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Role of Radiation Therapy for Retropharyngeal Lymph Node Area in Hypopharyngeal Cancer

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Abstract

Purpose: To retrospectively analyze the efficacy of irradiation of the retropharyngeal lymph node (RPLN) area in hypopharyngeal cancer without pretreatment RPLN metastasis.

Materials and Methods: We retrospectively identified patients with hypopharyngeal cancer irradiated curatively between May 2001 and August 2017. Patients in whom RPLN metastases were identified on pretreatment examination were excluded. The incidence of RPLN recurrence, and overall, progression-free survival probabilities were analyzed. Of a total of 90 consecutive patients who received curative radiotherapy at our institution, 11 patients (12%) were positive for RPLN metastasis on pretreatment examination. Thus, 79 patients were included in the analysis. Of these 79 patients, 62 patients underwent radiotherapy to the whole neck including the RPLN area, and 17 patients to the whole neck excluding the RPLN area. The median follow-up duration was 35 months (range: 4-193 months).

Results: RPLN recurrence was identified in 1 patient (1.2%). Overall survival probabilities at 5 years for patients irradiated to the whole neck including the RPLN area, and those excluding the RPLN area were 71% and 63%, respectively. The difference in overall survival probabilities between patients irradiated to the whole neck including the RPLN area, and those excluding the RPLN area was not statistically significant ($p = 0.314$). Progression-free survival probabilities at 5 years for patients irradiated to the whole neck including the RPLN area, and those excluding the RPLN area were 45% and 52%, respectively, and the difference was not statistically significant.

Conclusion: Irradiation for RPLN area in hypopharyngeal cancer without pretreatment RPLN metastasis may be unnecessary.

Keywords: Hypopharyngeal Cancer; Retropharyngeal Lymph Node; Irradiation; Rpln Recurrence; Overall And Progression-Free Survival Probabilities

Abbreviations: RPLN: Retropharyngeal Lymph Node; 3D-CRT: 3-Dimensional Conformal Radiotherapy; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; SUV: Standardized Uptake Value; BSA: Body Surface Area; PET: Positron Emission Tomography

Introduction

Hypopharyngeal cancer is relatively rare, accounting for fewer than 5% of head and neck cancers [1]. The prognosis of hypopharyngeal cancer remains more unfavorable than that of most other types of cancer, owing to its late presentation, with 70%-90% of patients having stage III or IV disease at the time of presentation. This is attributable to the rapid lymphatic spread of these tumors and the anatomical location of the hypopharynx [2]. Patients with hypopharyngeal cancer have low 5-year survival rates of 15%-30% owing to the high risk of recurrence [3]. Surgery, radiotherapy, and/or chemoradiotherapy are selected as treatment options. Chemoradiotherapy protocols can achieve locoregional control of head and neck cancer [4,5]. Prophylactic irradiation of the whole neck is necessary in patients with hypopharyngeal cancer, owing to high rates of cervical lymph node metastases, with 40% of patients having contralateral occult nodal metastases early in the course of the disease [3,6, 7]. Retropharyngeal lymph node (RPLN) metastasis is considered to be relatively common in patients with hypopharyngeal cancer. Investigators have reported that 13%-18% of patients had pathologically positive RPLNs in their surgical series [8-10]. The RPLN area is routinely defined as the radiotherapy target regardless of the clinical stage of the hypopharyngeal cancer [11,12]. However, it has been controversial whether performing radiotherapy to the RPLN area in patients with no evidence of RPLN metastasis has any beneficial effects. Some studies have been performed to analyze metastasis to the RPLN in patients with hypopharyngeal cancer who underwent pretreatment examinations. However, to our knowledge, the reports in the literature for RPLN recurrence after radiotherapy for hypopharyngeal cancer with no evidence of pretreatment RPLN

metastasis are insufficient. Therefore, the purpose of this study was to retrospectively analyze the benefits of irradiation to the RPLN area in patients having hypopharyngeal cancer without pretreatment RPLN metastasis.

Materials and Methods

Patients

Ninety consecutive patients with hypopharyngeal cancer who were curatively treated using 3-dimensional conformal radiotherapy (3D-CRT) between May 2001 and August 2017 at Tokyo Medical University Hachioji Medical Center were retrospectively identified. All patients provided written informed consent, and this study was approved by the Ethical Review Board of the authors' institution. Patients in whom RPLN metastases were detected on pretreatment examination were excluded. Of a total of 90 consecutive patients who received curative radiotherapy at our institution, 11 patients (12%) were positive for RPLN metastasis on pretreatment examination. Thus, 79 patients were included in this analysis. The patients' characteristics are summarized in Table 1. Seventy-six patients (96%) were men and 3 (4%) were women. The median age of the patients was 69 years (range, 39-90 years). Almost all patients (95%) had an Eastern Cooperative Oncology Group performance status of 0 or 1. The distribution of the primary site was as follows: piriform sinus in 53 patients, postcricoid area in 7 patients, and the posterior wall in 19 patients. More than 80% of the patients (n = 66, 83%) had advanced-stage disease (stages III or IV).

Table 1: Patients' characteristics.

No. of pts	79
Sex (percentage)	
Man	76 (96)
Woman	3 (4)
Age (years), median (range)	69 (39–90)
Performance status (percentage)	
0	64(81)
1	10 (13)
2	4 (5)
3	1 (1)
Tumor site (percentage)	
Piriform sinus	53 (67)
Postcricoid area	7 (9)
Posterior wall	19 (24)
Clinical stage (percentage)	
Stage I	3 (4)
Stage II	10 (13)
Stage III	21 (26)
Stage IV	45 (57)
No. of pts performed chemotherapy (percentage)	57 (72)
Induction	18 (23)
concomitant	54 (68)
No. of pts irradiated for whole neck (percentage)	
including RPLN area	62 (78)
excluding RPLN area	17 (22)

RPLN, retropharyngeal lymph node

Determination of the level of the cervical lymph nodes by imaging was in accordance with the Radiation Oncology Group consensus guidelines based on the Danish Head and Neck Cancer Group, European Organization for Research and Treatment of Cancer, Grouped' Oncologie Radiotherapie Tete et Cou, and National Cancer Institute of Canada [13]. Cervical lymph nodes with a shortest axial diameter of ≥ 10mm, and retropharyngeal lymph nodes with a shortest axial diameter of ≥ 5mm on computed tomography (CT) or magnetic resonance imaging (MRI) were defined as malignant. Lymph nodes of borderline size with abnormal enhancement were also determined as malignant [14, 15]. Lymph nodes with a maximum fludeoxyglucose activity of ≥ 2.5 standardized uptake value (SUV) were also regarded as malignant [16-18]. The disease stage was determined in accordance with the 2002 TNM classification (6th edition, International Union Against Cancer).

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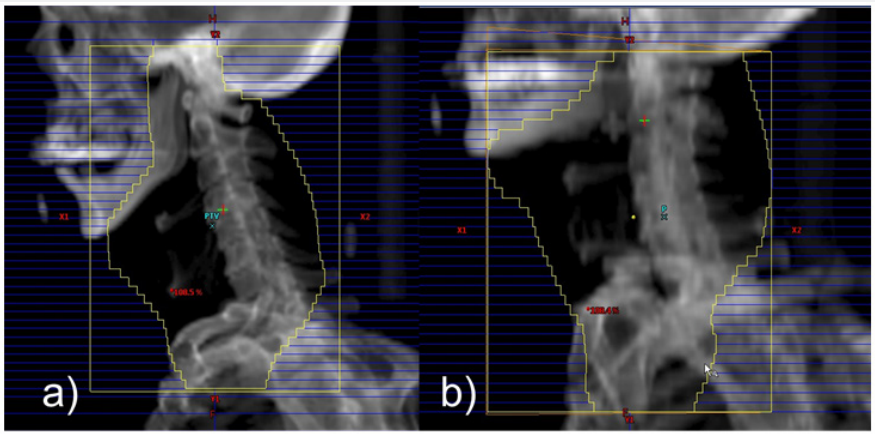
Treatments

The 3D-CRT treatment was planned and performed with the patient using a shell in the supine position. For treatment planning, all patients underwent cervical CT at a 2.5mm slice thickness. Typically, the whole neck was irradiated at a dose of 40Gy, and an additional dose of 20-30Gy was administered to the primary site and the lymph node metastases. The radiotherapy field of the whole neck included areas of levels II, III, and IV, the supraclavicular lymph nodes, and IB or V with or without the RPLN area. Typical fields of whole neck irradiation both including and excluding the RPLN area are shown in Figure 1. Patients were treated with photons of 4MV and 2.0Gy, once a day, for 5 days a week. Induction and concomitant chemotherapy were performed on patients with stage IV and those with stage II or higher disease, respectively. Patients were not treated with chemotherapy if they had renal dysfunction or an Eastern Cooperative Oncology Group performance status of 2 or more. From 2001 to 2013, docetaxel hydrate (80mg/m2 body surface area [BSA]), cisplatin (80mg/m2 BSA), and 5-fluorouracil (4,000mg/m2 BSA) were used as an induction chemotherapy 4 weeks before the start of radiotherapy, and they were used as a concomitant chemotherapy every 4 weeks during the radiotherapy. From 2014, induction chemotherapy consisted of docetaxel hydrate (60mg/m2 BSA), cisplatin (60mg/m2 BSA), and 5-fluorouracil (3,000mg/m2 BSA) administered 4 weeks before the start of radiotherapy. As a concomitant chemotherapy, either cisplatin or cetuximab was administered. Cisplatin (80 mg/m2 BSA) was administered every 3 weeks during radiotherapy. Cetuximab was administered at 400 mg/m2 BSA 1 week before the start of radiotherapy, and at a regular weekly dose of 250mg/m2 BSA during radiotherapy. In summary, 57 patients (72%) received induction or concomitant chemotherapy, and 62 patients (78%) were irradiated to the whole neck, including the RPLN area. The median follow-up duration of the patients was 35 months (range: 4-193 months).



(a) A typical field of whole neck irradiation, including the RPLN area. (b) A typical field of whole neck irradiation, excluding the RPLN area.

Figure 1: Beam's eye views of radiation treatment planning.

Follow-up procedures

Regular follow-up visits were performed once a month after completing radiotherapy for the first year, at 3 to 4 month intervals for the second and third years, and every 4 to 6 months thereafter, in the case of the absence of clinical symptoms. At each follow-up visit, the evaluation consisted of laryngoscopy, and medical history and physical examination. CT was performed every 6 months, and positron emission tomography-computed tomography (PET/CT) was performed once a year.

Statistical Analysis

The Fisher exact test was used to analyze differences in the incidences of RPLN recurrence between patients irradiated to the whole neck, including the RPLN area, and those excluding the RPLN area. The mean dose to the parotid glands was measured and compared between patients irradiated to the whole neck, including the RPLN area, and those excluding the RPLN area, using the Mann-Whitney U test. Survival curves were plotted using the Kaplan-Meier method, with statistical significance assessed by the log-rank test. Overall survival was defined as the time from the first day of radiotherapy to death due to any cause. Progression-free survival was defined as the time from the first day of radiotherapy to disease progression or death due to any cause. Overall and progression-free survival probabilities were compared between patients irradiated to the whole neck, including the RPLN area, and those excluding the RPLN area. Univariate logistic regression analyses were performed to analyze data using IBM SPSS Statistics 20.0 software (SPSS, Armonk, New York). A p-value of less than 0.05 was considered to indicate a statistically significant difference between 2 groups.

Results

RPLN recurrence and survival outcomes

The incidence of RPLN recurrence and mean dose of radiation to the parotid glands of patients irradiated to the whole neck, including the RPLN area, and those excluding the RPLN area

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are shown in Table 2. RPLN recurrence was identified in 1(1.2 %) of the 79 patients. This patient had received radiotherapy alone to the whole neck excluding the RPLN area, because of her advanced age (87 years) and weak condition (Performance status: 2). RPLN recurrence was identified on PET/CT at 7 months after radiotherapy. Information regarding the mean dose of irradiation to the parotid glands was available for 72 patients. The median mean dose of radiation to the parotid glands of patients irradiated to the whole neck, including the RPLN area, and those excluding the RPLN area were 37Gy (range: 24-43Gy) and 14Gy (1-27Gy), respectively, which showed a statistically significant difference (p< 0.001) (Table 3).

Table 2: The incident of RPLN recurrence and mean dose of parotid glands.

	Patients irradiated for whole neck		p
	Including RPLN	Excluding RPLN	
RPLN recurrence n = 79	0 n = 62	1 n = 17	0.2
Mean dose of parotid glands Median (range) n = 72	37 Gy (24-43 Gy) n = 55	14 Gy (1-27 Gy) n = 17	< 0.001

RPLN, retropharyngeal lymph node

Table 3: Clinical data for all cases.

No	Age	PS	T	N	M	Stage	Tumor site	Total dose	Irradiation of whole neck	Mean dose of parotid grand
1	66	1	3	0	0	3	Piriform sinus	70Gy/35fr	including RPLN area	-
2	65	0	4a	2b	0	4a	Piriform sinus	70Gy/35fr	including RPLN area	-
3	77	0	3	0	0	3	Posterior wall	70Gy/35fr	including RPLN area	-
4	77	0	3	0	0	3	Piriform sinus	68Gy/34fr	including RPLN area	-
5	79	1	3	1	0	3	Piriform sinus	70Gy/35fr	including RPLN area	-
6	47	0	2	2c	0	4a	Piriform sinus	60Gy/30fr	including RPLN area	-
7	70	0	2	1	0	3	Piriform sinus	60Gy/30fr	including RPLN area	-
8	83	1	3	2b	0	4a	Piriform sinus	54Gy/18fr	excluding RPLN area	6Gy
9	70	0	3	1	0	3	Piriform sinus	66.6Gy/37fr	including RPLN area	37Gy
10	70	0	2	2b	0	4a	Piriform sinus	60Gy/30fr	including RPLN area	37Gy
11	60	0	2	1	0	3	Postcricoid area	60Gy/30fr	including RPLN area	37Gy
12	60	0	2	2b	0	4a	Piriform sinus	60Gy/30fr	including RPLN area	39Gy
13	68	2	2	1	0	3	Posterior wall	66Gy/33fr	including RPLN area	40Gy
14	74	0	2	1	0	3	Piriform sinus	64Gy/32fr	including RPLN area	38Gy
15	78	0	4a	0	0	4a	Posterior wall	70Gy/35fr	including RPLN area	39Gy
16	71	0	4a	1	0	4a	Posterior wall	60Gy/30fr	including RPLN area	38Gy
17	58	0	4a	2c	0	4a	Posterior wall	70Gy/35fr	including RPLN area	38Gy
18	69	0	2	1	0	3	Piriform sinus	60Gy/30fr	including RPLN area	38Gy
19	66	0	4a	2b	0	4a	Piriform sinus	60Gy/30fr	including RPLN area	39Gy
20	76	0	2	2b	0	4a	Piriform sinus	60Gy/30fr	including RPLN area	39Gy
21	61	0	3	2b	0	4a	Piriform sinus	60Gy/30fr	including RPLN area	38Gy
22	80	0	4a	2b	0	4a	Piriform sinus	66Gy/33fr	including RPLN area	39Gy
23	58	0	4a	1	0	4a	Posterior wall	60Gy/30fr	including RPLN area	37Gy
24	65	0	4a	2b	0	4a	Postcricoid area	60Gy/30fr	including RPLN area	39Gy
25	57	0	4a	2a	0	4a	Piriform sinus	60Gy/30fr	including RPLN area	38Gy
26	84	1	1	2b	0	4a	Piriform sinus	66Gy/33fr	including RPLN area	39Gy
27	70	0	4a	2c	0	4a	Piriform sinus	58Gy/29fr	including RPLN area	37Gy
28	53	0	2	2b	0	4a	Piriform sinus	60Gy/30fr	including RPLN area	39Gy
29	70	0	2	0	0	2	Piriform sinus	60Gy/30fr	including RPLN area	36Gy

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30	80	0	2	0	0	2	Piriform sinus	60Gy/30fr	including RPLN area	37Gy
31	73	0	2	0	0	2	Piriform sinus	60Gy/30fr	including RPLN area	37Gy
32	75	1	3	2b	0	4a	Piriform sinus	60Gy/30fr	including RPLN area	38Gy
33	72	3	2	2a	0	4a	Piriform sinus	66Gy/33fr	including RPLN area	43Gy
34	53	0	2	0	0	2	Piriform sinus	60Gy/30fr	excluding RPLN area	27Gy
35	55	0	2	3	0	4b	Posterior wall	60Gy/30fr	including RPLN area	35Gy
36	90	1	3	0	0	3	Piriform sinus	60Gy/30fr	excluding RPLN area	1Gy
37	63	0	4	3	0	4b	Piriform sinus	66Gy/33fr	including RPLN area	31Gy
38	71	2	2	0	2	2	Posterior wall	60Gy/30fr	including RPLN area	36Gy
39	87	0	3	1	0	3	Posterior wall	52Gy/26fr	excluding RPLN area	1Gy
40	70	0	3	1	0	3	Posterior wall	50Gy/25fr	including RPLN area	37Gy
41	71	0	4	2b	0	4a	Posterior wall	60Gy/30fr	including RPLN area	34Gy
42	65	0	2	1	0	3	Posterior wall	60Gy/30fr	including RPLN area	36Gy
43	63	0	3	0	0	3	Posterior wall	60Gy/30fr	including RPLN area	37Gy
44	73	0	2	1	0	3	Piriform sinus	60Gy/30fr	including RPLN area	33Gy
45	57	0	2	2b	0	4a	Postcricoid area	60Gy/30fr	including RPLN area	38Gy
46	84	0	4a	2c	0	4a	Piriform sinus	66Gy/33fr	including RPLN area	37Gy
47	82	1	3	0	0	3	Postcricoid area	66Gy/33fr	including RPLN area	30Gy
48	69	1	4a	2a	0	4a	Piriform sinus	54Gy/27fr	including RPLN area	37Gy
49	67	0	2	1	0	3	Piriform sinus	60Gy/30fr	including RPLN area	37Gy
50	76	0	1	0	0	1	Piriform sinus	66Gy/33fr	excluding RPLN area	14Gy
51	52	0	2	0	0	2	Postcricoid area	60Gy/30fr	including RPLN area	33Gy
52	67	0	1	2a	0	4a	Piriform sinus	66Gy/33fr	excluding RPLN area	25Gy
53	74	0	2	1	0	3	Postcricoid area	66Gy/33fr	including RPLN area	36Gy
54	69	0	4b	1	0	4b	Posterior wall	60Gy/30fr	including RPLN area	32Gy
55	87	2	3	2b	0	4a	Piriform sinus	60Gy/30fr	excluding RPLN area	15Gy
56	61	0	2	2c	0	4a	Piriform sinus	60Gy/30fr	including RPLN area	37Gy
57	64	0	4a	3	0	4b	Piriform sinus	70Gy/35fr	excluding RPLN area	24Gy
58	68	0	1	0	0	1	Piriform sinus	70Gy/35fr	excluding RPLN area	16Gy
59	59	0	4a	2b	0	4a	Piriform sinus	60Gy/30fr	including RPLN area	37Gy
60	62	0	4a	1	0	4a	Piriform sinus	60Gy/30fr	including RPLN area	24Gy
61	49	0	2	3	0	4b	Piriform sinus	60Gy/30fr	including RPLN area	36Gy
62	62	0	2	2b	0	4a	Piriform sinus	66Gy/33fr	excluding RPLN area	19Gy
63	55	1	4a	2b	0	4a	Piriform sinus	66Gy/33fr	including RPLN area	39Gy
64	80	0	2	2c	0	4a	Piriform sinus	70Gy/35fr	excluding RPLN area	24Gy
65	62	0	3	0	0	3	Piriform sinus	66Gy/33fr	excluding RPLN area	9Gy
66	67	0	3	2b	0	4a	Piriform sinus	66Gy/33fr	excluding RPLN area	22Gy
67	39	0	3	2c	0	4a	Piriform sinus	70Gy/35fr	including RPLN area	27Gy
68	48	0	1	2c	0	4a	Piriform sinus	70Gy/35fr	including RPLN area	28Gy
69	84	2	2	2c	0	4a	Posterior wall	70Gy/35fr	excluding RPLN area	12Gy
70	64	0	2	2b	0	4a	Piriform sinus	70Gy/35fr	including RPLN area	34Gy
71	68	0	1	0	0	1	Posterior wall	70Gy/35fr	excluding RPLN area	9Gy
72	65	0	2	1	0	2	Piriform sinus	70Gy/35fr	excluding RPLN area	5Gy
73	74	0	2	2c	0	4a	Piriform sinus	70Gy/35fr	including RPLN area	37Gy
74	71	0	2	2b	0	4a	Posterior wall	70Gy/35fr	including RPLN area	37Gy
75	72	0	2	2c	0	4a	Postcricoid area	70Gy/35fr	including RPLN area	31Gy

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76	78	0	2	1	0	3	Piriform sinus	70Gy/35fr	including RPLN area	41Gy
77	61	0	2	0	0	2	Posterior wall	70Gy/35fr	including RPLN area	42Gy
78	75	0	2	1	0	2	Piriform sinus	70Gy/35fr	including RPLN area	38Gy
79	67	1	2	0	0	2	Posterior wall	66Gy/33fr	excluding RPLN area	14Gy

RPLN, retropharyngeal lymph node

Overall survival probabilities at 5 years for patients irradiated to the whole neck, including the RPLN area, and those excluding the RPLN area were 71% and 63%, respectively (Figure 2). The difference in overall survival probabilities between patients irradiated to the whole neck, including the RPLN area, and those excluding the RPLN area was not statistically significant (p = 0.314). Progression-free survival probabilities at 5 years for patients irradiated to the whole neck, including the RPLN area, and those excluding the RPLN area were 45% and 52%, respectively, and there was no statistically significant difference (p = 0.674) (Table 4) and (Figure 3).

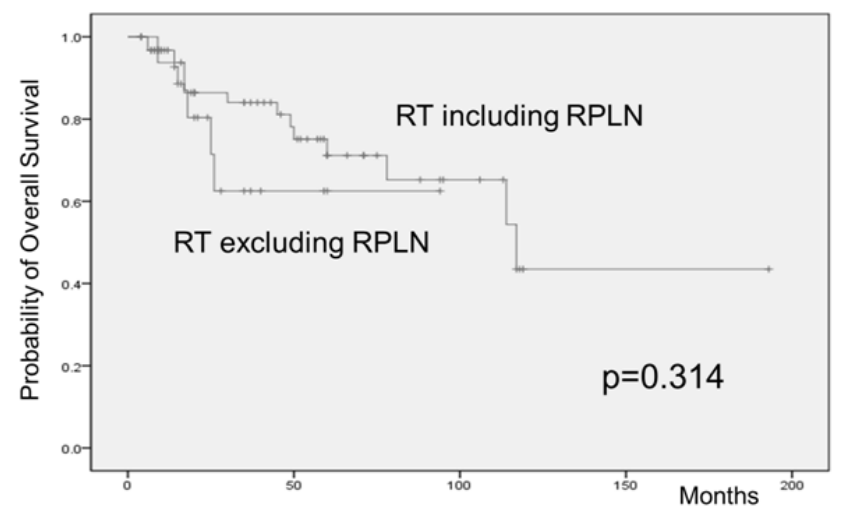

Figure 2: Overall survival probabilities at 5 years for patients irradiated to the whole neck, including the RPLN area, and those excluding the RPLN area. Kaplan-Meier analysis demonstrating no significant difference in overall survival between patients irradiated to the whole neck, including the RPLN area, and those excluding the RPLN area (p = 0.314). The 5-year progression-free survival probabilities in patients irradiated to the whole neck, including the RPLN area, and those excluding the RPLN area were 71% and 63%, respectively.

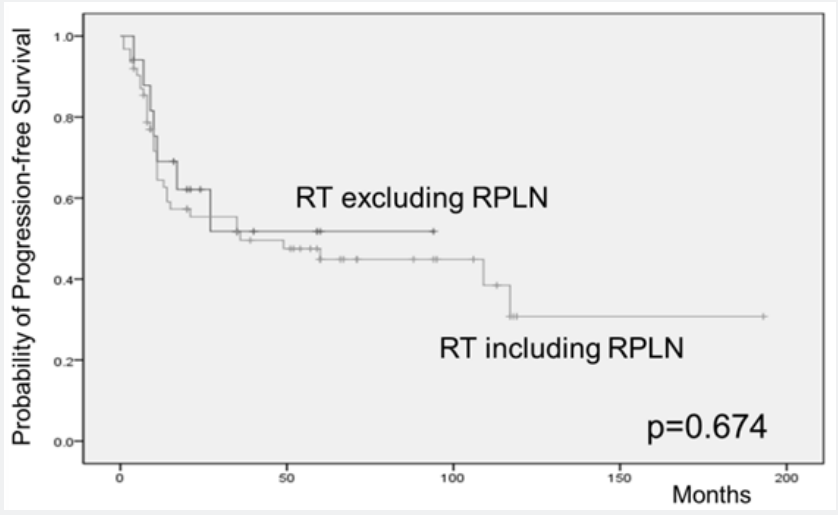

Figure 3: Progression-free survival probabilities at 5 years for patients irradiated to the whole neck, including the RPLN area, and those excluding the RPLN area. Kaplan-Meier analysis demonstrating no significant difference in progression-free survival between patients irradiated to the whole neck, including the RPLN area, and those excluding the RPLN area (p = 0.674). The 5-year progression-free survival probabilities in patients irradiated to the whole neck, including the RPLN area, and those excluding the RPLN area were 45% and 52%, respectively.

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Table 4: Chemotherapy and overall, progression-free survival for all cases.

No	Inductuin chemotherapy	Concomitant chemotherapy	Desease state	Recurremce site	Progression free duration (M)	Patient state	Overall survival duration (M)
1	DOC, CDDP, 5-FU	-	control	-	193	alive	193
2	-	DOC, CDDP, 5-FU	control	-	117	alive	117
3	-	DOC	control	-	88	alive	88
4	-	DOC	control	-	94	alive	94
5	-	-	recurrence	primary	6	alive	7
6	-	DOC	control	-	113	alive	113
7	-	DOC	recurrence	primary,lymph node	109	death	117
8	-	DOC	recurrence	primary	4	death	9
9	-	CDDP, 5-FU	recurrence	distant (liver)	3	death	6
10	-	DOC, CDDP, 5-FU	control	-	49	death	49
11	-	CDDP, 5-FU	control	-	114	death	114
12	-	DOC, CDDP, 5-FU	control	-	51	alive	51
13	-	-	control	-	60	death	60
14	-	DOC	recurrence	lymph node	35	death	78
15	-	-	recurrence	primary	13	alive	19
16	-	DOC, CDDP, 5-FU	recurrence	primary	5	alive	10
17	DOC, CDDP, 5-FU	CDDP	control	-	119	alive	119
18	-	DOC, CDDP, 5-FU	control	-	35	alive	35
19	-	DOC, CDDP, 5-FU	control	-	95	alive	95
20	-	DOC, CDDP, 5-FU	control	-	118	alive	118
21	-	DOC, CDDP, 5-FU	control	-	106	alive	106
22	-	CDDP	recurrence	lymph node	7	alive	9
23	DOC, CDDP, 5-FU	DOC	recurrence	primary,lymph node	9	death	14
24	DOC, CDDP, 5-FU	DOC, CDDP, 5-FU	recurrence	lymph node	3	death	15
25	-	DOC, CDDP, 5-FU	recurrence	lymph node	1	death	45
26	-	-	control	-	57	alive	57
27	-	DOC, CDDP, 5-FU	control	-	60	alive	60
28	-	DOC, CDDP, 5-FU	control	-	59	alive	59
29	-	DOC	recurrence	lymph node	35	death	50
30	-	CDDP	control	-	39	alive	39
31	-	DOC, CDDP, 5-FU	recurrence	primary	14	alive	58
32	-	DOC, CDDP, 5-FU	control	-	71	alive	71
33	-	-	recurrence	primary,lymph node	1	alive	46
34	-	-	control	-	94	alive	94
35	DOC, CDDP, 5-FU	DOC, CDDP, 5-FU	recurrence	lymph node, distant(skin)	11	alive	11
36	-	-	control	-	24	alive	24
37	DOC, CDDP, 5-FU	-	recurrence	primary,lymph node	8	alive	8
38	-	DOC, CDDP, 5-FU	recurrence	primary,lymph node	11	alive	75

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39	-	-	recurrence	lymph node	9	death	18
40	-	DOC, CDDP, 5-FU	control	-	54	alive	54
41	DOC, CDDP, 5-FU	DOC, CDDP, 5-FU	control	-	6	death	6
42	-	-	control	-	71	alive	71
43	-	DOC, CDDP, 5-FU	control	-	43	alive	43
44	-	DOC, CDDP, 5-FU	control	-	4	alive	4
45	-	DOC, CDDP, 5-FU	recurrence	primary,lymph node,	11	death	17
				distant(bone)			
46	-	-	recurrence	primary	10	alive	16
47	-	-	control	-	9	alive	9
48	DOC, CDDP, 5-FU	DOC, CDDP, 5-FU	recurrence	primary,lymph node	8	alive	9
49	-	DOC, CDDP, 5-FU	control	-	66	alive	66
50	-	-	control	-	59	alive	59
51	-	DOC, CDDP, 5-FU	control	-	60	alive	60
52	-	-	control	-	60	alive	60
53	-	-	recurrence	primary,lymph node	8	death	14
54	-	DOC, CDDP, 5-FU	control	-	52	alive	52
55	-	-	recurrence	RPLN	7	death	26
56	-	DOC, CDDP, 5-FU	recurrence	lymph node, distant(liver)	36	alive	37
57	-	cetuximab	recurrence	lymph node	10	alive	28
58	-	-	control	-	40	alive	40
59	DOC, CDDP, 5-FU	DOC, CDDP, 5-FU	recurrence	lymph node	21	alive	41
60	-	DOC, CDDP, 5-FU	recurrence	primary	10	death	30
61	DOC, CDDP, 5-FU	cetuximab	recurrence	lymph node, distant(bone)	11	death	15
62	-	cetuximab	control	-	20	alive	20
63	DOC, CDDP, 5-FU	-	recurrence	primary,lymph node	8	alive	35
64	-	-	recurrence	lymph node	11	death	25
65	DOC, CDDP, 5-FU	cetuximab	recurrence	primary	27	alive	37
66	DOC, CDDP, 5-FU	cetuximab	control	-	35	alive	35
67	DOC, CDDP, 5-FU	CDDP	control	-	20	alive	20
68	DOC, CDDP, 5-FU	cetuximab	recurrence	primary,lymph node	14	alive	20
69	-	-	control	-	17	death	17
70	DOC, CDDP, 5-FU	cetuximab	control	-	20	alive	20
71	-	-	control	-	21	alive	21
72	-	-	control	-	16	alive	16
73	-	CDDP	recurrence	distant(protid)	15	alive	15
74	DOC, CDDP, 5-FU	CDDP	recurrence	lymph node	10	alive	14

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75	DOC, CDDP, 5-FU	cetuximab	control	-	9	alive	12
76	-	-	recurrence	primary,lymph node	4	alive	10
77	-	-	control	-	8	alive	8
78	-	CDDP	control	-	7	alive	7
79	-	DOC, CDDP, 5-FU	control	-	4	alive	4

DOC; docetaxel hydrate, CDDP; cisplatin, 5-FU; 5-fluorouracil

Discussion

In the present study, RPLN recurrence was recognized in only 1(1.2%) of the 79 patients, and the differences in overall and progression-free survival probabilities between patients irradiated to the whole neck, including the RPLN area, and those excluding the RPLN area were not statistically significant. These results suggest that irradiation of the RPLN area in hypopharyngeal cancer without pretreatment RPLN metastasis might be unnecessary. The guidelines established by Gregoire proposed that radiotherapy to RPLNs should only be performed in specific cases. They suggest that prophylactic radiotherapy is not essential for patients with hypopharyngeal cancer classified as N0 or N1 [13,19,20]. Zheng et al. [21] reported that none of the N0 patients were found to exhibit RPLN metastasis, and T classification and local invasion was not significantly associated with RPLN metastasis.

Irradiation to the RPLN area might increase the incidence of adverse events, such as mucositis, dermatitis, and dry mouth, etc. In particular, dry mouth does not improve once it develops. Eisbruch et al. reported that most glands receiving a mean radiation dose higher than the threshold (24Gy for unstimulated and 26 Gy for stimulated saliva) produced little saliva with no recovery over time [22]. In the present study, the median mean dose of irradiation to the parotid glands in patients irradiated to the whole neck, including the RPLN area, and those excluding the RPLN area was 37Gy (range: 24 -43Gy) and 14Gy (range: 1-27Gy), respectively, and the difference was statistically significant ($p < 0.001$). This result suggests that irradiation to the whole neck, excluding the RPLN area, is reduces the risk of dry mouth.

Irradiation excluding the RPLN area might increase the risk of RPLN recurrence; however, RPLN recurrence was only identified in 1(1.2%) of the 79 patients in this study. Although the patient who developed RPLN recurrence did not receive radiotherapy to the RPLN area, this patient did not undergo chemotherapy either. We consider that chemotherapy may be able to control microscopic metastasis to the RPLN, which is undetectable on laryngoscopy, CT, MRI, PET/CT, etc. In fact, most patients (72%) in this study received chemotherapy, whereas chemotherapy was not used for the patient who demonstrated RPLN recurrence. The main limitation of this study is the possibility of bias regarding whether RPLN was included or not and whether chemotherapy was performed or not, owing to its retrospective nature. Further prospective studies are required to confirm our findings. In the future, we plan to perform prospective studies regarding RPLN metastasis in patients with hypopharyngeal cancer.

Conclusion

We demonstrated that RPLN recurrence in patients with hypopharyngeal cancer after radiotherapy is rare (1.2%), and the differences in overall and progression-free survival probabilities between patients irradiated to the whole neck, including the RPLN, and those excluding the RPLN area were not statistically significant. This indicates the possibility that irradiation to the RPLN area may be unnecessary in patients with hypopharyngeal cancer without pretreatment RPLN metastasis.

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