細に検討することが必要であろう．

肝切除可能な肝転移症例において，微小転移を消失させ根治性を向上させるという目的で，術前抗癌剤投与を施行後に肝切除を施行するべきかという議論がなされている．術前化学療法の病理組織学的効果が肝切除後の生存期間の予後因子となったとの報告や[44)~46)]，また術前化学療法施行により欧米でのいわゆるR1手術となった肝切除症例の予後とR0症例の予後に差異はなかったとの報告[47)]がなされたことから，術前化学療法施行症例はますます増えてくると考えられる[48)~51)]．現時点での補助療法を含めた大腸癌肝転移例に対する治療戦略をシェーマに示すが（Figure 3），先に述べた微小肝転移の問題を含め，まだ一定の結論は出ていないが，肝切除後の早期肝再発抑制のためには待機的肝切除か術前化学療法併用肝切除を施行するかなど，今後さらなる検討が必要と考えられる．また消化器専門医にとって肝転移はすでにステージIVであることから考えても，新規抗癌剤と分子標的治療剤の投与はますます増えてくると考えられる．肝切除は予後を有意に伸ばしうる治療法であることから肝臓外科医側からみると肝障害や術後の合併症や肝再生の点からも適切な抗癌剤投与方法・期間と切除の可否を含めそのタイミングを考慮することが肝要であることを注記したい．

おわりに

大腸癌肝転移に対する肝切除は手術手技や周術期管理の進歩により，安全に施行可能であり，肝切除・新規抗癌剤・分子標的薬を合わせた新たな治療戦略は今後ますます進歩していくであろう．

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Intermittent androgen suppression for prostate cancer: present status and perspectives

Introduction

For the management of advanced prostate cancer, endocrine therapy has been utilized as a principle modality of treatment. Since surgical castration was introduced as one of the most common strategies, endocrine therapy has been considered to continue permanently. Although the initial effect of endocrine therapy is prominent, progression to androgen-independent status often occurs within a few years. Therefore, a variety of attempts have been made to maintain the androgen-dependent status of the tumor as long as possible. Intermittent androgen suppression was proposed to prolong androgen dependency of prostate cancer, and was found to provide potential benefits resulting during the off-treatment period.

Concept of intermittent androgen suppression

In general, adenocarcinoma of the prostate shows androgen dependency; the tumor develops and grows in the presence of androgen, and regresses through apoptosis by withdrawal of androgen. However, the regressed tumor progresses after a while, and becomes an androgen-independent tumor. In *in vitro* and *in vivo* experiments using androgen-dependent models, androgen dependency can be maintained in the presence of androgen; androgen-dependent cancer cell lines can be serially cultured in the physiological concentration of androgen in the medium, and androgen-dependent xenografts are successfully transplanted into the male hosts. However, long-term withdrawal of androgen causes these cancer cells to become androgen-independent. Withdrawal of androgen could be a trigger for progression to androgen-independent status. Therefore, it is hypothesized that when the androgen-dependent tumor regresses following androgen withdrawal, if androgen is replaced again, the tumor might recover the potency of apoptosis induced by androgen withdrawal, and is expected to maintain androgen dependency for longer.

Intermittent androgen suppression in an animal model

Shionogi carcinoma is an androgen-dependent mouse mammary tumor; surgical castration of a tumor-bearing male mouse results in regression of the tumor through induction of apoptosis. Using the Shionogi model, four or five cycles of tumor regression and regrowth have been obtained by cycles of androgen withdrawal and replacement.[25] In a human prostate cancer cell line, LNCaP, which was transplanted into nude mice, serum prostate-specific antigen (PSA) level was maintained in an androgen-dependent manner for a longer period by intermittent androgen suppression, compared with continuous androgen suppression.

Clinical experiences of intermittent androgen suppression

Development of reversible hormonal agents, such as luteinizing hormone-releasing hormone (LHRH) agonists and anti-androgens, and prevalence of PSA as a reliable and feasible tool for monitoring have made it possible to apply endocrine therapy intermittently. Based on the promising results of investigational research using an androgen-dependent animal model, our group in Vancouver reported 47 cases of prostate cancer treated with intermittent androgen suppression. Thereafter, a number of clinical experiences of intermittent therapy have been published for various stages of prostate cancer by different methods and durations of endocrine therapy. Most of the studies demonstrated promising results and emphasized improved quality of life after intermittent androgen suppression.[26]

Randomized clinical trials comparing intermittent *vs* continuous androgen suppression

Several randomized comparative clinical trials have been conducted to compare the efficacy between intermittent and continuous androgen suppression (Table 3).[27–34] At the present time, while only a few trials have obtained the final results,[27] no report has demonstrated a significantly worse time to progression and survival with intermittent androgen suppression than with continuous androgen suppression. On the other hand, most trials have indicated that the benefits of intermittent therapy were fewer adverse effects and increased quality of life.

Although intermittent androgen suppression has been classified as an experimental method of treatment, the latest Guidelines on Prostate Cancer by the European Association of Urology indicated that 'intermittent androgen deprivation therapy is at present widely offered to prostate cancer patients in various clinical settings, and its status should no longer be regarded as investigational,' based on the recent clinical data.

Advantages and disadvantages of intermittent androgen suppression

Intermittent androgen suppression is able to achieve several benefits. Incidence and degree of adverse events of androgen

Table 3 Randomized control trials comparing intermittent *vs* continuous androgen suppression[27–34]

Author	Region	Case number	Subjects	Primary end-point
de Leval	Belgium	68	T3-4/N+/M+/recurrent after RP	Time to androgen-independence
Schasfoort	Europe/South America	290	T2-4NxM1/T2-4N1-3M0	Time to progression
Yamanaka	Japan	215	T3-4N0M0, as adjuvant following EBRT	PSA relapse-free survival
Miller	Germany	335	T1-4N1-3M0/T1-4N0-3M1	Time to clinical/PSA progression
Tunn	Germany/Italy	244	PSA relapse after RP	Time to progression
Hussain	USA	1345	Stage D2	Survival
Calais da Silva	South Europe	626	T3-4M0/T3-4M1	Time to progression
Salonen	Finland	564	T1-4M1/T1-4M0 (PSA20or60<)	Survival

EBRT, external beam radiation therapy; M, metastasis; N, node; PSA, prostate-specific antigen; RP, radical prostatectomy; T, tumor.

deprivation therapy will be decreased or improved by intermittent androgen suppression. Most of symptoms including sexual dysfunction, hot flush, and fatigue will be recovered during the off-treatment period, and risk of cardiovascular events and osteoporosis may be reduced by intermittent therapy. Several domains of quality of life are improved by stopping androgen deprivation therapy. From an economical point of view, the cost of treatment will be reduced by intermittent therapy, comparing continuous therapy with the same agents. Finally, it might be expected that intermittent androgen suppression will achieve prolonged progression-free and overall survival.

When applying intermittent androgen suppression, frequent measurements of serum PSA and testosterone will be required. Although it is not certain whether prostate cancer can be cured by endocrine therapy, the chance of cure might be missed by stopping the therapy. As serum PSA is thought to be a useful marker for monitoring the disease status, there is a risk of developing progression without an elevated level of serum PSA during intermittent therapy.

Future directions

Intermittent androgen suppression was initially used for patients with metastatic or advanced prostate cancer. However, recently there has been a dramatic increase in the number of curative therapies, such as radical prostatectomy and radiotherapy, at the early stage of the disease, probably due to the prevalence of serum PSA measurements. In recent years, a number of patients have developed PSA failure after curative therapy. Some of these patients have been treated with endocrine therapy and may be under control for a long time. Therefore, the adverse effects of endocrine therapy will be serious problems for these patients, and intermittent therapy could be an option for the long-term management of prostate cancer patients without metastasis.

A meta-analysis study demonstrated significant factors for progression-free survival of patients treated with intermittent therapy.[35] However, good candidates for intermittent therapy are still unknown. Moreover, a number of questions are still to be answered: Which is the appropriate method of endocrine therapy for each patient: LHRH agonist, anti-androgen alone, or combined androgen blockade? At which PSA levels should therapy be terminated and restarted? To resolve these questions, the accumulation of clinical data is crucial. A recent study of a mathematical model of intermittent androgen suppression may be able to suggest the future course of each patient by precise analysis of PSA kinetics.[36] This model will be extremely useful for the establishment of order-made therapy of intermittent androgen suppression.

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Estramustine phosphate-based combination therapy for hormone-refractory prostate cancer: a meta-analysis

Estramustine phosphate (EMP) is a prodrug that consists of 17β-estradiol bound to nor-nitrogen mustard. This compound was first synthesized in the mid-1960s for the treatment of breast cancer. In the 1970s, EMP was applied to the treatment of prostate cancer as a chemoendocrine agent based on the fact that it specifically accumulates in the prostate. EMP has been marketed in Japan since 1984. Recently, EMP has drawn attention for its synergistic effect when combined with doc-

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Carbon Ion Radiotherapy for Treatment of Prostate Cancer and Subsequent Outcomes after Biochemical Failure

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Abstract. *Background/Aim: Carbon ion radiotherapy is expected to be suitable to treat localized prostate cancer because it yields great biological and physical effects. The aim of this study was to examine long-term results and subsequent outcomes after biochemical failure. Patients and Methods: A total of 254 patients were treated from the beginning of 2003 and followed through 2009. Long-term hormone therapy was also used for some intermediate-risk and high-risk patients. Results: Among the patients examined, 54 patients experienced biochemical failure. Failure-free survival was 76%, 91% and 76% at eight years in low-risk, intermediate-risk and high-risk patients, respectively. Clinical progression occurred only in high-risk patients, with 89% progression-free survival at eight years. After biochemical failure, diseases of most patients were well controlled by salvage therapy but twelve high-risk patients (5%) died of prostate cancer. Conclusion: Carbon ion radiotherapy had an excellent effect on localized prostate cancer. Factors influencing salvage therapy included PSA kinetics and duration between radiation and failure.*

In 2005 in Japan, 42,997 men were diagnosed with prostate cancer (an incidence of 42.0 per 100,000 men), and 9,264 men died of prostate cancer (1). The proportion of patients with cancer at the localized stage has increased and radiotherapy and surgery are critical curative treatments for such patients. Carbon ion beam is characterized by high cytocidal effects, high linear energy transfer and excellent radiation dose distribution. Based on its biological and physical effects, carbon ion radiotherapy is considered as a new treatment modality for solid tumors. The National Institute of Radiological Sciences in Japan constructed the Heavy Ion Medical Accelerator in Chiba (HIMAC) in 1993 and started to use carbon ion radiotherapy to treat localized and locally advanced prostate cancer in 1995. Preliminary short-term results have been reported (2-4). Since then, this is the first one to assess the long-term outcomes of patients who received carbon ion radiotherapy between 1995 and 2003. Because some patients experienced biochemical failure, the present study examined the influence of adjuvant therapy on the subsequent outcome.

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Key Words: External beam radiation therapy, PSA-doubling time.

Patients and methods

Patients. Patients with confirmed histological adenocarcinoma and T1b-T3N0M0 cancer were enrolled in the study. Between the start of treatment (October 1995) and October 2003, 254 consecutive patients received carbon ion radiotherapy. Patients had not received previous treatment for prostate cancer. Clinical records for all patients were collected in 2009. The follow-up period lasted for a mean of 98 months with a median of 96 months and a range of 5-178 months. To establish the sufficient radiation modality, the three following Protocols were adapted sequentially (2): 35 cases used Protocol 9402 with a dose escalation of 54.0-72.0 Gy equivalent (GyE), 62 cases used Protocol 9703 with a dose escalation of 60.0-66.0 GyE and a fixed dose of 66.0 GyE, and 157 cases used Protocol 9904 with a fixed dose of 66.0 GyE in 20 fractions. Stages were defined using the UICC (2002). Before treatment, prostate biopsy with eight or more cores was performed and Gleason scores were estimated by a central pathologist (MH). Patients were divided into low-risk, intermediate-risk and high-risk groups using the NCCN classification system (5).

Hormone therapy was used according to risk classification as follows: no hormone therapy for low-risk and intermediate-risk patients with T2ab, and two to six months of neoadjuvant hormone therapy and one year or more of adjuvant hormone therapy for other intermediate-risk patients with T2c or with Gleason score of 7 and all high-risk patients. Hormone therapy generally consisted of a luteinizing hormone-releasing hormone agonist and a daily dose of 80 mg of bicalutamide. After biochemical failure, conventional hormone therapy, second-line hormone therapy and chemotherapy were successively employed.

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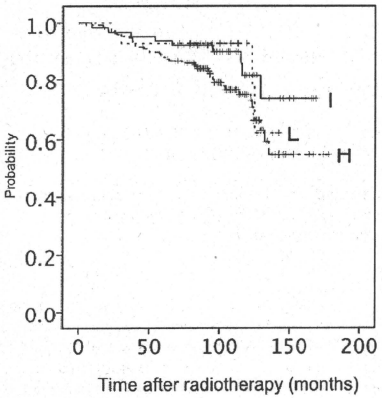

Figure 1. *Overall survival rates of prostate cancer patients treated with carbon ion radiotherapy. The patients are separated by the following risk groups: L, low-risk (29 patients); I, intermediate-risk (66 patients); H, high-risk (159 patients). The vertical axis indicates overall survival probability.*

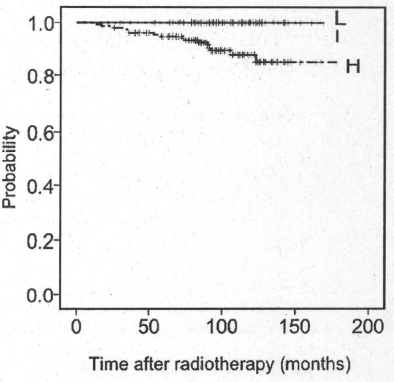

Figure 3. *Clinical progression-free survival rates of prostate cancer patients treated with carbon ion radiotherapy. The patients are separated by the following risk groups: L, low-risk (29 patients); I, intermediate-risk (66 patients); H, high-risk (159 patients). The vertical axis indicates clinical progression-free survival probability.*

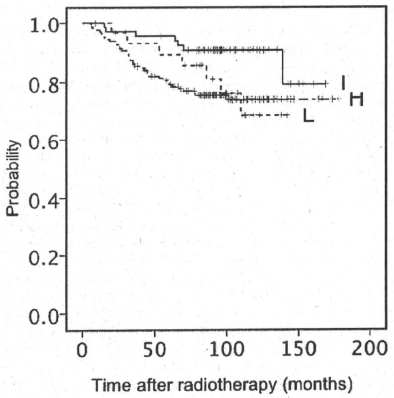

Figure 2. *Biochemical failure-free survival rates of prostate cancer patients treated with carbon ion radiotherapy. The patients are separated by the following risk groups: L, low-risk (29 patients); I, intermediate-risk (66 patients); H, high-risk (159 patients). The vertical axis indicates biochemical failure-free survival probability*

Table 1. *Risk classification. The number of patients with biochemical failure is shown in parenthesis.*

		Low-risk	Intermediate-risk	High-risk
Cases number	29 (7)	66 (7)	159 (40)	
Age (years)	≤60	2	7	10
	61-65	6	12	22
	66-70	8	15	52
	71-75	10	23	54
	76-80	3	8	18
	≥81	0	1	3
Stage	T1bc	19	27	14
	T2ab	10	12	9
	T2c	0	27	37
	T3	0	0	99
Gleason score	≤6	29	26	27
	7	0	40	73
	≥8	0	0	59
Initial PSA (ng/ml)	≤4	4	1	0
	>4-<10	25	21	17
	≥10-20	0	49	29
	> 20-50	0	0	69
	>50-100	0	0	31
	>100	0	0	13

Table II. *Relationship between hormone therapy and biochemical failure. Other failures occurred after termination of hormone treatment.*

	Low risk		Intermediate risk		High risk	
Hormone therapy	No failure	Failure	No failure	Failure	No failure	Failure
none or <1 year	21	7	22	6	15	10
1-2 years	1	0	13	0	32	12
>2 years			24	1	72	4
During treatment[a]						14

[a]Biochemical failure during hormone treatment.

Patients underwent digital rectal examinations and determination of prostate-specific antigen (PSA) every three to six months. If abnormal findings were suspected, an imaging examination including a bone scan and magnetic resonance imaging scan was carried out along with frequent PSA assays. The primary endpoint was biochemical failure, and overall and clinical progression-free survival rates were calculated.

Rates of acute and late morbidities were estimated using the RTOG/EORTG system (6).

PSA kinetics. Total PSA (PSA) was determined using commercial kits (AxSYM PSA Dainapack, Abbot Chiba Japan). Biochemical failure was judged by Phoenix criteria, when PSA elevated by 2 ng/ml or more over baseline (7). PSA-doubling time (PSA-DT) and velocity before biochemical failure were calculated by linear regression. A slope was obtained from three or more points by the least-squares fitting method using the natural logarithm (ln) of PSA (for calculation of PSA-DT) or PSA (for calculation of velocity). Consequently, PSA-DT was calculated as ln 2/slope (8) and velocity was determined as the difference in PSA increase per year (9). The response to salvage hormone therapy was evaluated as follows: a partial response (PR) was defined as a decrease in PSA ≥50% from baseline, progressive disease (PD) was designated as an increase in PSA ≥25% over baseline, and no change (NC) was denoted as any change between PR and PD.

Carbon ion radiotherapy. The technique of carbon ion radiotherapy was previously reported (2). Briefly, the head and feet of the patients were positioned in a customized cradle and the pelvis was immobilized with a thermoplastic sheet. The bladder was filled with 100 ml of sterilized water in the anterior direction at a computed tomography (CT) planning and at each session from the anterior direction. The rectum was emptied with a laxative or enema, if necessary.

The clinical target volume was designed for the prostate and seminal vesicle after referring to a 5-mm thick CT scan. The initial planning target volume was created by adding 10-mm anterior and lateral margins and 5-mm posterior margin. After the first 10 fractions, the posterior margin was set on the anterior wall of the rectum to limit the dose received by the rectum to <50 GyE. Radiation was performed with one anterior-posterior port and a pair of lateral ports which were alternated at each session once a day in four fractions per week for five weeks.

Statistical analysis. Survival was calculated with the Kaplan-Meier method. Statistical differences were determined by the unpaired two-group *t*-test and *p*-value of ≤0.05 was considered statistical significant. All calculations were performed with the SPSS statistical computer program (SPSS Inc, Tokyo, Japan).

Results

Risk groups and outcomes. The risk distribution of the patients was 11%, 26% and 63% in the low-risk, intermediate- risk and high-risk groups, respectively (Table I).

Five patients showed local recurrences (2%)□some of which were due to insufficient radiation doses in the initial Protocols. Distant metastases were detected in a total of 15 patients (6%) distributed as follows; ten in bone, three in abdominal lymph nodes, one in liver and one in lung. Twelve patients (5%) died of cancer-specific causes, all of them were high-risk patients (8% of the high-risk group). Forty-three patients (17%) died of other diseases: four (14%), nine (14%) and thirty (19%) belonged to the low-, intermediate- and high-risk groups, respectively. These patients showed no signs of biochemical failure until death.

The rates of overall survival in all patients at five and eight years after radiotherapy were 90% and 84%, respectively, while the respective rates of biochemical failure-free survival were 85% and 79%. In each group separately, three-, five- and eight-year overall survival rates were 93%, 93% and 93% in the low-risk group, 96%, 94% and 90% in the intermediate-risk group and 95%, 88% and 79% in the high-risk group, respectively (Figure 1). The respective rates for biochemical failure-free survival were 93%, 85% and 76% in the low-risk group, 97%, 95% and 91% in the intermediate-risk group and 85%, 79% and 76% in the high-risk group, respectively (Figure 2). No clinical progression was detected in the low-risk and intermediate-risk groups. Three-, five- and eight-year progression-free survival rates in the high-risk group were 96%, 93% and 89%, respectively (Figure 3, p=0.005).

At G0, G1, G2, G3 and G4, the incidence of acute and late morbidities in the bladder/urethra were 70%, 27%, 3%, 0% and 0% (acute morbidities) and 70%. 21%, 6%, 3% and 0% (late morbidities), respectively, and the incidence of acute and late morbidities in the rectum was 97%. 3%, 0%, 0%

Table III. *Response to salvage therapy after biochemical failure. Data are shown as mean, median (range).*

	PR (37)a	NC and PD (17)a	*p*-value
Risk[b]	7 : 7 : 23	0 : 0 ; 17	
Initial PSA (ng/ml)	31.0, 19.0, (2-174)	50.2, 29.1, (8.2-260)	0.24
Radiation-failure (months)	47, 43, (6-112)	33, 19, (6-139)	0.15
Nadir PSA (ng/ml)	0.81, 0.24, (0.003-10.3)	0.62, 0.2, (0.06-2.8)	0.60
PSA-DT (months)[c]	8.9. 6.5, (1.2-24.9)	4.5, 2.9, (0.65-17.5)	0.009
Velocity (ng/ml/year)[c]	5.4, 1.7, (0.34-68.2)	29.8, 3.0, (0.6-205.2)	0.12

PR: PSA decrease ≥50%, PD: PSA increase ≥25%, NC: any change between PR and PD, [a]Number of cases; [b]Low :Intermediate: High, [c]Value from one case (a patient with lymph node metastasis) was excluded.

and 0% (acute morbidities) and 85%. 9%, 4%, 2% and 0% (late morbidies), respectively.

Effect of hormone therapy. Patients were treated with hormone therapy or left untreated according to the risk classification (Table II). Of 254 patients, 54 (21%) experienced biochemical failure; 24%, 11% and 25% in the low-, intermediate- and high-risk groups, respectively. The relatively high rate of biochemical failure in the low-risk patients may be partially due to the small number of patients in this group compared to the others; moreover, the low-risk group may contain underdiagnosed cases without adjuvant hormone therapy. Biochemical failure occurred infrequently in the intermediate-risk patients, due perhaps to the long-term adjuvant hormone therapy provided to T2c patients. In contrast, no hormone therapy was scheduled for T2ab patients. As the failure rate was rather low in the high-risk patients, hormone therapy seemed to be beneficial and a two-year treatment duration appeared to be better for avoiding biochemical failure compared to shorter treatments.

After biochemical failure, the patients without or after adjuvant hormone therapy were treated with conventional hormone therapy for two years or more. Most patients in the low- and intermediate-risk groups responded well with PR. No cancer deaths were observed in these groups.

Of 159 high-risk patients, 40 (25%) experienced biochemical failure. Twenty-six patients showed failure without or after adjuvant hormone therapy. These patients were treated with conventional hormone therapy repeatedly and 23 patients showed PR and three showed PD. Of these patients, three died of prostate cancer after an average period of 62 months (range 32-106 months) after radiotherapy.

Fourteen high-risk patients progressed to a castration-resistant state despite continuous hormone treatment, nine of whom died of prostate cancer after an average period of 43 months (range 16-91 months) from radiotherapy (Figure 4). The period between radiotherapy and biochemical failure was shorter for these patients (average 20 months: range 6-38 months) than for the other high-risk patients who experienced biochemical failure (average 42 months: range 6-95months; p=0.0002).

The factors influencing the salvage therapy for biochemical failure were examined (Table III). PSA-DT was found to affect response, and a PSA-DT bigger than ten months indicated a good response to salvage hormone therapy (data not shown).

Discussion

Radiotherapy for prostate cancer in Japan is generally reserved for rather advanced stage of the disease. Based on the results determined from 162 patients with prostate cancer at 50 facilities in 1999-2000, 80% of the patients were high-risk, and overall and biochemical failure-free survival rates at three years were 86.7% and 86.1%, respectively. Two-thirds of patients received hormone therapy (10). In the present study, 63% of patients were high-risk.

Low-risk patients are candidates for radiotherapy alone, and such patients achieved favorable outcomes. Treatment for intermediate-risk patients involves consideration of whether or not radiotherapy alone is sufficient. Some of the patients experienced biochemical failure with carbon ion radiotherapy alone. However, patients with a more advanced stage in the intermediate-risk group, namely T2c, showed favorable outcomes after the addition of hormone therapy. This suggests that hormone therapy may be advisable as a supplement for certain intermediate-risk patients.

In the case of high-risk patients, radiotherapy alone is considered to be insufficient. The five-year biochemical failure-free survival rate after radiotherapy with 66Gy was approximately 30% (11). Increasing the radiation dose to 78 Gy using three-dimensional conformal radiotherapy or intensity-modulated radiation therapy improved biochemical failure-free survival rates compared to radiation with less than 72 Gy for high-risk patients (12-13). A radiation dose of 74 Gy for T3 patients with hormone therapy for 1-6

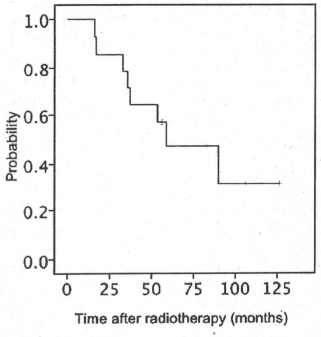

Figure 4. *Cause-specific survival of fourteen high-risk patients with disease progression under continuous hormone treatment after radiotherapy.*

months yielded a biochemical failure-free survival rate of 46% after four years (14). For high-risk prostate cancer, therefore, high radiation doses greater than 72Gy may be required for treatment, and such high doses may be used without serious adverse effects (15). The extension of the target volume to the pelvic area has been proposed (16), but because of the possible adverse effects on the neighboring organs, this technique is still controversial (17). Proton beam radiotherapy resulted in five-year biochemical-free survival rate of 48% in high-risk patients (18). Because carbon ion radiotherapy was the first trial, establishment of radiation modality was arranged from the results of initial Protocols with referring to carbon ion beam property (19). After the initial Protocols, the proper radiation dose was set up to be 66.0 GyE in 20 fractions. The cytocidal effect of this dose was assumed to be comparable to that of high doses of photon. Taking into account other beneficial properties, carbon ion radiotherapy may be considered to be one of the best treatment methods for prostate cancer. Acute and late morbidities associated with treatment are only minor and comparable to those associated with photon radiation (20).

The addition of hormone therapy has generally been recommended before, during and/or after radiotherapy to improve results for high-risk patients (21). In the literature, the reported durations of hormone therapy vary between four months and five years (22). A consensus on the optimal duration has not yet been achieved. Hormone therapy for four months led to improved biochemical failure (22), but longer durations of hormone therapy, ranging from eight to thirty-six months, showed increased biochemical failure-free survival compared to either radiation alone or short-term hormone therapy (23-25). The RTOG 92-02 Trial showed that for high-risk patients 70 Gy of radiation with two years of hormone therapy led to 67% and 44 % of biochemical failure-free rates at five and ten years, respectively (26-27). External beam radiotherapy with hormone therapy showed outcomes similar to those achieved with surgery (28-29). In the present study, high-risk patients were treated with adjuvant hormone therapy and this treatment seems to have achieved considerable biochemical failure-free outcomes in conjunction with carbon ion radiotherapy. Hormone therapy for two years may be sufficient. It is claimed that the addition of hormone therapy is generally credited with improving biochemical failure-free and clinical progression-free survivals, but has no benefit to overall survival. This is an important issue that needs to be further clarified. Recently, studies have reported adverse effects of hormone therapy (30), and trivialized its beneficial effects (31). On the contrary, the addition of hormone therapy is protective to the genitourinary and gastrointestinal tracts (32). Based on these findings, careful use of adjuvant hormone therapy may be beneficial. After biochemical failure, early induction of hormone therapy is more effective than delayed therapy (33). Salvage hormone treatment after failure as judged by the Phoenix criteria was also effective as shown in the present cohort. Factors influencing the response to hormone therapy included PSA-DT before the time of failure and the duration between radiotherapy and biochemical failure, suggesting a correlation with rapidly growing tumors.

A subset of high-risk patients progressed to a castration-resistant state, despite radiotherapy to the prostate and continuous hormone treatment. Most of these patients scarcely showed response to second-line hormone therapy. Clinically distant metastases may occur at certain times after biochemical failure (34-35). Treatments for these patients were performed following EAU guidelines (36), but the patients progressed to a more severe disease state in general. The duration from the start of hormone therapy to biochemical failure in highly advanced prostate cancer patients, such as those at the metastatic stage, was generally one to two years and similar disease progression intervals were observed after radiotherapy. Factors affecting the rapid progression to a castration-resistant state included the duration between radiotherapy and biochemical failure, and PSA kinetics including velocity and PSA-DT (37-38), but other definitely influencing factors have not been determined yet (39). Further advances are awaited in the development of treatment strategies for rapidly growing prostate cancer.

In summary, carbon ion radiotherapy is suitable and tolerable for the treatment of localized prostate cancer, especially for locally advanced stage.

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原　著　Original Article

前立腺癌患者における quality of life（QOL）効用値の評価：QOL 効用値指標 EQ-5D および VAS と健康関連 QOL 質問表 SF-36 および EPIC との比較

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要旨：

（目的）局所前立腺癌の治療法として様々な選択肢があるが，その比較には医療経済的評価が不可欠である．また，費用対効用分析においては，単なる生存期間の比較ではなく QOL を加味した質調整生存年（QALY：quality adjusted life year）の評価が重要である．そこで，QALY 算出に最も広く用いられている QOL 効用値指標である EuroQol-5D（EQ-5D）ならびに visual analogue scale（VAS，0～100 points）の前立腺癌患者における有用性を検討した．

（対象と方法）前立腺癌患者 81 例を対象として，包括的および前立腺癌特異的 QOL 調査票である SF-36 と EPIC を用いて，EQ-5D と VAS との関連を調べた．

（結果）SF-36 の全ての下位尺度において EQ-5D および VAS との有意な相関を認めた．一方，EPIC の下位尺度である排尿，排便，性，ホルモンに関しては QOL 効用値指標に大きな影響はなかった．SF-36 の結果から VAS 効用値を変換算出すると，実際に得られた値と有意で強い相関がみられた（相関係数 0.53, $p < 0.0001$）．

（結論）前立腺癌患者において EQ-5D ならびに VAS を用いた QOL 効用値指標の算出が妥当であり，費用対効用分析に用いる可能性が示された．また，これまでに蓄積されている SF-36 のデータを用いて QOL 効用値指標を変換算出できる可能性が示唆された．

（日泌尿会誌　102(1)：9～13, 2011）

キーワード：前立腺癌，費用対効用分析，質調整生存年（QALY）

緒　言

我が国においては，前立腺癌の罹患率および死亡率は近年上昇を続けており，今後も増加傾向を示すと推測されている[1]．また，人口の高齢化が進行するため，高齢者に多い前立腺癌の有病率は極めて高く，患者総数はさらに増大すると考えられる[2]．したがって，前立腺癌の治療法としては，治療効果が優れているのみならず，費用が適切であることが要求される．このため，前立腺癌に対する治療法の比較にあたっては医療経済的評価が不可欠である[3]．局所前立腺癌の治療法としては，様々な選択肢が存在している．いずれの治療法にも特徴，長所，短所があるが，その比較に際しては，抗腫瘍効果，有害事象やQOL（quality of life）への影響が考慮されるべきである．

一方，治療法別の費用対効用分析においては，単なる生存期間の比較ではなく，QOL 評価を加味した質調整生存年（QALY：quality adjusted life year）の評価が重要である[4]．健康関連 QOL の評価にはさまざまな調査票があるが，いずれも複数の測定尺度を含むため QALY 算出に直接用いることはできない．QALY 算出に最も広く用いられている QOL 効用値指標は EuroQol-5D（EQ-5D）ならびに visual analogue scale（VAS）[5][6]である．そこで，前立腺癌患者におけるこれらの QOL 効用値指標の有用性を明らかにするために，包括的および前立腺癌特異的 QOL 調査票である SF-36[7][8]と EPIC[9]を用いて，EQ-5D と VAS との関連を調べた．

対象・方法

東京厚生年金病院に通院中の前立腺癌患者 81 例を対象とした．年齢は 51～82 歳，平均 70.4±6.9 歳であった．主たる治療法としては，active surveillance（PSA 監視療法）5 例，手術療法（前立腺全摘除術）22 例，放射線療法 38 例，内分泌療法 16 例であり，放射線療法の内訳は，小線源治療 3 例，リニアック外部照射 14 例，粒子線照射 21 例であった．14 例に再発ないし再燃を認め，67 例では再発・再燃なしであった．

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付表　患者効用値（VAS：0～100点）の算出式

VAS＝社会生活機能得点×0.007＋身体機能得点×0.143＋心の健康得点×0.1＋日常役割機能（精神）得点×0.01＋体の痛み得点×0.04＋日常役割機能（身体）得点×0.024＋活力得点×0.182＋全体的健康感得点×0.31

表1　QOL効用値とSF36の関連

SF36（下位尺度8項目）	EQ-5D		VAS	
	相関係数	有意確率	相関係数	有意確率
身体機能	0.474	0.000	0.400	0.000
心の健康	0.251	0.025	0.254	0.030
日常役割機能（身体）	0.400	0.000	0.324	0.006
日常役割機能（精神）	0.295	0.008	0.291	0.013
体の痛み	0.455	0.000	0.401	0.000
全体的健康感	0.439	0.000	0.517	0.000
活力	0.376	0.001	0.401	0.000
社会生活機能	0.232	0.037	0.362	0.002

表2　QOL効用値とEPICの関連

EPIC（下位尺度4項目）	EQ-5D		VAS	
	相関係数	有意確率	相関係数	有意確率
排尿	0.125	0.273	0.300	0.010
排便	0.138	0.232	0.091	0.452
性	0.023	0.843	−0.023	0.852
ホルモン	0.167	0.147	0.120	0.322

2008年9月から12月に自己記入式の質問表によりアンケート調査を行った．QOL効用値指標としては，EQ-5DとVASスケールを用いた．EQ-5Dは，移動の程度，身の回りの管理，ふだんの活動，痛み/不快感，不安/ふさぎ込み，の5項目について3段階で評価する質問表であり，回答結果からQOL効用値が計算される．VASは，想像できる最も悪い健康状態（0ポイント）から想像できる最も良い健康状態（100ポイント）までの直線上に，現在の健康状態を自己評価しプロットするスケールである．包括的および前立腺癌特異的QOL尺度としては，それぞれSF-36およびEPICを使用した．また，SF-36の結果からVASへの変換式（付表）を用いてQOL効用値を算出し，実際の測定値と比較した[10]．

解析はDr. SPSS II（エス・ピー・エス株式会社，東京）を用いて行った．相関の解析にはPearsonの相関分析を使用し，$p<0.05$を有意とした．

結　果

全患者におけるEQ-5DおよびVASとSF-36との関連を下位尺度項目別に示す（表1）．SF-36の全ての下位尺度において，EQ-5DおよびVASとの相関が認められた．両者の相関係数は小さいものの統計学的に有意な相関であった．SF-36の8つの下位尺度のうちでは，身体機能とEQ-5D，全体的健康感とVASとの相関係数が比較的大きかった（図1，2）．全患者におけるEQ-5Dおよび

図1　EQ-5Dと身体機能（SF-36）

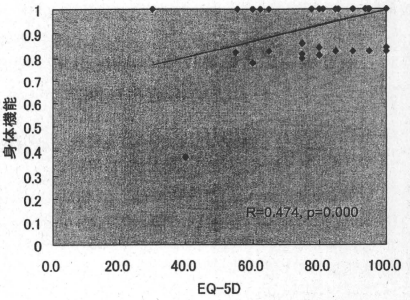


図2　VASと全体的健康感（SF-36）

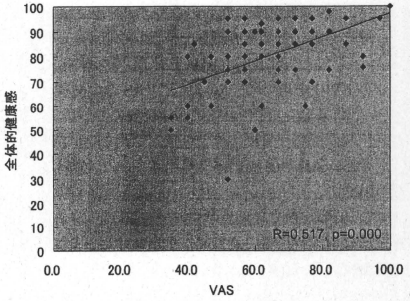
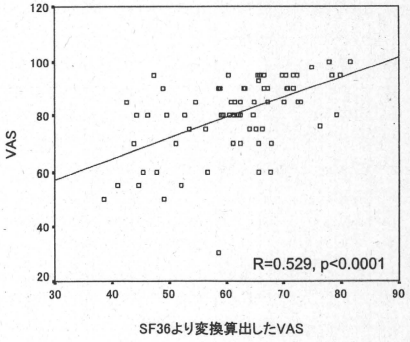


図3　SF-36より変換算出したVASとVAS実測値



VASとEPICとの関連を下位尺度項目別に示す(表2). EPICの排尿尺度とVASとの間に弱い相関を認めたが, それ以外に有意な相関を示すものはなかった. 放射線療法を受けた患者38例のみで解析を行ったところ, 同様に, EQ-5DおよびVASは, SF-36のすべての下位尺度との相関を認め, EPIC下位尺度との強い関連はなかった(data not shown).

EQ-5DとVASとの関連を検討すると, 両者には有意な相関が認められた(相関係数0.36, $p=0.0008$)[11]. 報告された方法によりSF-36の結果からVASスケールの効用値を変換算出すると, 実際に得られた値と有意で強い相関がみられた(相関係数0.53, $p<0.0001$, 図3).

年齢とEQ-5DおよびVASの間には相関はなかった. また, 治療法別にEQ-5DおよびVASを比較したが, 有意な差は認められなかった. 再発・再燃例では, EQ-5DおよびVASが低かったが, 有意な差ではなかった.

考　察

転移のない局所前立腺癌患者に対しては, 手術療法, 放射線療法, 内分泌療法, あるいはそれらの組み合わせなど, 多くの治療選択肢が提示される[12]. これらの比較においては, 抗腫瘍効果に基づく治療効果, 予測される有害事象のリスク以外に, QOLへの影響が重要視されるべきである. また, 医療経済的側面からみると, QOLへの影響を加味した質調整生存年(QALY)による評価が有用である[6].

前立腺癌患者における健康関連QOL評価には種々の質問票が用いられてきた. 包括的質問表としてはSF-36やSF-8, 癌特異的質問票ではEORTC QLQ-C30やFACT-G, 前立腺癌特異的質問表としてはFACT-PやUCLA-PCIやEPICなどが代表的である[7][13]~[17]. これらの質問票はいずれも複数の下位尺度からなっており, 全体として各患者のQOLを評価測定してQALYを算出することは困難であった. 一方, 各種治療法の費用対効用分析においては, QOLへの影響を加味した生存期間を比較することが要求される. そこで, QOL効用値指標を算出するためにEQ-5DやVASスケールが開発され使用されてきた.

今回の検討により, 前立腺癌患者において治療後のQOL効用値指標は一般的QOL評価の全ての下位尺度を反映することが明らかになった. すなわち, EQ-5DおよびVASは健康関連QOLのあらゆる側面から影響をうけていることが示唆され, 効用値評価として用いることは妥当であると考えられた. 一方, 前立腺癌に特異的なQOL下位尺度である排尿, 排便, 性, ホルモンに関しては, QOL効用値指標に大きな影響はなかった. 日本人前立腺癌患者では, 包括的QOL評価に挙げられているすべての下位尺度項目が, 自身の健康評価に重要であり, 疾患やその治療に関連する事象は容認可能であると推測される. また, SF-36のデータから変換算出したQOL効用値指標が, 直接測定したVASと強い相関を示したことより, SF-36質問表のデータが蓄積された前立腺癌患者コホートを費用対効用分析研究の対象として使用可能であることが示唆された.

以上より, 前立腺癌患者においてもEQ-5DならびにVASを用いたQOL効用値指標の算出が妥当であり, 費用対効用分析に用いる可能性が示された. 今回の検討は横断的研究であり, 患者背景や治療期間にばらつきがあったために, 治療法別にみてQOL効用値指標に有意差は認められなかった. 今後, 症例数を増やした縦断的研究により治療法別の比較が可能となると思われる. さらに, 生存期間とあわせてQALYを算出して, 各治療法を評価し比較することが望まれる.

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EVALUATION OF UTILITY INDEX OF QUALITY OF LIFE (QOL) IN PROSTATE CANCER PATIENTS: COMPARISON OF QOL UTILITY INDEX EuroQol-5D (EQ-5D) AND VISUAL ANALOGUE SCALE (VAS) WITH HEALTH-RELATED QOL QUESTIONNAIRES SF-36 AND EPIC

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Abstract:

(Purpose) For the management of patients with localized prostate cancer, a number of therapeutic options are available. To compare the therapeutic modalities, it is important and necessary to evaluate economical aspects based on cost-effectiveness analysis. In addition, the survival time adjusted by quality of life (QOL), quality adjusted life year (QALY), is more reliable than the crude survival time. Thus, the usefulness of the commonly used QOL utility indexes, EuroQol-5D (EQ-5D) and visual analogue scale (VAS, 0–100 points), was investigated in prostate cancer patients.

(Patients and methods) A total of 81 patients with prostate cancer were included. The patients were asked to answer the four sets of questionnaires (EQ-5D, VAS, SF-36 and EPIC). The QOL utility indexes (EQ-5D and VAS) were evaluated in relation to the general and prostate cancer-specific QOL questionnaires (SF-36 and EPIC, respectively).

(Results) The results of EQ-5D and VAS were significantly correlated to all domains of the general QOL questionnaire (SF-36). On the contrary, no remarkable relationship of EQ-5D and VAS was observed with any domain (urinary, bowel, sexual or hormonal) of the prostate cancer-specific QOL questionnaire (EPIC). There was significant and close correlation between the actual values of VAS and the estimates of VAS calculated from SF-36 data ($R = 0.53$, $p < 0.0001$).

(Conclusions) The QOL utility indexes (EQ-5D and VAS) are pertinent to evaluation of QOL utility index in prostate cancer patients and can be utilized for cost-utility analysis. It is suggested that the accumulated data of SF-36 could be used by conversion to QOL utility index.

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Keywords: prostate cancer, cost-effectiveness analysis, QALY (quality adjusted life year)

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Outcome of Photodynamic Therapy Using NPe6 for Bronchogenic Carcinomas in Central Airways >1.0 cm in Diameter

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Abstract

Purpose: Most centrally located early lung cancers (CLELC) <1.0 cm in diameter do not invade beyond the bronchial cartilage, and photodynamic therapy (PDT) with Photofrin is currently recommended as a treatment option for such lesions. NPe6 is a second-generation photosensitizer, and because it has a longer absorption band (664 nm) than Photofrin (630 nm), we hypothesized that NPe6-PDT would exert a strong antitumor effect against cancer lesions >1.0 cm in diameter, which are assumed to involve extracartilaginous invasion and to be unsuitable for treatment with Photofrin-PDT.

Experimental Design: Between June 2004 and December 2008, 75 patients (91 lesions) with CLELC underwent NPe6-PDT after the extent of their tumors had been assessed by fluorescence bronchoscopy for photodynamic diagnosis and tumor depth had been assessed by optical coherence tomography.

Results: Seventy cancer lesions ≤1.0 cm in diameter and 21 lesions >1.0 cm in diameter were identified, and the complete response rate was 94.0% (66 of 70) and 90.4% (19 of 21), respectively. After the mass of large tumors and deeply invasive tumors had been reduced by electrocautery, NPe6-PDT was capable of destroying the residual cancer lesions.

Conclusion: NPe6-PDT has a strong antitumor effect against CLELCs >1.0 cm in diameter that have invaded beyond the bronchial cartilage, thereby enabling the destruction of residual cancer lesions after mass reduction of large nodular- or polypoid-type lung cancers by electrocautery. The PDT guidelines for lung cancers should therefore be revised because use of NPe6-PDT will enable expansion of the clinical indications for PDT. *Clin Cancer Res; 16(7); 2198–204. ©2010 AACR.*

Photodynamic therapy (PDT) consists of using a tumor-specific photosensitizer and laser irradiation to induce production of reactive oxygen species in cancer cells. It is used as a treatment modality for many cancers (1, 2), and it is widely used as a treatment option for solid cancers (3). Since the first modern clinical trial of PDT was reported by Dougherty et al., the photosensitizer Photofrin has been applied to the treatment of many kinds of cancers, and it has been approved by the U.S. Food and Drug Administration for the treatment of centrally located early lung cancer (CLELC) as well as advanced lung cancer. PDT allows lung function to be preserved and is recommended for CLELCs in the evidence-based clinical practice guidelines of the American College of Chest Physicians (4).

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The second-generation photosensitizer mono-L-aspartyl chlorine e6 (talaporfin sodium, NPe6), which has a major absorption band at 664 nm, was recently approved for the treatment of CLELC by the Japanese Ministry of Health, Labour and Welfare (5, 6). A phase II clinical study of NPe6 and a diode laser for the treatment of CLELCs showed an excellent antitumor effect and safety, including significantly lower skin photosensitivity than with Photofrin-PDT (7). Because (630 nm) the mechanism of action of NPe6-PDT differs from that of Photofrin-PDT, because the absorption band of NPe6 is longer than that of Photofrin (5, 8–10), we hypothesized that NPe6-PDT would have a stronger antitumor effect on deeper lesions than Photofrin-PDT does.

Based on their analysis of the histopathologic features of CLELC, Furukawa et al. (11) concluded that it is important to accurately define tumor extent before doing Photofrin-PDT. In their study, the complete response (CR) rate of the group with lesions ≤1.0 cm and the group with lesions >1.0 cm in maximum diameter was 92.8% and 59.1%, respectively (11). In our previous study, we classified 264 lesions treated by PDT into four groups based on the maximum diameter of the longitudinal axis—<0.5 cm group,

Translational Relevance

Photodynamic therapy (PDT) is recommended as a treatment option for centrally located early lung cancers (CLELC), meaning, roentgenographically occult squamous cell carcinomas that are located no more distally than segmental bronchi and, histologically, are either carcinoma *in situ* or carcinoma associated with only limited invasion. Because CLELC patients who are heavy smokers are at fairly high risk of developing a second primary lung cancer, they require treatment that will preserve their cardiopulmonary function. However, although PDT using Photofrin has not been recommended for large tumors or deeply invasive tumors, such as nodular-type lesions, in the past, if their mass is reduced by electrocautery, PDT with the NPe6 second-generation photosensitizer has been found to be capable of destroying the residual cancer lesion. Thus, the PDT guidelines for lung cancer need to be revised because the availability of NPe6-PDT will enable expansion of the clinical indications to many solid cancers.

0.5 to 0.9 cm group, 1.0 to 2.0 cm group, and >2.0 cm group (5, 6)—and their CR rates were 94.4%, 93.5%, 80%, and 44.1%, respectively. Miyazu et al. (12) examined the relationship between bronchoscopic appearance and the depth of tumor invasion estimated by endobronchial ultrasonography and found that most lesions >1.0 cm in diameter were diagnosed as extracartilaginous lesions by endobronchial ultrasonography and were considered unsuitable for treatment by PDT. In 2003, therefore, PDT was recommended only for small lesions (≤1.0 cm in diameter) in the guidelines established by the American College of Chest Physicians (4). Also in 2003, the Japan Photodynamic Association and the Japanese Society for Laser Surgery and Medicine established the following indications for PDT: (*a*) early-stage lung cancer based on an endoscopic evaluation, (*b*) normal chest X-ray and computed tomography findings, (*c*) no evidence of lymph node metastasis, and (*d*) tumor diameter no greater than 1.0 cm (5, 6).

Evaluation of tumor extent and tumor depth is very important to the success of PDT (6, 11, 13). We previously assessed the usefulness of a photodynamic diagnosis (PDD) system consisting of autofluorescence bronchoscopy SAFE-3000 (14) and NPe6 as a means of accurately defining the tumor margin before PDT (13). Although it was difficult to clearly identify tumor extent and to accurately radiate the tumor, we were able to clearly detect red fluorescence emanating from the tumor with the PDD system before PDT, and the PDD system consisting of SAFE-3000 and NPe6 allowed more accurate assessment of the tumor margin and the quality and efficacy of PDT (13).

Optical coherence tomography (OCT) is a new micron-scale resolution optical imaging method used in studies of the eye, gastrointestinal tract, and bronchial lesions. Coxson et al. (15) found that OCT can be used to measure airway wall dimensions. Tsuboi et al. (16) obtained high-resolution, cross-sectional microscopic images of tissue by OCT, potentially enabling optical biopsy to substitute for conventional excisional biopsy. Bronchial lumens were evaluated by inserting the OCT catheter into the working channel of the bronchoscope. In OCT images, the bronchial mucosal and submucosal layers appear in the presence of an extracellular matrix, and CLELCs are visualized as unevenly distributed high backscattering areas and loss of the normal layer structure. The depth range of OCT is sufficient to penetrate through the upper layers of exposed tissue on the airway surface (maximal depth average, 2-3 mm), where many endobronchial and bronchogenic carcinomas originate or spread. Ultrasound has been principally used to evaluate the degree of invasion by lung cancer, and OCT can provide high-resolution images of the bronchial surface, thereby enabling detailed examination of intraepithelial lesions (15, 16). Moreover, Lam et al. (17) reported that autofluorescence bronchoscopy-guided OCT imaging of bronchial lesions was feasible and OCT was a promising nonbiopsy tool for diagnosis of lung cancer.

In the present study, we assessed tumor extent by autofluorescence bronchoscopy (SAFE-3000; refs. 13, 14) and tumor depth by OCT, and we retrospectively evaluated the antitumor effect of NPe6 on tumors >1.0 cm in diameter to revise our indications for PDT and propose a new strategy for the treatment of centrally located lung cancers.

Materials and Methods

Photosensitizer. NPe6 (Meiji Seika) is a second-generation, water-soluble photosensitizer with a molecular weight of 799.69, and it has a chlorine annulus. Its maximum absorption peak is at a wavelength of 407 nm, and there is a second peak at 664 nm (5–7, 13). NPe6 has high tumor affinity, and it is excited by visible red light with a longer wavelength of 664 nm, enabling deeper and superior penetration into living tissues (5–7).

Laser unit. A diode laser (Matsushita Electric Industrial Co.) emitting continuous-wave laser light at a wavelength of 664 nm was used as the light source for excitation of NPe6 (5–7, 13). We can use two kinds of fiber-optic tips: a straight type and a cylindrical type. We usually use the straight-type fiber-optic tip. We use the cylindrical type for tumors that have spread to the bronchial wall.

Diagnostic criteria for CLELC. CLELCs were defined as a lung cancer located no more distally than the segmental bronchi, diagnosed histologically as squamous cell carcinoma, and determined to be carcinoma *in situ* or carcinoma associated with only limited invasion and no evidence of invasion beyond the bronchial cartilage (18–21). We routinely determined tumor depth by OCT to confirm that tumors had not invaded the bronchial wall beyond the level of the cartilage and were confined to the basal membrane of the mucosa, submucosa, or intracartilaginous

Table 1. Clinicopathologic characteristics of the patients who underwent NPe6-PDT (2004.7-2008.12)

Characteristics	No.
Patients (lesions)	75 (91 lesions)
Age (y)	67-83
Gender	Male: 75
	Female: 0
Smoking history	Positive: 75 (>30 pack-years)
Histology	Squamous cell carcinoma: 91 lesions

layers of the bronchial wall (15–17, 22, 23). Immediately before doing PDT, we accurately defined the tumor margin by using autofluorescence bronchoscopy (SAFE-3000) for PDD (6, 13).

PDD procedure, PDT procedure, and follow-up. Laser irradiation (664 nm) for NPe6-PDT was transmitted via quartz fibers inserted through the biopsy channel of the endoscope 4 to 6 h after administration of the photosensitizer NPe6 (40 mg/m^2; refs. 5–7, 13). The total energy of the laser irradiation was 100 J/cm^2 (150 mW/cm^2). Just before starting the PDT, we did PDD with SAFE-3000 and a diode laser (408 nm) to define the tumor margin based on the red fluorescence emitted by the tumor. Immediately after NPe6-PDT, we again did PDD with SAFE-3000 to compare the intensity of the red fluorescence with its intensity just before the PDT (13). As previous reports (5–7), skin photosensitivity after NPe6-PDT was low. Thus, patients were usually prohibited from going out into direct sunlight for 1 wk after administration of NPe6.

The Japanese government approved the use of PDT for CLELCs in 2003. NPe6 became available in Japan in June 2004 (5–7, 13), and we have been using NPe6 for PDT ever since then. Fiber-optic bronchoscopy with cytologic and histologic examination was done at 1, 2, and 3 mo after PDT and at 3-mo intervals during the first year after that, and 6-mo intervals during the second year. The antitumor effect of the initial treatment was rated based on endoscopic measurements of tumor size with forceps, the morphologic appearance of the tumors, and the pathologic findings in biopsy specimens according to the general rules of the Japan Lung Cancer Society and the Japan Society of Clinical Oncology (5–7, 13). Antitumor effect was evaluated again at 3 mo after PDT, and at that time, the tumors were classified as showing a CR (no microscopically demonstrable tumor in the brushings and or biopsy specimens over a period of 4 wk; refs. 5–7, 13). We used fluorescence bronchoscopy (SAFE-3000) as part of the follow-up examination after NPe6-PDT (6, 13).

Patient selection. At the Tokyo Medical University Hospital between June 2004 and December 2008, we found 75 patients with CLELC by bronchoscopic examination because of abnormal sputum production and/or sputum cytologic abnormalities. NPe6-PDT was used to treat patients who met the criteria for NPe6-PDT after obtaining their informed consent in accordance with institutional guidelines (4–6). The clinicopathologic characteristics of the patients are listed in Table 1. Their median age at diagnosis was 75 y (range, 67-84 y). All of the patients were men and heavy smokers with a smoking history of >30 pack-years.

Statistics. The relationship between tumor size and clinical response was statistically analyzed by using the Mann-Whitney test (24, 25). The local control after CR by NPe6-PDT until recurrence was plotted by the Kaplan-Meier method (26, 27). The log-rank test was used to compare the relapse-free probability of tumors ≤1.0 and >1.0 cm in diameter.

Results and Discussion

Between June 2004 and December 2008, 75 patients (91 lesions) with CLELCs underwent NPe6-PDT and PDD based on the diagnostic criteria indications (Table 1). The histologic type of all of the cancers was squamous cell carcinoma. In accordance with the guidelines for PDT for the treatment of lung cancer, we estimated tumor depth by OCT (15–17, 24) and tumor extent by fluorescence bronchoscopy (SAFE-3000; refs. 13, 14). The Japanese Lung Cancer Society classifies CLELCs on the basis of the endoscopic findings into a thickened type, polypoid type, and nodular type (5–7, 13). The thickened type is characterized by superficial lesions manifested by subtle mucosal changes on the bronchial surface, and it is the predominant type (5–7, 13). Of the 91 lesions examined in this study, 70 had a diameter ≤1.0 cm, and 69 of them were the thickened type and 1 was the polypoid type. Of

Table 2. Relationship between the size of tumor and outcome of NPe6-PDT (2004.7-2008.12)

	Tumor size ≤1.0 cm	Tumor size >1.0 cm
Endoscopic findings	CR	CR
Thickened type	69 (65) lesions	17 (15) lesions
Polypoid type	1 (1)	3 (3)
Nodular type	0 (0)	1 (1)
CR rate	94% (66 of 70 lesions)	90.4% (19 of 21 lesions)