cancer treated with brachytherapy followed by 45 Gy EBRT[13]. Patients with Gleason scores of 2 to 5 were treated with I-125 at a minimum peripheral dose of 120 Gy, while a minimum peripheral dose of 90 Gy Pd-103 was used for those with Gleason scores of 7 to 10. The incidence of urinary retention was 1.5%. Pellizzon et al reported that the 5-year actuarial urinary retention rate was 13.8% and interestingly retention episodes for the cohort began about 40 months after therapy, which certainly represents a long-term complication[14]. It is generally believed that brachytherapy is a gentler, less invasive treatment for localized prostate cancer. Grills et al described[15] that "prostatic brachytherapy is the most convention treatment and may have the lowest rate of long-term complications compared to radical prostatectomy or external beam radiotherapy". However, it is too early to confirm the safety of HDR brachytherapy boost to EBRT for prostate cancer, because the follow-up periods are still limited.

There are no consensuses about the role of naoadjuvant and adjuvant endocrine therapy in combination with brachytherapy for high-risk prostate cancer at the present time. Based on published results demonstrating improved outcome for patients with locally advanced prostate cancer treated with combined EBRT and endocrine therapy, we have integrated 6 months' neoadjuvant endocrine therapy followed by 3 years of adjuvant endocrine following radiation therapy in our protocol. Additional long-term follow-up is needed to confirm our results for high-risk patients, and there is still controversy in the literature about the optimal timing and duration of endocrine therapy when used in conjunction with EBRT. Trials are currently underway to examine the efficacy in patients with locally confined disease[16, 17].

In the future prospective randomized trials are needed to demonstrate which patients benefit from neoadjuvant and adjuvant endocrine therapy combined with HDR brachytherapy and EBRT for prostate cancer.

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References

1) International Union Against Cancer (1992) TNM Atlas, 3rd Ed, 2nd revision. New York : Springer, pp 241-250
2) D'Amico AV, Whittington R, Malkowicz SB, et al (1998) Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 280 : 969-974
3) American Society of Therapeutic Radiation and Oncology Consensus Panel. Consensus statement (2001) : guideline for PSA following radiation therapy. Int J Radiat Oncol Biol Phys 37 : 1035-1041
4) Syed AMN, Puthawala A, Austin P, et al (1992) Temporary iridium-192 implant in the management of carcinoma of the prostate. Cancer 69 : 2515-2524
5) Egawa S, Shimura S, Irie A. et al (2001) Toxicity and health-related quality of life during and after high dose rate brachytherapy followed by external beam radiotherapy for prostate cancer. Jpn J Clin Oncol 11 : 541-547

6) Benoit RM, Naslund MJ, Cohen JK (2000) Complications after radical retropubic prostatectomy in the medicare population. Urology 56 : 116
7) Eastham JA, Kattan MW, Rogers E, et al (1996) Risk factors for urinary incontinence after radical prostatectomy. J Urol 156 : 1707-1713
8) Demanes DJ, Rodriguez RR, Schour L, et al (2005) High-dose-rate intensity-modulated brachytherapy with external beam radiotherapy for prostate cancer:California endocurietherapy's 10-year results. Int J Radiat Oncol Biol Phys 61 : 1306-1316
9) Jo Y, Hiratsuka J, Fujii T, et al (2004) High-dose-rate iridium-192 afterloading therapy combined with external beam radiotherapy for T1c-T3bN0M0 prostate cancer. Urology 64 : 556-560
10) Syed AM, Puthawala A, Sharma A, et al (2001) High-dose-rate brachytherapy in the treatment of carcinoma of the prostate. Cancer Control. 8 : 511-521
11) Brenner DJ, Hall EJ (1999) Fraction and protraction of radiotherapy of prostate carcinoma. Int J Radiat Oncol Biol Phys 43 : 1095-1101
12) Algan O, Stobbe CC, Helt AM, et al (1996) Radiation in activation of human prostate cancer cells : the role for apotosis. Radiat Res 146 : 267-275
13) Zeitlin SI, Sherman J, Raboy A, et al (1998) High dose combination radiotherapy for the treatment of localized prostate cancer. J Urol 60 : 91-95 ; discussion 95-96
14) Pellizzon AC, Salvajoli JV, Maia MA, et al (2004) Late urinary morbidity with high dose prostate brachytherapy as a boost to conventional external beam radiation therapy for local and locally advanced prostate cancer. J Urol 171 : 1105-1108
15) Grills IS, Martinez AA, Hollander M, et al (2004) High dose rate brachytherapy as prostate cancer monotherapy reduces toxicity compared to low dose rate palladium seeds. J Urol 171 : 1098-1104
16) Pilepich MV, Winter K, Lawton CA, et al (2005) Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. Int J Radiat Oncol Biol Phys 61 : 1285-1290
17) Pilepich MV, Winter K, John MJ, et al (2001) Phase III radiation therapy oncology group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. Int J Radiat Oncol Biol Phys 50 : 1243-1252
18) Galalae RM, Martinez A, Mate T, et al (2004) Long-term outcome by risk factors using conformal high-dose-rate brachytherapy (HDR-BT) boost with or without neoadjuvant androgen suppression for localized prostate cancer. Long-term outcome by risk factors using conformal high-dose-rate brachytherapy (HDR-BT) boost with or without neoadjuvant androgen suppression for localized prostate cancer. Int J Radiat Oncol Biol Phys 58 : 1048-1055

化学放射線療法

肺癌

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Point

- PS 0～2の限局型小細胞肺癌の標準治療は、PE療法4コースを行い、早期に総線量45Gyの加速過分割照射で胸部放射線療法を同時併用する治療方法である。
- T4ならびにsuperior sulcus tumorの切除可能な局所進行非小細胞肺癌に対しては、近年術前に導入化学放射線療法を行うことが試みられるようになった。
- T4ならびにsuperior sulcus tumor以外のⅢA期、ⅢB期の切除可能な局所進行非小細胞肺癌に対する術前化学放射線療法については、適切に選択された症例において施行可能な治療法と認識されているが、有効性に関する十分なコンセンサスは得られていない。
- 70歳以下のPSの良好な切除不能局所進行非小細胞肺癌に対しては、シスプラチンを含む多剤併用化学療法と放射線療法とを早期に併用することが有用であると考えられる。

肺癌における治療方針は、組織型が小細胞肺癌（small cell lung cancer；SCLC）であるのか、非小細胞肺癌（non-small cell lung cancer；NSCLC）であるのか、臨床病期、performance status（PS）、年齢によって決定される。本稿ではEvidence-based Medicine（EBM）の手法による肺癌の診療ガイドライン策定に関する研究班による“EBMの手法による肺癌診療ガイドライン2003年度版[1]”に基づき肺癌の化学放射線療法の適応、標準治療および最新の知見に関し解説をする。

小細胞肺癌（small cell lung cancer；SCLC）

SCLCは、治療方針、予後の推定の面からTNM分類以外の、限局型（limited disease；LD）と進展型（extensive disease；ED）に分ける病期分類が用いられている。LDは腫瘍が一側胸腔内、同側肺門・両側縦隔・鎖骨上窩リンパ節に限局しているもの、EDはこれを越えて進展しているものと定義されている。SCLCはNSCLCと比較し、放射線療法・化学療法に対する感受性が高いと

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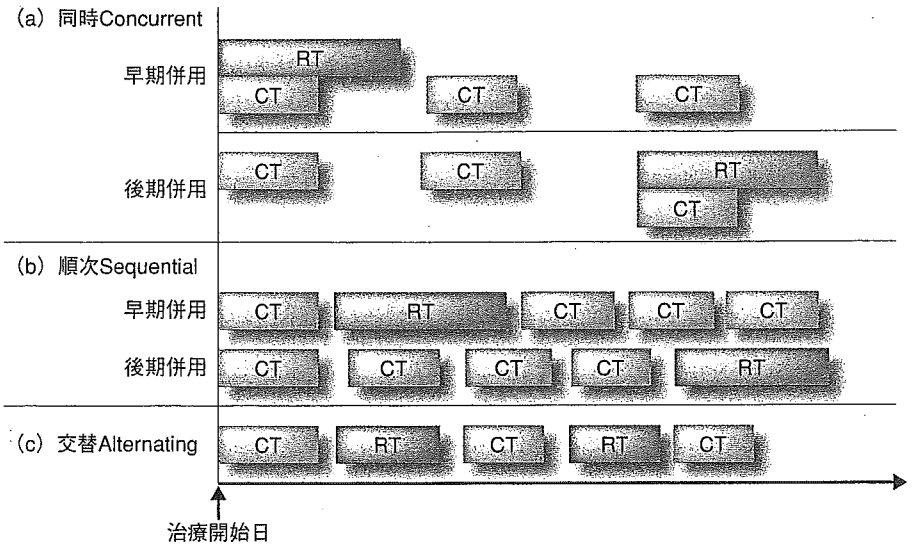

図1●放射線療法・化学療法の併用のタイミング

RT：放射線治療、CT：化学療法

いう特徴をもつ。SCLCではLD症例において化学療法単独よりも化学療法に胸部放射線療法を加えることで局所制御ならびに生存率が向上することが1992年に2つのメタアナリシスによって示されている[2,3]。このため、低肺機能などの根治照射困難な症例以外は化学療法に胸部放射線療法を加えることが推奨されている。放射線療法を実施する時期については、①早期同時併用、②後期同時併用、③交代併用、④順次併用がある(**図1**)。Murrayらはシクロホスファミド/ドキソルビシン/ビンクリスチン療法(CAV療法)とシスプラチン/エトポシド療法(PE療法)の交替療法の早期に40Gyの放射線療法を同時併用する方法と、後期に同時併用する方法の比較試験で、早期併用群が後期併用群に対して生存期間中央値(median survival time；MST) 21.2ヵ月 vs 16ヵ月、5年生存率20% vs 11%と生存が改善することを示した[4]。また、Japan Clinical Oncology Group (JCOG)でもPE療法を4コース行い、1コース目に45Gyの加速過分割照射を行う群と、4コース後に逐次併用する群との比較試験が行われ、MST 27.2ヵ月 vs 19.7ヵ月、5年生存率23.7% vs 18.3%と同時併用群が優れていた[5] (**表1**)。照射のスケジュール(**図2**)に関しては、4コースのPE療法の1コース目に通常分割照射(1回1.8Gy、1日1回、総線量45Gy)を行う群と、加速過分割照射(1回1.5Gy、1日2回、総線量45Gy)を行う群との比較試験が行われ、加速過分割照射群で食道炎の頻度が高かったが、MST 19ヵ月 vs 23ヵ月、5年生存率16% vs 23%と加速過分割照射群が優れていた[10]。

化学療法のレジメンに関しては、Pujolらの行ったシスプラチン有無の比較試験のメタアナリシスで、シスプラチンを含むレジメンは、含まないレジメンに比較して、1年における死亡率が20%低下することが示されている[11]。また、化

Study	化学療法	放射線療法 (Gy)	MST(月) 早期	MST(月) 後期	5年生存率(%) 早期	5年生存率(%) 後期	p-value
CALGB[6]	CAVE	50	13.0	14.5	6.6	12.8	NS
Murray[4]	CAV/PE	40	21.2	16.0	20.0	11.0	0.008
Jeremic[7]	CBDCA+E	54	34.0	26.0	30.0	15.0	0.027
JCOG[5]	PE	45	27.2	19.7	23.7	18.3	0.097
Work[8]	CAV/PE	40～50	10.7	12.9	10.0	10.0	NS
James[9]	CAV/PE	40	13.5	15.1	NR	NR	NS

表1●限局型小細胞肺癌に対する化学療法と放射線療法の併用時期に関する比較試験

C：cyclophosphamide、A：doxorubicin、V：vincristine、E：etoposide、P：cisplatin、
CBDCA：carboplatin、MST：median survival time、NR：not reported、NS：not significant

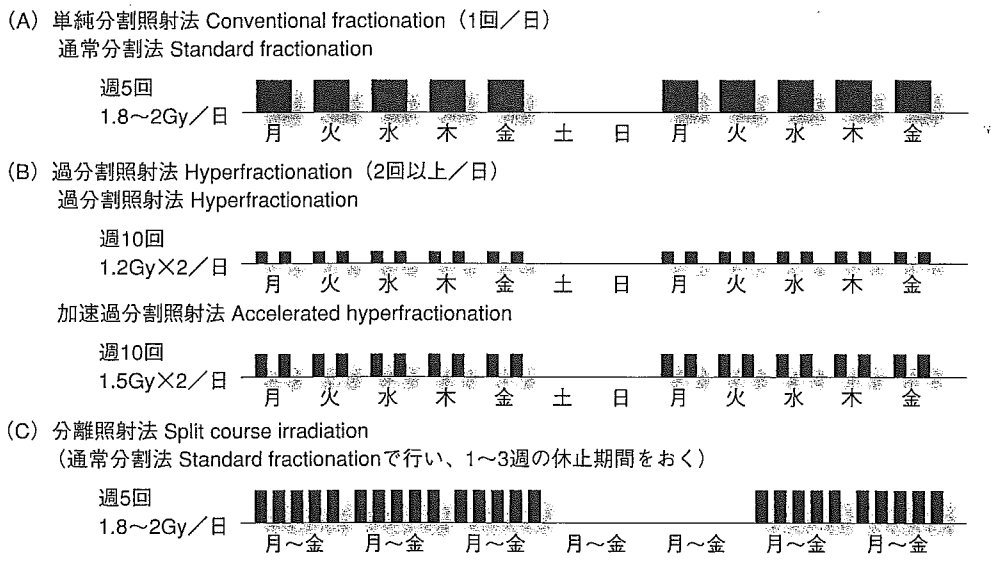

図2●肺癌に対する化学放射線療法で胸部照射に用いられている分割照射法

学療法と加速過分割照射を同時併用する比較試験では、主にPE療法が用いられている。このため化学療法のレジメンとしてはPE療法が推奨されている。

以上まとめると、現時点ではPS 0～2のLDのSCLCの標準治療は、PE療法4コースを行い、早期に総線量45Gyの加速過分割照射を同時併用する治療方法であると考えられている。

わが国では、EDのSCLCに対して行われたPE療法とシスプラチン/イリノテカン療法（IP療法）の第Ⅲ相比較試験で奏効率が67.5% vs 84.4%、MST 9.4ヵ月 vs 12.8ヵ月と有意に優れていたこと

study	stage	n	化学療法	放射線療法 (Gy)	Response rate (%)	Resection rate (%)	MST(月) (Survival rate)
CALGB[17]	ⅢAN2	41	FVP×2	30	51	61	16
SWOG[18]	ⅢAN2	75	PE×2	45	69	76	13
	ⅢB	51			45	63	17
Rice[19]	ⅢAN2	42	PE×1	27	57	79	21
	ⅢB						
Choi[20]	ⅢAN2	42	FVP×2	42	73	93	28 (5yr：37%)
Eberhardt[21]	ⅢAN2	94	PE×4	45		53	(4yr：31%)
	ⅢB						(4yr：26%)

表2◉局所進行型非小細胞肺癌の術前化学放射線療法の第Ⅱ相試験（文献22より一部改変引用）

F：fluorouracil（5-FU）、V：vinblastine、P：cisplatin、
E：etoposide、MST：median survival time

から[12]、LDのSCLCに対する、PE療法と胸部放射線多分割照射同時併用療法に引き続く、IP療法とPE療法を比較する第Ⅲ相試験（JCOG0202）が現在進行中である。

非小細胞肺癌（non-small cell lung cancer：NSCLC）

非小細胞肺癌における化学放射線療法の適応は、局所進行型の術前療法と切除不能局所進行型である。

1. 局所進行型の術前化学放射線療法

悪性胸水および悪性心膜液貯留を除くT4ならびにsuperior sulcus tumor（SST）は、局所進行癌のなかでも特殊な位置付けがされている。この病期の場合、リンパ節転移がなければ外科療法によってある程度の長期生存が得られることが経験的に示されてきた。これに対して近年術前に導入化学放射線療法を行うことが試みられるようになった。しかし、現時点では第Ⅱ相試験の報告に止まっている[13-15]。RuschらはSSTに対してPE療法と45Gyの放射線療法を行った後に外科療法を行い、登録111例中76例に完全切除が行われ、70%の2年生存率を報告している[16]。

上記以外のⅢA期、ⅢB期の局所進行肺癌に対する術前化学放射線療法についても、第Ⅱ相試験の報告に止まっている。**表2**[22]に示す通り、報告によるばらつきが大きい[17-21]。Choiら[20]やEberhardtら[21]は30%を超える5年生存率を報告しているが、症例数自体が少なく、選りすぐられた症例に対して行われた結果と考えられている。2003年の米国臨床腫瘍学会でAlbainらによりStageⅢA期pN2症例を対象に、化学放射線療法同時併用群（CT/RT群）と、化学放射線療法後に外科的切除を行う群（CT/RT/S群）を比較する第Ⅲ相試験の中間解析の結果が報告され、CT/RT/S群でprogression free survival（PFS）の有意な延長が認められたが、生存期間に有意差は認められなかった[23]。また、German Lung Cancer Cooperative Group（GLCCG）では、PE療法3コース後にカルボプラチン/ビンデシンによる化学療法と45Gyの多分割照射の放射線療法の併用を加え、その後に外科的切除を行う群（CT→CRT→S群）と、PE療法3コース後に外科的切除を行い、その後に54Gyの通常分割の放射線療法を行う群（CT

study	n	Regimen	MST (月)	Survival rate
West Japan[31]	320	PVdM+RT (56Gy ; split course)	16.6 (p=0.03998)	2yr : 34.6% 5yr : 15.8%
		PVdM→RT (56Gy ; continuous)	13.3	27.4% 8.9%
GLOT-GFPC[32]	212	PE+RT (66Gy) →PN	15 (p=NS)	2yr : 35% (p=NS)
		PN→RT (66Gy)	13.8	23%
RTOG[33]	610	PVi→RT (60Gy)	17	4yr : 12%
		PVi+RT (60Gy)	14.6 (p=0.046)	21% (p=0.046)
		PE+HFx-RT (69.6Gy)	15.6 (p=NS)	17% (p=NS)
Czech Republic[34]	102	PN+RT (60Gy)	16.6 (p=0.023)	3yr : 18.6%
		PN→RT (60Gy)	12.9	9.50%

表3 切除不能局所進行型非小細胞肺癌の化学療法と放射線療法の同時併用と順次併用の比較試験
(文献35より一部改変引用)

P : cisplatin、Vd : vindesine、M : mitomycin、E : etoposide、N : vinorelbine、Vi : vinblastine、RT : radiotherapy、HFx-RT : hyperfractionated radiotherapy、MST : median survival time、NS : not significant

→S→RT群) で比較を行ったが、やはり有意な差は得られなかった[24]。現在Radiation Therapy Oncology Group (RTOG) と Southwestern Oncology Group (SWOG) が共同して、シスプラチン/ドセタキセルによる化学療法と45Gyの放射線療法を併用後に外科的切除を行い、その後さらにドセタキセル単剤の化学療法を3コース行う群とシスプラチン/ドセタキセルによる化学療法後に外科的切除を行い、その後さらにドセタキセル単剤の化学療法を3コース行う群での比較試験を行っている。

以上より現時点では、この病期における術前化学放射線療法は、適切に選択された症例において施行可能な治療法と認識されている。

2. 切除不能局所進行型

切除不能局所進行非小細胞肺癌に対する放射線療法単独と化学放射線療法の比較試験をまとめたメタアナリシスの結果、シスプラチンを含む化学療法と放射線療法の併用群の生存率が放射線単独群の生存率に比して有意に良好であった[25-27]。化学療法単独と化学放射線療法を比較したメタアナリシスは報告されていないが、2つの比較試験の報告があり、いずれも生存期間全体では有意な差は認められなかったが、長期生存率、局所コントロールで有意に化学放射線療法が優れているという結果であった[28,29]。RTOG、Eastern Cooperative Oncology Group (ECOG)、SWOG共同のランダム化比較試験の解析では、70歳以上の高齢者では放射線単独療法に比して化学放射線療法による生存率の向上は認められなかったと報告されている[30]。化学療法と放射線療法の併用時期は、同時併用の方が順次併用より効果は高い[31-34]。同時併用 (**表3**)[35]では、急性の有害事象の頻度が高く、慢性の有害事象は順次併用と同等であると報告されている[36]。放射線療法の照射方法については、1回2Gyの通常分割照射法が古くから検討されており、化学療法と併用する場合でも60Gy/30回 (6週) が最低推奨線量とされている[37]。化学療法と多分割照射の併用に関しては、通常分割との比較で多分割照射法の有用性を示した報告がない。分離照射法に関