RESEARCH ARTICLE

Value of Postoperative Radiation Therapy for Regional Control after Dissection in Head and Neck Squamous Cell Carcinoma Cases

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Abstract

Objective: We aimed to define clinicopathologic risk factors associated with regional recurrence (RR) and thus the effectiveness of postoperative radiotherapy (PORT) for neck control for head and neck squamous cell carcinomas (HNSCCs) with differing cervical lymph node status. Methods: A retrospective study was performed in 196 HNSCC patients with pathologically positive neck node (N+) to evaluate the high-risk factors for RR and to define the role of PORT in control after neck dissection and postoperative radiotherapy (PORT). Results: Overall, the RR rate after neck dissection and PORT was 29%. Extracapsular spread (ECS) was confirmed to be the only independent risk factor for RR. There were no significant risk factors associated with RR in the ECS- group. The 5-year disease-specific survival rate was 45%, which descended to 10% with the emergence of RR. Conclusions: ECS remains a determined risk factor for RR after neck dissection and PORT in patients with N+. PORT alone is not adequate for preventing RR in the neck with ECS after neck dissection. More intensive postoperative adjuvant therapies, especially combined chemotherapy and radiotherapy, are needed to prevent regional failure in HNSCC patients with ECS.

Keywords: HNSCC - neck node metastasis - dissection - postoperative radiotherapy - regional recurrence

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Introduction

It is well known that HNSCC is a loco-regional disease and its treatment regimen should include management of both primary tumor and cervical metastatic disease. Even with significant advances in surgery and radiotherapy for HNSCC treatment in the past several decades, there are still many patients failed in the neck, especially in advanced cases. RR has become a major and specific type of tumor recurrence in HNSCC, which is widely considered to be difficult to manage and represents an important cause of morbidity (Deschamps et al., 2010). Thus, adequate neck management has a major impact on the survival of patients with HNSCC.

Nowadays, neck dissection and/or radiation therapy remains the mainstay of the treatment modalities for neck metastases. Although the incidence of recurrent diseases following neck dissection with adjuvant radiotherapy for neck metastases is reasonably low, which maintains 10%-20% (Jones et al., 2008), the deteriorated survival after RR makes us to seek more effective therapeutic modalities for neck control. With the advent of new techniques in chemotherapy and biological therapy, clinical oncologists are making efforts to explore individualized combined-therapeutic regimens for HNSCC patients to prevent recurrence by targeting the identified high risk factors. Therefore, it is imperative to identify clinicopathologic risk factors for RR and take special therapeutic approaches to improve the prognosis of HNSCC.

A review of literature reveals the impacts of clinicopathologic factors on neck recurrence. For example, if residual disease after neck dissection, 2 or more pathologic lymph nodes, ECS, more than 3 cm-diameter pathologic lymph node and invasion of soft tissue are found in neck dissection specimens, the risk of RR is considered to be high (Barzan and Talamini, 1996). However, the majority of the literatures draw these conclusions in the absence of adjuvant radiotherapy. Furthermore, these factors have no statistical significance in predicting regional failure following neck dissection and adjuvant PORT (Santa-Maria et al., 2007; Buck et al., 2008). Therefore, it remains controversial on which risk factors associated with neck failure could be eradicated by adjuvant PORT after neck dissection. It is also to be determined when the additional therapies, such as chemotherapy, should be added to the management of regional neck node metastasis. Since neck dissections for HNSCC vary from selective neck dissection (SND) to radical neck dissection (RND), we analyze clinicopathologic risk factors for RR in a group of N+

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patients treated with neck dissections and PORT in an attempt to identify a special subgroup of patients who need more intensive adjuvant therapies such as combined PORT and chemotherapy.

Materials and Methods

Patients

Between January 2003 and December 2007, a total of 196 HNSCC patients underwent neck dissection and postoperative radiotherapy (PORT) for N+ diseases in the neck. The clinicopathologic data were entered into a computerized database for further investigation.

There were 168 men and 28 women included in the study, with a median age of 62 years (range, 26 to 88 years). No patients received any therapy at primary tumor and neck node before admission. All patients underwent uni- or bilateral neck dissections, in combination with surgical resection of the primary tumor. Patients with a malignancy other than squamous cell carcinoma and distant metastatic disease at presentation were excluded. All patients enrolled in this study were diagnosed to have cervical lymph node metastasis by postoperative pathological assessment, and each received a PORT at the N+ neck.

A 5-year follow-up for surviving patients in this series was performed. Survival was calculated from the time of neck dissection until the date of last contact or death. Time of RR was defined as the interval between the date of surgery and date of diagnosis of regional failure. During the follow-up period, conventional cervical lymph node ultrasound and clinical examination were performed regularly to screen RR. Percutaneous needle aspiration biopsy, high-resolution CT or MRI were used for the detection of recurrent lymph nodes in the presence of suspected complaints and findings.

Patients with simultaneous local and regional/distant recurrence were defined as having local recurrence; similarly, patients with regional and distant recurrence were recorded as having regional recurrence. Because many patients received combination of neck dissections and the interest of this study is focused on risk factors for regional failure, we categorized RR as relapsed tumor occurring in a previously dissected field or out of this treated field, either within the ipsilateral side or within the untreated contralateral side.

Clinicopathologic Factors

The clinicopathologic factors recorded for the present investigation were age, sex, primary tumor site, pathologic T and N stage, tumor growth pattern, tumor resection margin, level of tumor invasion, histological grade, size and number of pathologic lymph node, number of levels with pathologic lymph node, ECS, invasion of nonlymphatic structures and types of neck dissections. Tumor site was classified as oral cavity (33 cases), oropharynx (51 cases), hypopharynx (75 cases), or larynx (37 cases). The tumor stage was determined according to the TNM classification recommended by UICC (2002). Pathologic slides were reviewed by 2 pathologists who were not given any information on the patients. Using a step serial sectioning approach, the pathologic features of neck dissection specimens were evaluated. According to the postoperative pathological examination, a summary of the T and N classification is provided in Table 1.

Table 1. T and N Classification According to the Postoperative Pathologic Examination in 196 Patients

T classification	No. of patients by N classification					Total
	1	2a	2b	2c	3	
1	3	-	6	-	2	11
2	12	2	22	-	1	37
3	15	2	31	3	8	59
4	29	8	32	10	10	89
Total	59	12	91	13	21	196

Table 2. The Details of 243 Neck Dissections Performed in 196 Patients

Types of neck dissections	No. of neck dissections
Comprehensive	
Extended	5
Classical	21
Modified	109
Selective	
Level I-III	19
Level I-IV	17
Level II-IV	38
Level II-V	34
Total	243

Statistical Analysis

The statistical analysis was performed with SAS 8.0 for windows (SAS Institute Inc, Cary, NC). All tests for significance were two-sided. *P* values <.05 were considered statistically significant. Descriptive statistics were calculated. Univariate chi-square tests were used to analyze the association of categorical variables for RR, and then the differences in subset were assessed by Fisher's exact tests. Multivariate analysis was performed using a stepwise logistic regression model where indicated in univariate analysis. Kaplan-Meier method was used to calculate overall survival and disease-specific survival for the RR and ECS+ groups.

Results

Treatment

A total of 243 neck dissections were performed in 196 patients, with 47 patients undergoing bilateral neck dissections. Surgical approaches for neck dissection included RND, MRND and SND depending on the site, size, and extent of the primary tumor and regional metastases. Fifty-five patients underwent unilateral SNDs, and 13 patients received bilateral SNDs for the primary tumors extending beyond the midline, representing 35% (68/196) of the total. The remaining 128 patients received comprehensive dissections, including 102 (52%, 102/196) modified RNDs (MRNDs) , among which 27 contralateral SNDs were carried out simultaneously. Classical RNDs and extended RNDs were performed in 21 and in 5 patients, respectively, among which 7 patients underwent MRNDs on the contralateral sides. The detailed

Table 3. Univariate Analysis of Correlation Between Clinicopathologic Factors and Regional Recurrence (RR) after Neck Dissection and PORT

Clinicopathologic factor	No. of patients	Patients with RR (%)	*P*
Sex			
Male	168	48 (29)	ns
Female	28	9 (32)	
Age			
<40	11	4 (36)	ns
40-60	73	27 (37)	
>60	112	26 (23)	
Pathologic T stage			
T1	11	2 (18)	ns
T2	37	11 (30)	
T3	59	19 (32)	
T4	89	25 (28)	
Pathologic N stage			
N1	59	11 (19)	0.001
N2a	12	2 (17)	
N2b	91	26 (29)	
N2c	13	4 (31)	
N3	21	14 (67)	
Primary tumor site			
Oral cavity	33	5 (15)	0.0379
Oropharynx	51	16 (31)	
Hypopharynx	75	29 (39)	
Larynx	37	7 (19)	
Tumor growth pattern			
Exophytic	20	6 (30)	ns
Endophytic	99	27 (27)	
Mixed	77	24 (31)	
Resection Margin			
Negative	174	50 (29)	ns
Positive	22	7 (32)	
Levels of tumor invasion			
Stromal level	28	4 (14)	ns
Muscular level	97	28 (29)	
Cartilage/Bone level	71	25 (35)	
Histological grade			
Well differentiated	64	16 (25)	ns
Moderately differentiated	100	29 (29)	
Poor differentiated	32	12 (38)	
No. of levels with pathologic node			
1	114	27 (24)	0.0498
>1	82	30 (37)	
Size of pathologic node			
<3 cm	136	29 (21)	<0.0001
3-6 cm	39	14 (36)	
>6 cm	21	14 (67)	
No. of pathologic node			
1	75	15 (20)	0.0247
2-3	80	24 (30)	
≥4	41	18 (44)	
Extracapsular nodal spread			
Absent in pN^+	107	17 (16)	<0.0001
Present in pN^+	89	40 (45)	
Invasion of nonlymphatic structure			
No	138	28 (20)	<0.0001
Yes	58	29 (50)	
Types of neck dissection*			
Selective	68	12 (18)	0.0005
Modified radical	102	29 (28)	
Radical	21	13 (62)	
Extend radical	5	3 (60)	

ns, not significant; *according to the main type preformed in bilateral neck dissections

distribution of types of neck dissections performed are seen in Table 2.

Each patient underwent conventional radiotherapy at the N+ neck after surgery for a total median dose of 65 Gy (60-70 Gy, 30-35 fractions in 6-8 weeks). The radiotherapy schedule was composed of 2.0 Gy per fraction, one fraction per day, and five days per week.

Histological Findings

In the cross-check of clinical and pathologic T classifications, complete coherence of the two classifications was observed in all patients after the surgery. However, this situation was different in N classification, in which 16 patients were down-staged and 33 patients was upstaged after neck dissections. ECS was found in 89 patients. The incidence rates of ECS were 33% in oral cavity (11/33), 47% in oropharynx (24/51), 55% in hypopharynx (41/75), and 35% in larynx (13/37), respectively. The occurrence of ECS varied greatly in different neck node statuses including N1 (19%, 11/59), N2a (58%, 7/12), N2b (47%, 43/91), N2c (54%, 7/13), and N3 (100%, 21/21).

Follow-up

No patient was lost in follow-up in this series. Patients who referred to other centers to finish their PORT continued to be reviewed at our centre or called back to trace the post-treatment progress. The minimum follow-up time was 5 years for surviving patients and three months for the dead, with a median follow-up time of 25 months. During the follow-up period, a total of 110 patients were observed to have developed recurrent diseases at different sites, among which were local sites in 36 patients, regional sites in 57 patients, and distant sites in 17 patients. In patients with local failure, the primary site for recurrence was most likely to be the oral cavity (24%, 8/33). Meanwhile, the most common site of metastasis was lung (n=11) in patients with distant failure.

As observed in the present study, regional recurrence developed between 3 and 55 months (median, 7 months) after the initial surgery of the primary tumors. The primary tumor sites most likely to develop recurrent neck diseases were oropharynx (31%, 16/51) and hypopharynx (39%, 29/75). Overall, the RR rate after neck dissection and PORT was 29% (57/196), being 18% (12/68) for SND only and 35% (45/128) for combination of comprehensive dissections. In 57 patients with RR, 23 patients received metastasesectomy by RND, 25 patients received palliative radio- and/or chemotherapy, and 9 patients abandoned any further treatment.

Survival

Eighty patients had been surviving at the end of 5-year follow-up, and 116 patients died in 5 years after surgery. The causes of death were locoregional recurrence (n=69), distant metastases (n=26), the secondary malignances (n=9), fistula and its respiratory complication (n=1), heart or brain disease (n=9), and others (n=2). According to Kaplan-Meier survival curve, the cumulative 3-year and 5-year overall survival rate was 43% and 40%, and the disease-specific survival was 48% and 45% at 3 years

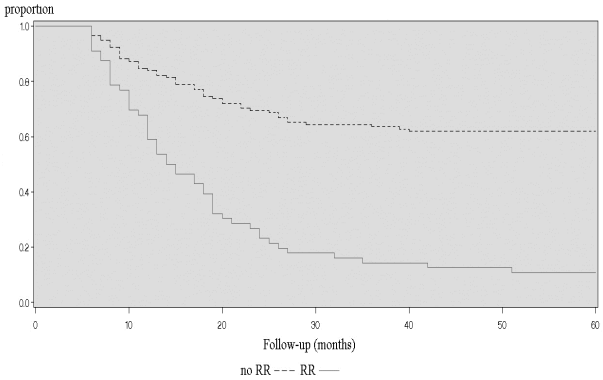

Figure 1. Disease-specific Survival by ECS

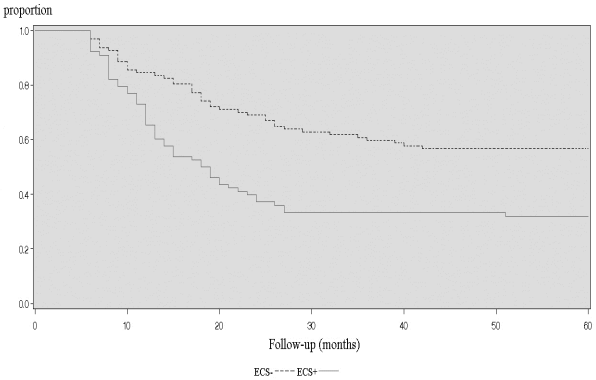

Figure 2. Disease-specific Survivals of Those Having a Neck Dissection and PORT with No Regional Recurrence (RR) Versus Those Developing RR

Table 4. Multivariate Analyses of Risk Factors for Regional Recurrences from Head and Neck Squamous Cell Carcinoma with Stepwise Logistic Regression Model

Risk Factors	OR	95% CI	*P*
Extracapsular nodal spread			
Absent in pN+	0.231	0.119-0.450	<0.0001
Present in pN+	1	Reference	

OR, odds ratio; CI, confidence interval

and 5 years, respectively. With the presence of ECS, the 5-year disease-specific survival was 32%, in comparison with 56% in patients without ECS (Figure 1). What is worse, the 5-year disease-specific survival descended to 10% with the development of RR (Figure 2).

Univariate Analysis of Risk Factors

Table 3 summaries the characteristics of patients with RR according to different clinicopathologic risk factors. In the analysis by univariate Chi-square test, there was no significant difference in RR rating by age, sex, pathologic T stage, tumor growth pattern, tumor resection margin, histological grade and level of tumor invasion. The development of RR was significantly associated with primary tumor site (p=0.0379), pathologic N stage (p=0.0010), size of pathologic node (p<0.0001), number of levels with pathologic lymph node (p=0.0498), number of pathologic node (p=0.0247), ECS (p<0.0001), invasion of nonlymphatic structure (p<0.0001), and type of neck dissection (p=0.0005).

Multivariate Analysis

A stepwise logistic regression was carried out with the associations identified in Table 4. As is seen, ECS were found to be the most important risk factor associated with RR. Other factors including primary tumor site, pathologic N stage, size of pathologic node, number of levels with pathologic lymph node, number of pathologic node, invasion of nonlymphatic structure and types of neck dissection were excluded from this model.

Clinicopathologic Risk Factors in patients with and without ECS

Since ECS was confirmed to be the most significant risk factor of RR in our study, we proceeded to analyze the clinicopathologic risk factors associated with RR in patients with and without ECS. Under an analysis by univariate Chi-square test, there was no significant difference in RR rates by other fourteen parameters as determined above in patients without ECS; and the presence of RR was only significantly associated with size of pathologic node (p=0.0467) in patients with ECS.

Discussion

Treatment failure is notoriously known to be an unpleasant impacting factor responsible for the reduced survival of patients with HNSCC, and RR has become the most common type of tumor recurrence in patients with neck metastases (Layland et al., 2005). As demonstrated in our study, RR represents 52% of the total of tumor recurrence, which is significantly higher than that of local recurrence (33%) or of distant failure (15%). Although the introduction of radiotherapy into the treatment of cervical metastatic disease has improved the regional control in patients with HNSCC over the past 3 decades, the notion that status of cervical lymph node metastasis determines the RR and prognosis of patients with HNSCC remains irrefutable.

ECS is considered to be a very important risk factor for RR by most authors. In one study, a number of important predictive factors for RR after neck dissection alone have been reported, which include the presence of positive nodes, ECS, 2 or more positive lymph nodes, invasion of the soft tissues of the neck, invasion of vascular or lymphatic spaces (Buck et al., 2008). In another study (Mendenhall et al., 2003), some clinicopathologic factors including two or more positive nodes, largest node more than 3 cm, and particularly the presence of ECS have been correlated with RR after surgery and PORT. Our results in univariate analysis also showed that the development of RR after combined neck dissection and PORT was associated with primary tumor site, pathologic N stage, size of the pathologic node, number of levels with pathologic lymph node, number of pathologic node, ECS, and invasion of nonlymphatic structures. However, a multivariate analysis demonstrated that the ECS was the only determinate factor for RR after neck dissection and PORT in HNSCC.

Although the practical value of PORT for improving survival in HNSCC is well acknowledged (Schiff et al.,

1990), it remains controversial whether this adjuvant treatment could prevent RR in patients having ECS. Some authors found that PORT dose of 63 Gy and more could increase neck control rates in patients with ECS treated with neck dissection and PORT for HNSCC (Peters et al., 1993). However, others reported that the 3-year recurrence rates in the neck were 10.7% in patients without ECS and 49.6% with ECS in laryngeal cancer, and PORT did not appear to improve the outcome (Peters et al., 1993). Furthermore, PORT could not decrease the rate of RR in patients having ECS in oral cavity cancer (Shingaki et al., 2003). These findings suggest that the exact value of PORT in controlling the ECS-related RR after surgery needs to be further documented.

For improving regional control, some investigators (Cooper et al., 2004; Kang et al., 2011; Strojan et al., 2012) included two high-risk factors, two or more positive nodes and/or ECS, as indications for combined chemotherapy and radiotherapy after neck dissection in patients with HNSCC. However, in the present investigation, no significant risk factors were found to be associated with regional failure in the group of patients without ECS undergoing neck dissections and PORT. In support of our findings, Leemans et al. (Leemans et al., 1990) found that the neck control of the patients with one or two positive nodes without ECS can be improved by PORT. Since the results of neck control after neck dissection and PORT in patients without ECS are favorable, and no high-risk factors for RR are found, it is strongly suggested that PORT alone is adequate for neck control after treatment neck dissections in N+ necks without ECS. On the contrary, ECS was found to be the most significant risk factor for RR even after combined neck dissection with PORT as shown in the present study. In support of our findings, some investigators (Vaidya et al., 2001; Jäckel et al., 2008) found that the majority of recurrences in patients undergoing primary tumor resection and PORT for HNSCC came from N+ necks with ECS. Taken together, PORT alone is not adequate for preventing RR in patients with ECS; N+ necks with and without ECS must be treated separately in patients with HNSCC. To avoid treatment-related morbidities, other lymph node factors are less important for neck control after neck dissection and PORT and thus not indications for more aggressive adjuvant therapies such as concurrent chemotherapy and radiotherapy (CCRT).

Neck dissections have been proven to be effective surgical procedures for patients presenting neck disease. However, to achieve a satisfactory neck control, surgical extirpation alone is not adequate for a number of neck node statuses, especially for advanced neck diseases. Hence, whether in comprehensive neck dissections or in SNDs, PORT should be performed in N+ necks to improve regional control (Clark et al., 2005). As evidenced in the present study, PORT alone is not sufficient to prevent RR in N+ necks with ECS after neck dissection, suggesting that more aggressive adjuvant therapies are required for this situation. ECS rather than multiple positive nodes are absolutely indicated for postoperative CCRT. Lately, CCRT was also introduced for neck control before neck dissection (Nishimura et al., 2012; Hanai et al., 2013). However, the plausibility and efficacy of the regimen is yet to be further determined.

In conclusion, the presence of ECS remains a determined risk factor for RR after surgery and adjuvant PORT in N+ patients with HNSCC. There were no significant risk factors associated with regional failure in patients without ECS. Expect for PORT, no additional adjuvant therapy is required for N+ patients without ECS. However, more intensive adjuvant therapies such as CCRT are to be carried out in HNSCC patients with ECS after neck dissection for the purpose of a more effective neck control.

References

Barzan L, Talamini R (1996). Analysis of prognostic factors for recurrence after neck dissection. *Arch Otolaryngol Head Neck Surg*, **122**, 1299-302.

Buck G, Huguenin P, Stoeckli SJ (2008). Efficacy of neck treatment in patients with head and neck squamous cell carcinoma. *Head Neck*, **30**, 50-7.

Clark J, Li W, Smith G, et al (2005). Outcome of treatment for advanced cervical metastatic squamous cell carcinoma. *Head Neck*, **27**, 87-94.

Cooper JS, Pajak TF, Forastiere AA, et al (2004). Radiation Therapy Oncology Group 9501/Intergroup. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med*, **350**, 1937-44.

Deschamps DR, Spencer HJ, Kokoska MS, et al (2010). Implications of head and neck cancer treatment failure in the neck. *Otolaryngol Head Neck Surg*, **142**, 722-7.

Hanai N, Kawakita D, Ozawa T, et al (2013). Neck dissection after chemoradiotherapy for oropharyngeal and hypopharyngeal cancer: the correlation between cervical lymph node metastasis and prognosis. *Int J Clin Oncol*, DOI 10.1007/s10147-013-0518-9 [Epub ahead of print].

Jäckel MC, Ambrosch P, Christiansen H, et al (2008). Value of postoperative radiotherapy in patients with pathologic N1 neck diseases. *Head Neck*, **30**, 875-82.

Jones AS, Tandon S, Helliwell TR, et al (2008). Survival of patients with neck recurrence following radical neck dissection: utility of a second neck dissection? *Head Neck*, **30**, 1514-22.

Kang CJ, Lin CY, Wang HM, et al (2011). The number of pathologically positive lymph nodes and pathological tumor depth predicts prognosis in patients with poorly differentiated squamous cell carcinoma of the oral cavity. *Int J Radiat Oncol Biol Phys*, **81**, e223-30.

Layland MK, Sessions DG, Lenox J (2005). The influence of lymph node metastasis in the treatment of squamous cell carcinoma of oral cavity, oropharynx, larynx, and hypopharynx: N0 versus N+. *Laryngoscope*, **115**, 629-39.

Leemans CR, Tiwari R, van der Waal I, et al (1990). The efficacy of comprehensive neck dissection with or without postoperative radiotherapy in nodal metastases of squamous cell carcinoma of the upper respiratory and digestive tracts. *Laryngoscope*, **100**, 1194-8.

Mendenhall WM, Amdur RJ, Hinerman RW, et al (2003). Postoperative radiation therapy for squamous cell carcinoma of the head and neck. *Am J Otolaryngol*, **24**, 41-50.

Nishimura G, Matsuda H, Taguchi T, et al (2012). Treatment evaluation of metastatic lymph nodes after concurrent chemoradiotherapy in patients with head andneck squamous cell carcinoma. *Anticancer Res*, **32**, 595-600.

Peters LJ, Goepfert H, Ang KK, et al (1993). Evaluation of the

dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. *Int J Radiat Oncol Biol Phys*, **26**, 3-11.

Peters LJ, Goepfert H, Ang KK, et al (1993). Extracapsular spread and desmoplastic pattern in neck lymph nodes: two prognostic factors of laryngeal cancer. *Ann Otol Rhinol Laryngol*, **108**, 672-6.

Santa-Maria PL, Sader C, Preston NJM, et al (2007). Neck dissection for squamous cell carcinoma of the head and neck. *Otolaryngol Head Neck Surg*, **136**, 41-5.

Schiff PB, Harrison LB, Strong EW, et al (1990). Impact of the time interval between surgery and postoperative radiation therapy on locoregional control in advanced head and neck cancer. *J Surg Oncol*, **43**, 203-8.

Shingaki S, Takada M, Sasai K, et al (2003). Impact of lymph node metastasis on the pattern of failure and survival in oral carcinomas. *Am J Surg*, **185**, 278- 84.

Strojan P, Ferlito A, Langendijk JA, et al (2012). Indications for radiotherapy after neck dissection. *Head Neck*, **34**, 113-9.

Vaidya AM, Petruzzelli GJ, Clark J, et al (2001). Patterns of spread in recurrent head and neck squamous cell carcinoma. *Otolaryngol Head Neck Surg*, **125**, 393-6.