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The Role of Adjuvant Postoperative External Beam Radiotherapy for Locoregional Control in Recurrent Advanced Papillary Thyroid Carcinoma : Preliminary Report in a Single Institute

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재발된 진행 갑상선 유두암의 국소 및 부위 치료를 위한 수술후 보조 외부방사선의 역할

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= 국 문 초 록 =

목적 : 국소 재발한 진행된 갑상선 유두암의 치료로 수술 후 외부방사선의 역할을 알아보고자 하였다.

대상 및 방법 : 원자력병원에서 2000년 1월부터 2012년 2월까지 사이버나이프 혹은 외부방사선 치료를 받은 수술과 방사선요오드 치료 후 국소 재발한 진행된 갑상선 유두암 환자 13 명을 대상으로 하였다. 경과관찰 기간 동안 국소 및 부위 재발이 발생환 환자는 6 명이었다. 몇몇의 위험인자를 찾기 위해서 Kaplan-Meier method와 log-rank test를 이용하여 성별, 종양단계, 방사선 치료 전 수술 횟수, 방사선요오드치료 횟수, 수술 후 잔존 암의 여부, 원격전이에 대해 단변량 분석하였다.

결과 : 방사선 치료 후 평균 추적관찰기관은 53.8개월(범위, 36～108개월)이고 그중 남자는 4 명이었다. 1년, 2년의 무진행 생존률은 각각 76.9와 53.8%였다. 단병량 분석은 성별과 잔존 암여부($p = 0.0475$ and $p = 0.0475$, 각각)에 따라 무진행 생존률이 진행한 그룹과 진행하지 않은 그룹 사이에 유의한 차이가 있다는 것을 보여줬다.

결론 : 외부 방사선 치료 전에 잔존 암이 없었던 환자의 100%에서 국소 및 부위 재발이 일어나지 않았다. 외부방사선 치료는 수술과 방사선요오드 치료에 반응하지 않는 환자 중 수술 후 잔존 암이 없는 경우에 효과적인 치료 방법이 될 수 있다.

중심 단어 : 갑상선 유두 · 외부방사선치료.

Introduction

Papillary thyroid cancer (PTC) is the most common type of thyroid cancer, representing 75～85% of all thyroid cancers. The recurrence rate of PTC is 35% over 40 years, and two-thirds of recurrences are known to manifest within 10 years after initial treatment.[1] The most common recurrence pattern is locoregional failure (LRF), which accounts for more than 50% of recurrences in all high-risk groups.[2] The management of PTC involves a combination therapy of surgery, thyroid-stimulating hormone suppression, and radioactive iodine (RAI) therapy. External beam radiotherapy (EBRT) is a controversial treatment because of the lack of randomized controlled trials supporting its utility.

The American Thyroid Association (ATA) recommends

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EBRT for patients older than 45 years with grossly visible extrathyroidal extension (ETE) at the time of surgery and with a high likelihood of microscopic residual disease, as well as for patients with gross residual tumors in whom further surgery or RAI treatment would likely be ineffective.[3] To diminish the LRF rate in these patients, adjuvant postoperative EBRT has been used in many institutions. However, the role of adjuvant EBRT in the survival and prognosis of patients with advanced PTC has not been validated. In this study, we analyzed the role of adjuvant EBRT for patients with PTC and frequent recurrence. The aim of this study was to evaluate the potential role of EBRT in the management of patients treated with conservative surgery for recurrent locally advanced PTC.

Materials and Methods

1. Patients

Thirteen patients who were diagnosed with recurrent locally advanced PTC after surgery between January 2000 and February 2012 in Korea cancer center hospital received a course of EBRT. All patients underwent thyroid operation and neck dissection and received ablative RAI therapy after surgery. This retrospective study was performed via a review of past medical records. The patients' characteristics are shown in Table 1. Of the 13 patients, 4 were men, and 9 were women. The median patient age was 61 years (range, 54～79 years). The initial tumor stage of patients before radiotherapy (RT) was T4 in 12 patients. Meanwhile, 3 patients had central neck lymph node metastasis, 4 patients had lateral neck lymph node metastasis, and 6 patients (46.2%) had distant metastases. In most cases, we were able to reclassify the cancer stages using the pathologic and operative records based on the American Joint Committee on Cancer classification 7th edition.[4] Complete response (CR) was defined as the disappearance of all extranodal target lesions and a decrease in the short axis of pathologic lymph nodes after RT to <10 mm. Partial response (PR) was defined as a decrease (>30%) in the sum of diameters of target lesions, taking the baseline sum of diameters as a reference. Stable disease (SD) was defined as a state in which the lesions displayed neither sufficient shrinkage to qualify as PR nor a sufficient increase to qualify as progressive disease (PD). PD was defined as cancer in which the sum of the diameters increased by at least 20% from the smallest value on study or that demonstrates an absolute increase of at least 5 mm in diameter.[5] Patients with CR, PR, or SD comprised the non-progression group; those with PD comprised the progression group.

Table 1. Patients characteristics

No		N=13
Sex(F:M)		9(69.2%) : 4(30.8%)
Median age (years)		61.0±8.4 (54~79)
Median F/U (month)		26.0 (24~96)
Initial tumor stage	T3 T4	1 (7.7%) 12(92.3%)
Distant metastasis	Yes No	6(46.2%) 7(53.8%)
Postoperative gross residual mass (immediate before RT)	Yes No	9(76.9%) 4(30.1%)
Operation number before RT		3.8
RAI number before RT		4.4

2. Treatment

All patients underwent thyroid operation and neck dissection and received ablative RAI therapy after surgery. The initial thyroid operation performed before EBRT is listed in Table 2. The first round of RAI therapy was performed 1～3 months after surgery. RAI therapy was repeated every 3～6 months after the first therapeutic dose until no significant ^{131}I uptake was recorded. All patients received thyroid hormone in doses sufficient to suppress the endogenous production of thyroid-stimulating hormone. RAI therapy was administered to all patients. The mean number of rounds of RAI therapy was 4.4. The mean number of operations before EBRT was 3.8. EBRT was planned for patients who experienced repeated recurrences after serial surgeries and RAI therapies, for those for whom an additional surgery could result in serious complications such as vocal cord palsy, and for those who refused further surgery and RAI therapy because of old age. Progression-free survival (PFS) was defined as the duration between a finding of no RAI uptake after ablative RAI therapy and revision surgery. Twelve patients were treated with EBRT, and only 1 patient underwent CyberKnife surgery. Immediately before RT, 9 patients were found to have gross residuum through a review of operative records and imaging studies.

EBRT was administered at a total dose of 30～70 Gy on thyroid bed and bilateral regional neck node areas. CyberKnife was administered at a total dose of 1.8 Gy on both retrotracheal and paraesophageal area. Patients received thyroid hormone replacement therapy, and they were followed

Table 2. Clinicopathologic features of patients

Number	Sex /Age	Pathology	Operation number before RT	Recurrence number before RT	Gross residual before RT	Local or regional residual mass	RT type & dose	Distant metastasis	Disease progression after RT	Follow up after RT (month)	status
1	M/59	PTC	2	1	N	No	EBRT 6000	N	N	96mo	alive
2	M/79	PTC	1	1	Y	local (trachea)	CK 180	Y	N	79mo	alive
3	F/65	PTC	4	3	N	No	EBRT 6600	N	N	54mo	alive
4	M/69	PTC	3	2	N	No	EBRT 6600	N	N	44mo	alive
5	F/66	PTC	3	2	N	No	EBRT 5000	N	N	39mo	alive
6	F/54	PTC	7	6	Y	regional(pphx,lateral LN)	EBRT 6000	Y	N	25mo	alive
7	M/64	PTC	5	5	Y	regional(central LN)	EBRT 6600	N	N	28mo	alive
8	F/77	PTC	3	3	Y	local(trachea, esophagus) & regional(lateral LN)	EBRT 7000	Y	Y	38mo	alive
9	F/57	PTC	2	1	Y	local(RLN)	EBRT 6000	N	Y	27mo	alive
10	F/59	PTC	4	3	Y	regional(central LN)	EBRT 6000	N	Y	25mo	alive
11	F/61	PTC	2	4	Y	local(trachea) & regional(lateral LN)	EBRT 5500	Y	Y	38mo	alive
12	F/76	PTC	2	1	Y	regional(lateral LN)	EBRT 3000	Y	Y	26mo	alive
13	F/73	PTC	3	3	Y	regional(central LN)	EBRT 5500	Y	Y	24mo	alive

up at intervals of 6～12 months and were assessed via thyroid function testing (thyroglobulin and thyroid-stimulating hormone levels), computed tomography or ultrasonography, ^{131}I whole-body scintigraphy, and other radiologic studies if necessary. The median follow-up duration was 50.0 months (range, 36～96 months) after RT.

3. Statistical analysis

The data were statistically analyzed using a statistical software program, MedCalc version 13.0 (MedCalc Software, Belgium). Clinicopathological features were calculated using the chi-squared test, and PFS was calculated using the Kaplan-Meier method and log rank test. To identify the risk factors, several potential risk factors such as sex, tumor stage, the number of pre-RT operations, the number of rounds of RAI therapy before RT, presence of postoperative residual masses (immediate before RT), and distant metastasis were subjected to univariate analyses by the Kaplan-Meier method and log-rank test. The significance level in the statistical tests in this study was set at $p < 0.05$.

Results

1. Patterns of failure

Of 13 patients, 7 patients were categorized into the non-progression group, and the remaining patients comprised the progression group. In total, 4, 3, 3, 1, and 2 patients experienced recurrence on 1, 2, 3, 4, and 5 occasions, respectively. The mean PFS duration before the first recurrence was 62 months (n = 13), compared to 40, 35, 23, and 23 months before the second (n = 9), third (n = 6), fourth (n = 3), and fifth (n = 2) recurrences, respectively.

2. Survival

The clinicopathological features of the patients are listed in Table 2. Six patients had distant metastasis before RT. PFS curves are shown in Fig. 1. The PFS rates at 1 and 2 years were 76.9 and 53.8%, respectively. Disease progression occurred in 6 patients during the follow-up period after EBRT. The mean periods until disease progression were 29.5 months after RAI and 64.1 months after RT in the non-progression

Table 3. Univariate analysis of the prognostic factors

		Post RT progression (-) (N=7)	Post RT progression (+) (N=6)	P-value
Median age		61.0±7.3	64.5±9.8	0.4375
Gender	F	3	6	0.0475
	M	4	0	
Stage	T3	1	0	0.4141
	T4	6	6	
Operation number before RT	≤ 3	4	3	0.9306
	≥ 4	3	3	
RAI number before RT	≤ 4	4	5	0.3466
	≥ 5	3	1	
Postoperative residual mass (immdiate before RT)	Yes	3	6	0.0475
	No	4	0	
Distant metastasis	Yes	2	4	0.0700
	No	5	2	

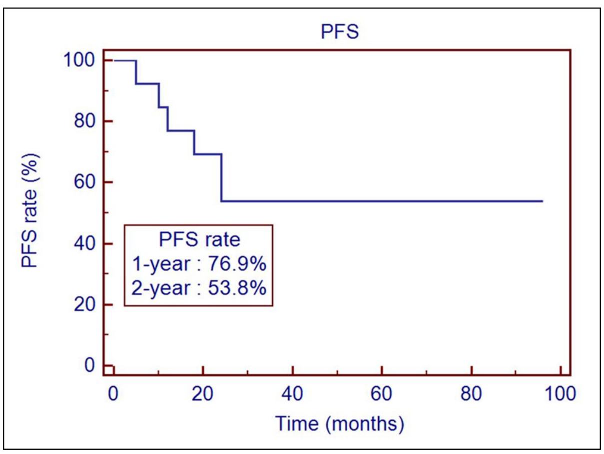

Fig. 1. Kaplan-Meier curve for progression-free survival (PFS)

group. Among them, 5 patients displayed prolonged post-RT PFS compared to the findings before RT.

3. Analysis of prognostic factors

To determine the prognostic factors influencing PFS, all patients were categorized into the progression or non-progression group, and several clinicopathological variables were evaluated by univariate analysis. Specifically, sex, tumor stage, the number of pre-RT operations, the number of rounds of pre-RT RAI therapy, presence of postoperative residual mass, and distant metastasis were considered. The results of univariate analysis are summarized in Table 3. The analysis uncovered significant differences in PFS according to sex (p = 0.04) and the presence of postoperative residual (p = 0.0475) between the two groups. Tumor stage (p = 0.4141), the number of pre-RT operations (p = 0.9306), the number of rounds of pre-RT RAI therapy (p = 0.3466), and distant metastasis (p = 0.0700) did not influence disease progression (Fig. 2).

4. Complications of RT

Four complications were noted in all patients who underwent RT. All patients complained of symptoms such as skin reaction, laryngeal irritation, hoarseness, and xerostomia because of acute sialadenitis. No irreversible morbidities such as lesions of the spinal cord in patients after RT were observed.

Discussion

Our retrospective analysis of 13 cases illustrated the advantages of RT in preventing recurrence. This study revealed 1- and 2-year PFS rates of 76.9 and 53.8%, respectively. In our study, in the 7 patients in the non-progression group, the duration of PFS was increased to 64.1 months after RT, compared to 29.5 months after RAI therapy (p = 0.579).

EBRT was very effective in patients with a gross residual tumor due to frequent recurrence after surgery. Many data had showed the benefit of EBRT for locoregional control. In a study by Kwon et al., PFS at 5 years was lower in patients with gross residuum in those without gross residuum (57.9% vs. 96.2%), although the difference was not significant in multivariate analysis.[6] According to Tsang et al.,[7] there was a beneficial effect of EBRT in patients with papillary tumors and microscopic residuum. They observed superior 10-year cancer specific survival (100%) and PFS (93%) rates in the irradiated group compared with the non-irradiated group (cancer specific survival = 95%, p = 0.038; PFS = 78%, p = 0.01).

In our study, the PFS rate was lower than that observed in other studies. This finding was related to the selection of patients who did not respond to the treatment and who did not show more than one recurrence. Our data illustrated that EBRT can improve PFS in patients without gross postoperative residual masses. EBRT was found to be effective in patients without gross residual mass after incomplete surgery in our study. Our study data suggest resection of as much of the residual mass as possible results in better outcomes after RT when complete resection is impossible.

Many studies identified prognostic factors that affect the outcome of RT in patients with PTC. According to Kwon

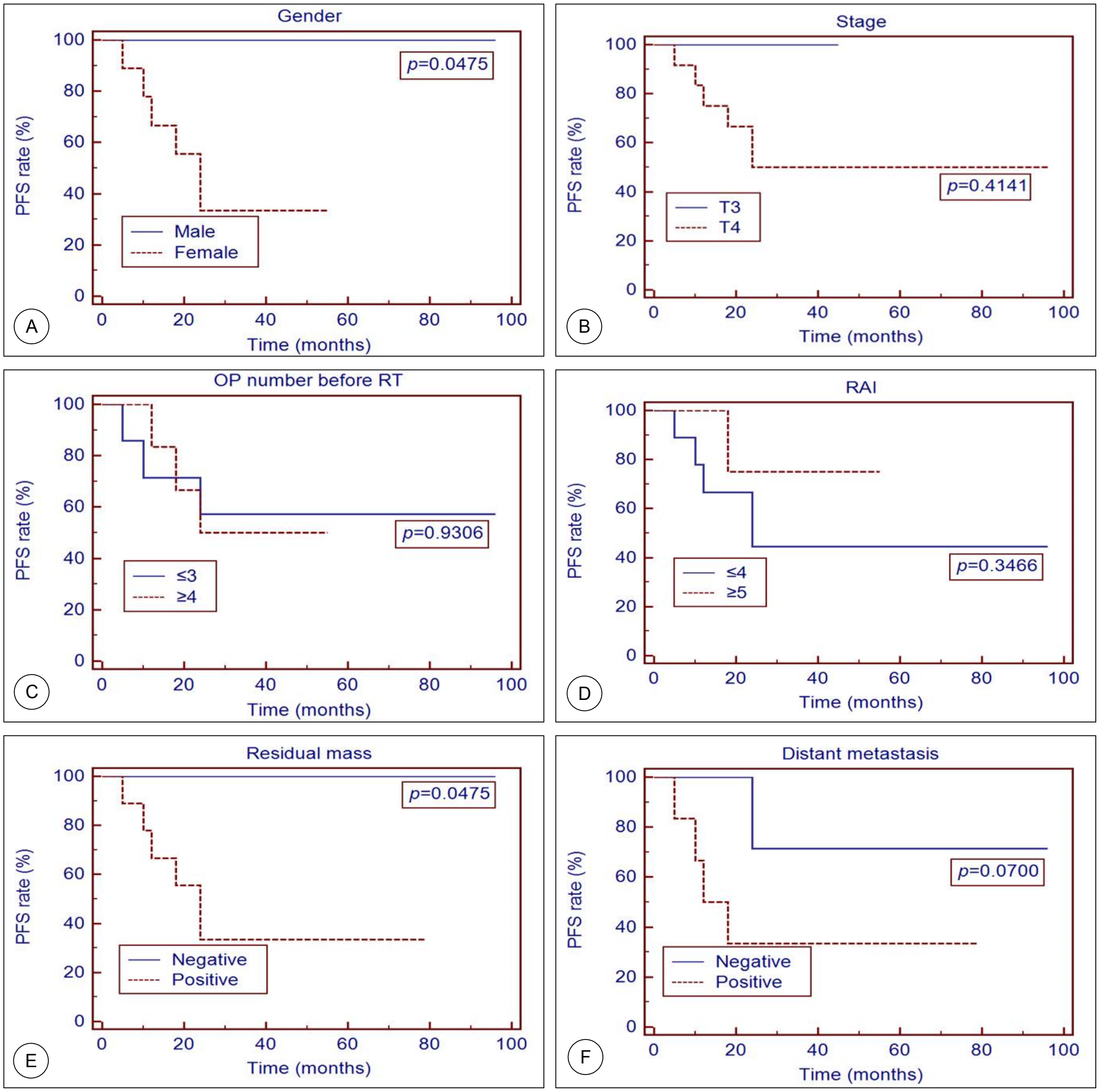

Fig. 2. Effect of sex (A), tumor stage (B), number of pre-radiotherapy (RT) operations (C), number of cycles of pre-RT radioactive iodine (RAI) therapy (D), presence of postoperative residual mass (E), and distant metastasis (F) on progression-free survival (PFS) according to univariate analysis.

et al.,[6] PFS significantly decreased considering the male sex (63.6% vs. 100%, $p = 0.020$), gross residuum after resection (57.9% vs. 96.2%, $p = 0.002$), positive tumor close to or at the surgical margin (37.5% vs. 92.0%, $p = 0.044$), and tracheal invasion (93% vs. 50.0%, $p = 0.040$), and the extent of surgery and EBRT method did not display a relationship with recurrence. In our study, there was a significant difference in PFS according to sex ($p = 0.0475$) and the presence of postoperative residual masses ($p = 0.0475$). Tumor stage ($p = 0.4141$), the number of pre-RT operations ($p = 0.9306$), the number of rounds of pre-RT RAI therapy ($p = 0.3466$), and distant metastasis ($p = 0.0700$) did not influence disease progression.

In our study, EBRT was indicated for patients who experienced repeated recurrence after serial surgeries and RAI therapies, for those in whom additional surgery could create serious complications such as vocal cord palsy, and for those who refused further surgery or RAI therapy because of old age. The ATA proposed the indications for EBRT. EBRT is used infrequently in the management of thyroid cancer except as a palliative treatment for locally advanced, otherwise unresectable disease.[8] There are reports of responses among patients with locally advanced disease,[9,10] as well as improved relapse-free and cause-specific survival.[11] Adjuvant EBRT to treat PTC is indicated in patients with many adverse features. Keum et al.[12] observed that EBRT significantly lowers the LRF rate in patients with PTC invading the trachea despite a higher frequency of microscopic or macroscopic residual tumor in the irradiated group. Hu et al.[13] reviewed 55 patients with stage III well differentiated thyroid carcinoma and the presence of ETE in those who received EBRT. In the study by Kim et al.,[14] who analyzed 91 patients with PTC and ETE or lymph node involvement, the PFS rate at 5 years was significantly improved at 95.2% with EBRT, compared to 67.5% without EBRT (p = 0.0408).

The role of adjuvant EBRT in the treatment of PTC is controversial. Until recently, it was unclear whether postoperative EBRT was beneficial, particularly in patients with repeatedly advanced PTC. This uncertainty resulted from the fact that all of the studies evaluating adjuvant EBRT for PTC were retrospective, the extent of disease was different in each study, and different radiation fields and doses were used.[12,15,16] Side effects exist, including skin reactions, laryngeal irritation, hoarseness, and xerostomia because acute sialadenitis, in addition to irreversible morbidities such as lesions of the spinal cord. In our study, patients had no irreversible morbidities. There are many concerns concerning EBRT because of its side effects despite its effectiveness in extending PFS.

Most doctors have prescribed RAI therapy as an adjuvant treatment for PTC. Many studies revealed that the benefit of EBRT was limited to only reducing the risk of LRF. By contrast, it appears that RAI therapy could both reduce the LRF rate and improve cause-specific survival, and the use of whole-body iodine scintigraphy permits an evaluation of disease progression. However, RAI therapy and EBRT are not alternative options. Several institutions also applied EBRT in high-risk patients with PTC to lower the risk of LRF.[13,14]

The mean duration of PFS before the first recurrence was 62 months (n = 13) in our study, compared to 40, 35, 23, and 23 months before the second (n = 9), third (n = 6), fourth (n = 3), and fifth (n = 2) recurrences, respectively. These data illustrate that the duration of PFS tends to decline with repeated recurrence, indicating that the effect of conventional treatments such as RAI therapy or surgery decreases.

This study has some limitations. Patients who did not receive EBRT were not included in this study. In addition, this study had a small number of patients and a relatively short follow-up period. To define the role of EBRT accurately for PTC, more patients are needed.

Conclusion

Our locoregional control rate was 100% during follow-up in patients without residual masses after EBRT. EBRT in patients with frequently recurrent advanced PTC could be an effective treatment option for those without postoperative residual masses and those who did not respond to standard therapy(e.g., surgery, RAI, and thyroid hormone suppression).

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