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CLINICAL INVESTIGATION **Head and Neck**

CERVICAL LYMPH NODE METASTASES FROM OCCULT SQUAMOUS CELL CARCINOMA: CUT DOWN A TREE TO GET AN APPLE?

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Purpose: To review the value of extended diagnostic work-up procedures and to compare the results of comprehensive or volume-restricted radiotherapy in patients presenting with cervical lymph node metastases from clinically undetectable squamous cell carcinoma.

Methods and Materials: A systematic review was undertaken of published papers up to May 2000.

Results: Positron emission tomography (PET) has an overall staging accuracy of 69%, with a positive predictive value of 56% and negative predictive value of 86%. With negative routine clinical examination and computerized tomography (CT) or magnetic resonance imaging (MRI), PET detected primary tumors in 5–25% of patients, whereas ipsilateral tonsillectomy discovered carcinoma in about 25% of patients. Laser-induced fluorescence imaging with panendoscopy and directed biopsies showed some encouraging preliminary results and warrants further study. All together, the reported mucosal carcinoma emergence rates were 2–13% (median, 9.5%) after comprehensive radiotherapy and 5–44% (median, 8%) after unilateral neck irradiation. The corresponding nodal relapse rates were 8–45% (median, 19%) and 31–63% (median, 51.5%), and 5-year survival rates were 34–63% (median, 50%) and 22–41% (median, 36.5%), respectively. Retrospective single-institution comparisons between comprehensive and unilateral neck radiotherapy did not show apparent differences in outcome. Prognostic determinants for survival are the N stage, number of nodes, extracapsular extension, and histologic grade. No data were found to support the benefit of chemotherapy in this disease.

Conclusion: Physical examination, CT or MRI, and panendoscopy with biopsies remain the standard work-up for these patients. Routine use of PET or laser-induced fluorescence imaging cannot be firmly advocated based on presently available data. Although combination of nodal dissection with comprehensive radiotherapy yielded most favorable results, its impact on the quality of life should be recognized, and the confounding effects of patient selection for various treatment modalities on therapeutic outcome cannot be ruled out. A randomized trial comparing the therapeutic value of comprehensive vs. volume-limited radiotherapy is being considered.

Squamous cell carcinoma, Comprehensive radiotherapy, Volume-limited radiotherapy, Unknown primary tumor, Lymph node metastases.

INTRODUCTION

Cervical nodal metastasis from clinically undetectable primary squamous cell carcinoma (SCC) accounts for 1–2% of head-and-neck malignancies (1–3), most frequently manifests in the jugulodigastric and mid-jugular lymph nodes (3, 4), and presents both a diagnostic and therapeutic challenge. Routine work-up includes physical examination, biopsy or excision of the enlarged lymph node(s), CT and/or MRI, and panendoscopy with or without random or directed biopsies. Commonly, treatment consists of lymph node dissection and elective irradiation of the putative mucosal sites and bilateral neck, plus supraclavicular, nodes (5–7). However, unilateral radiotherapy (RT) to the involved side (2, 8), as well as combination of chemotherapy plus comprehensive irradiation (9, 10), have also been proposed.

In the absence of comparative trial results, the optimal treatment strategy remains controversial due to a number of considerations. Briefly, first, the potential gain with comprehensive radiotherapy in controlling the putative primary carcinoma should be weighed against its effect on quality of life resulting from increased acute and persistent morbidity, such as xerostomia. Second, it is possible that a head-and-neck carcinoma detected later in this patient subset is actually a second primary tumor instead of the putative cancer. Finally, the feasibility of reirradiating the head-and-neck region is being recognized should a cancer emerge after ipsilateral radiotherapy. The objective of this review is to evaluate the value of extended diagnostic work-up and to compare the results of comprehensive and volume-restricted RT in this group of patients.

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DIAGNOSTIC EXAMINATIONS

Physical examination and assessment under anesthesia conducted by experienced otolaryngologists or head and neck surgeons detect primary head-and-neck SCC in over 50% of patients presenting with cervical lymph node metastases (11). Of course, characteristic epidemiologic pattern of such tumors in different parts of the world should be taken into account. CT or MRI may identify suspicious areas guiding biopsy sampling. A recent retrospective analysis by Mendenhall and colleagues on 130 patients with confirmed cervical lymph node metastases from clinically occult SCC showed that in the absence of physical or radiographic suspicion panendoscopy with biopsies yielded a 17% detection rate (12). The yield rate increased to 52–56% if either clinical examination or imaging was suggestive and to 65% if both were suggestive. Repeat panendoscopy did not appear to increase the detection rate. The sites of primary tumors found through endoscopy and biopsy were tonsillar fossa and base of tongue in 82% of patients. This finding is in contrast to a previous report of high likelihood of finding nasopharyngeal or hypopharyngeal cancers (20–40% for each site) (1). Tonsillectomy was performed in 10 patients without and 24 patients with clinical suspicion and revealed SCC in 1 and 10 (42%) patients, respectively (12). Two other groups found tonsillar carcinoma in 9 of 37 (24%) patients (13) and 23 of 87 (26%) patients (14) and also advocated ipsilateral tonsillectomy in the absence of suspicious lesions.

THE ROLE OF ^{18}F-FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY (FDG-PET) FOR DETECTING OCCULT PRIMARY TUMORS

It has been suggested that FDG-PET is more accurate than CT or MRI for staging of both head-and-neck primary tumors and lymph node metastases (15). A study by Stokkel *et al.* (16) of 68 patients with oral cavity or oropharyngeal SCC examined within 3 weeks of diagnosis showed that clinical examination, chest X-ray, or CT detected second primary tumors in 5 patients (7%) whereas PET detected second aerodigestive tract primary tumors in 11 patients (16%, $p = 0.03$), along with one thyroid carcinoma. In the series by Mendenhall *et al.* (12), 24 of the 130 patients underwent PET. Of the 20 patients with positive PET scans, primary tumor was discovered in only 7 (35%). Six of these 7 patients had suggestive findings by clinical examination and/or conventional imaging. Among the 4 patients with negative PET scans, biopsies detected a primary tumor in 2 patients.

Braams *et al.* investigated the potential "added value" of PET to detect unknown primary tumors in the absence of CT and/or MRI abnormality (17, 18). Endoscopy and random biopsies were performed after PET, and when no tumor was found histologically, more biopsies were taken from the PET-positive regions. Among 10 patients with nodal metastasis from SCC, PET identified 2 head-and-neck primary neoplasms, but a suggested lung primary was not confirmed by bronchoscopic biopsy. Furthermore, PET failed to identify one small tumor at the base of tongue.

Greven *et al.* reported on 13 patients with cervical lymph node metastases from clinically occult primary, who underwent PET before treatment (19). PET detected a tonsil tumor, confirmed by tonsillectomy, in 1 patient (8%) but gave false-positive results for 6 patients (46%). Two tonsil tumors were found by random biopsies after negative imaging and panendoscopy. Among 10 patients with occult primary tumor after complete staging, no primary tumors emerged after therapy (no details reported) during a mean follow-up period of 27 months. In contrast, Safa *et al.* (20) examined a comparable group of 14 patients and found that PET identified a pathologically confirmed primary tumor in 3 patients (21%) and was false positive in 2 cases. Again, after treatment (no details reported), a primary lesion was never found in all patients with negative staging procedures ($n = 9$; median follow-up, 22 months). In the study by Aasar *et al.* (21), PET was sometimes performed before completion of routine staging and thereby may have resulted in a higher primary tumor detection rate (8 of 15 histologically confirmed tumors). There were, however, 2 false-positive results.

Table 1 summarizes the data of reports presented above along with other series (17, 19–25). In aggregate, PET has a positive predictive value of 56%, a negative predictive value of 86%, and an overall accuracy of 69%. However, there is a substantial variation among series. In general, with negative clinical examination and imaging, PET detected primary tumors in less than 25% of the cases. In the study by Mendenhall *et al.* (12), PET detected the primary tumor in an additional 1 of 24 patients (4%). Therefore, it is not generally recommended for routine use.

MORE RECENTLY INTRODUCED DIAGNOSTIC METHODS

A recent report suggested that laser-induced fluorescence imaging could increase the primary tumor detection rate (26). In a series of 13 patients who underwent conventional assessment, panendoscopy with random biopsies detected 2, whereas fluorescence-guided biopsies detected 5 primary tumors. Despite false-positive results in 8 locations from 4 patients, the number of unnecessary biopsies with fluorescence-guided biopsies was much lower than that of a random biopsy strategy. Considering these encouraging results, further evaluation of laser-induced fluorescence imaging appears to be warranted.

Detection of Epstein–Barr virus (EBV) in metastatic lymph nodes by *in-situ* hybridization may indicate a nasopharyngeal primary tumor, as reported by Lee *et al.* (27). In their study, 10/10 neck metastases from the nasopharynx but none of 19 specimens from other primary sites were EBV positive. Human papillomavirus (HPV) can be detected by polymerase chain reaction and might be more

Table 1. Overview of PET studies for detection of unknown head and neck primary tumors in patients with cervical lymph node metastases from squamous cell carcinoma

Reference first author [no.]	*n*	Specificity	Sensitivity	PPV	NPV	Accuracy
Braams [17]	10	6/7	2/3	2/3	6/7	8/10
Greven [19]	13	5/11	1/2	1/7	5/6	6/13
Safa [20]	14	8/10	3/4	3/5	8/9	11/14
Aassar [21]	16	5/8	8/8	8/11	5/5	13/16
Mukherij [22]	19	3/8	9/11	9/14	3/5	12/19
Lassen [23]	7	2/5	1/2	1/4	2/3	3/7
Bohuslavizki [24]	27	NR	NR	9/15	NR	NR
Schipper [25]	16	9/12	4/4	4/7	9/9	13/16
Σ	122	38/61	28/34	37/66	38/44	66/95
		62%	82%	56%	86%	69%

Abbreviations: PPV = positive predictive value (both PET and biopsy positive); NPV = negative predictive value (both PET and biopsy negative); NR = not reported.

frequent in oropharyngeal cancers (28). Approximately 21% of tumors with neck node metastases were found to be HPV positive (29). Whether time and cost for such analysis can be justified in routine work-up of metastatic SCC in cervical lymph nodes without known primary tumor remains to be shown in future studies.

Califano *et al.* performed microsatellite analysis on nodal metastatic tumors and histologically benign surveillance biopsy specimens obtained from 18 patients with unknown primary HNSCC (30). Most patients were treated with neck dissection followed by radiation therapy to the affected neck and ipsilateral Waldeyer's ring, and were followed up to 13 years with continuing surveillance for primary mucosal tumors. In 10 patients (55%), at least 1 histopathologically benign mucosal biopsy specimen from defined anatomic sites (i.e., most likely sites for an occult primary tumor) demonstrated a pattern of genetic alterations identical to that present in cervical lymph node metastases. Four patients eventually developed clinically detectable mucosal disease in their upper aerodigestive tract between 1 and 13 years later. Interestingly, 1 patient harboring genetic alterations in the tongue base and 2 patients in the tonsil subsequently developed SCC in the identical or adjacent mucosal region. All 3 of these tumors had genetic changes identical to those in the benign mucosal biopsy specimens and in the metastatic lymph nodes. The authors concluded that histopathologically benign mucosa of the upper aerodigestive tract may harbor foci of clonal, preneoplastic cells that are genetically related to metastatic SCC in cervical lymph nodes and that such mucosal sites are the sites of origin of unknown primary SCC. Microsatellite analysis may represent a clinically useful tool for determining such sites. More studies of this nature are needed to elucidate the role of molecular assays in this group of patients.

RESULTS OF SURGERY ALONE

Grau *et al.* recently reported a series of 277 patients treated with radical intent in 5 cancer centers in Denmark (3). Therapy consisted of radical surgery as the only treatment in 23 (9%), irradiation of the ipsilateral neck in 26 (10%), and radiotherapy to both sides of the neck and the mucosa in 224 patients (81%). The incidence of emerging primary in the head and neck was significantly higher in patients treated with surgery alone than those treated with radiotherapy (5-year actuarial risks of 54 ± 1% as opposed to 15 ± 3%, $p < 0.0001$). However, the cause-specific and overall survival rates of patients undergoing surgery alone were not significantly worse than those receiving combined therapy, most likely due to selection of patients with more favorable nodal stage for surgery alone and those with more advanced nodal disease for adjunctive radiotherapy.

Combining data of surgery alone from four available series (3, 31–33), however, revealed a crude mucosal carcinoma emergence rate of about 25% (30 of 121 patients), a median nodal recurrence rate of around 34%, and a 5-year overall survival rate of approximately 66%. These data suggest that selected patients, particularly those with pN1 neck disease with no extracapsular extension, can be treated adequately with surgery alone (32).

RESULTS OF RADIOTHERAPY WITH OR WITHOUT NODAL EXCISION OR DISSECTION

Comprehensive irradiation of bilateral cervical nodes along with putative primary sites

Nodal excision or dissection followed by radiotherapy. Colletier *et al.* (7) evaluated a series of 136 patients who received radiotherapy after either excisional nodal biopsy (39 patients) or neck dissection (97 patients). The majority of patients (88%) received radiation with comprehensive portals. The mucosal carcinoma emergence rate was 10% (10-year actuarial rate of 14%), the nodal failure rate was 9%, the distant metastases rate 18%, and the 5-year survival rate was 60%. Strojan and Anicin (34) also reported a mucosal primary emergence rate of 9%, a neck relapse rate of 18%, a distant metastases rate of 11%, and a 5-year survival rate of 52% in a series of 56 patients treated with

nodal resection and radiotherapy (given through extended portals in 48 patients). The data of six earlier reported series (35–40) combined are consistent with these findings. Of an aggregate of 389 patients, 370 received postoperative and 19 preoperative radiotherapy, delivered to large volume including pharyngeal axis in virtually all patients. Mucosal carcinoma emergence was recorded in 8% of patients, nodal relapse in 18%, distant metastases in 20%, and overall 5-year survival rate ranged from 35–63%.

Radiotherapy alone. Grau *et al.* (3) evaluated a group of 213 patients treated with comprehensive radiation alone and observed a 5-year actuarial mucosal carcinoma emergence rate of 16% (crude rate of 8%), nodal relapse rate of 50%, distant metastases rate of 14%, and survival rate of 37%. Harper *et al.* (41) found a mucosal primary emergence rate of 12% (10-year actuarial rate: 20%), nodal relapse rate of 20%, and a 5-year survival rate of 48% in a series of 69 patients of whom 39 (57%) received radiotherapy alone. It should be noted that patients selected for nodal dissection plus radiotherapy may represent a more favorable subset (e.g., medically fit to undergo anesthesia and having no fixed nodal disease) than those assigned to receive radiation alone.

Radiotherapy to ipsilateral neck

The available series generally include less favorable patients with poorer performance status (judged not to be able to tolerate wide-field or high-dose radiotherapy), higher N-stage, unresected nodes, or lower dose radiotherapy. In the series of Glynne-Jones *et al.* (8), bilateral irradiation was given to only 9 patients of 87 patients receiving curative or palliative treatment. For the whole group, 5-year survival rate was 33%, head-and-neck primary tumor emerged in only 7%, nodal relapse developed in 41% of patients (31% in patients treated with curative intent), and distant metastases occurred in 38% of patients treated for cure. Similar results were reported by Sinnathamby *et al.* (2) in 69 patients, of whom 48 received ipsilateral irradiation. A total of 9 primary tumors appeared in the head and neck for a 10-year actuarial incidence of 30%. In contrast, 37 patients (54%) relapsed in the neck. The 5-year survival rate was 36%. In univariate analysis, there were significant correlations between N stage and tumor grade and overall relapse-free survival but not bilateral portals. The authors concluded that after thorough initial assessment with CT and panendoscopy, routine comprehensive mucosal irradiation could be avoided.

Retrospective single institution comparisons of both approaches

Weir *et al.* (42) compared the outcome of 85 patients irradiated to the involved nodal regions alone with that of 59 patients irradiated to both the nodes and putative primary sides. Mucosal primary tumors emerged in 7% of patients receiving irradiation to involved nodal regions compared with 1.7% in those with putative sites irradiated. The overall nodal relapse rate was 49%, and 5-year survival rate was 41%. In multivariate analysis, no difference in survival or cause-specific survival was found between the two groups, whereas N stage and dose of radiotherapy ($<$50 Gy vs. $>$50 Gy) had a significant, independent impact on prognosis. Similarly, the study by Marcial-Vega *et al.* (43) in 80 patients did not show a significant impact of portal volume on mucosal primary emergence rate (5–14%) and 5-year survival (37–39%). Nodal control rate was not reported.

Reddy and Marks (5) compared the outcome of 36 patients receiving bilateral irradiation (including the pharyngeal axis) with that of 16 patients treated with unilateral electron beams. Whereas the ipsilateral nodal failure rate was lower (19% vs. 31%), the contralateral nodal failure rate was much higher (44% vs. 14%) in the electron beam group. Additionally, mucosal primary emergence rate was significantly higher in the electron beam group (44% vs. 8%, overall 19%). However, there was no significant difference in 5-year survival (overall 40%) or disease-free survival (DFS) rates (47% vs. 53%, overall 51%). Of note is that the studies by Weir *et al.* (42) and Marcial-Vega *et al.* (43), discussed above, included many patients who received involved neck radiation with techniques delivering higher doses to the upper aerodigestive mucosa than with electron beams.

In the series by Grau *et al.* (3), 26 patients received irradiation to the ipsilateral neck only with various techniques. In multivariate analyses, there was no significant difference in the rates of mucosal primary emergence, nodal failure, disease-specific survival, or overall survival compared with patients receiving more comprehensive irradiation. However, combining all relapses above the clavicle, patients treated with unilateral neck irradiation had a relative risk of 1.9 ($p = 0.05$) compared with those receiving bilateral neck and mucosa irradiation.

Summary and discussion of results of radiotherapy

The actuarial risk of emergence of head-and-neck carcinoma after comprehensive radiotherapy was less than 10% at 2 years, less than 15% at 5 years, and up to 20% at 10 years (1). These rates are similar to the rates of occurrence of second primary tumors (approximately 3% per year and most frequently located in the lung, esophagus, or abdomen) in patients cured of detectable common head-and-neck tumors, such as tonsillar and pyriform sinus carcinomas (8, 10, 11, 42). Therefore, the predominant pattern of relapse in patients receiving radiotherapy with or without neck dissection is nodal recurrence (2, 3, 6) or distant metastases (7). The crude risk for either nodal recurrence or distant metastases is at least twofold higher than for emergence of a mucosal primary tumor (Table 2). There is some evidence that ipsilateral neck control rate is higher after resection plus radiation than after radiotherapy alone (5).

Depending on patient and tumor characteristics, reported 5-year actuarial survival rates range from 18% to 48% in some series (1–3, 8, 10, 42), but 10-year survival rates of 40% to 56% have also been documented (7, 35, 44). Prognostic determinants for patient survival include N-stage,

Table 2. Reported results of comprehensive and limited radiotherapy

Endpoint	Unilateral radiotherapy (2, 3, 5, 8, 42, 43)	Comprehensive radiotherapy (3, 5, 7, 34–41, 43)
Median mucosal primary emergence rate (range)	8% (5–44)	9.5% (2–13)
Median neck relapse rate (range)	51.5% (31–63)	19% (8–49)
Median distant metastases rate (range)	38% (only given in Ref. 8)	19% (11–23)
Median 5-year overall survival rate (range)	36.5% (22–41)	50% (34–63)

number of nodes, grading, extracapsular extension, and performance status (2, 3, 6, 7, 42).

The two radiotherapy strategies adopted for the treatment of this patient population are comprehensive irradiation of bilateral neck nodes plus the pharyngeal axis and irradiation of the ipsilateral cervical nodes. Table 2 summarizes the reported results. Details of relatively large series are presented below. Lack of comparative studies, however, makes it difficult to determine the optimal radiotherapy strategy. On the one hand, literature data suggest that patients receiving nodal resection and radiotherapy to bilateral neck nodes and the pharyngeal axis might have a higher locoregional control probability and survival rate than do patients receiving nodal resection followed by ipsilateral irradiation or radiation alone. On the other hand, a few retrospective single-institution studies suggest that radiation to the ipsilateral cervical nodes is not associated with reduced overall survival, shorter DFS, or higher mucosal primary emergence rates. Data on distant metastases are not available from these studies. Considering the morbidity induced by radiation to bilateral neck nodes and putative mucosal sites, it seems prudent to determine whether the latter approach could be reserved for a defined subset of patients, e.g., those with bilateral nodal metastases, extensive unilateral involvement with regard to number and levels of nodal metastases, unfavorable grading, etc. With increasing availability of intensity-modulated radiotherapy, realization of risk-adapted individually tailored radiotherapy plans that provide at least partial sparing of the salivary glands might be possible even in situations where ipsilateral irradiation is considered inappropriate.

ROLE OF CHEMOTHERAPY

Debaud *et al.* (4) suggested improved survival by addition of chemotherapy in a report of 41 patients, of whom 16 had one of several chemotherapy regimens before, during, or after radiotherapy. The sample size and heterogeneous disease characteristics did not allow in-depth analysis.

In the series of Kirschner *et al.* (10) 40 of 64 patients had SCC, 48 underwent nodal resection and comprehensive radiotherapy, and 11 received concurrent chemotherapy (cisplatin and fluorouracil). The primary tumor emerged in 6% and nodal relapse occurred in 9% of patients. The overall 5-year actuarial survival rate was 39%, but was higher in patients treated with resection and radiation. There was no obvious advantage for chemoradiation.

SUMMARY

Several clinically relevant issues have been derived from this literature review. The available data show that diagnostic imaging (CT or MRI) plus panendoscopy with or without random biopsies remains the standard work-up of patients presenting with cervical nodal metastasis with no primary tumor detected by physical examination. The role of laser-induced fluorescence imaging in aiding white light panendoscopy to guide biopsy sampling requires further assessment. In the absence of panendoscopy detectable lesions, ipsilateral tonsillectomy can discover carcinoma in about a quarter of the patients. PET scan can identify tumors in about 20% of patients, but its use is currently restricted because of limited availability and high cost.

Retrospective studies suggest that neck relapse is more common than emergence of mucosal primary tumors. In aggregate, literature data suggest that patients receiving nodal resection and radiotherapy to bilateral neck nodes and putative mucosal sites appear to have higher reported control probability above the clavicle and survival rate then do patients receiving nodal resection and ipsilateral irradiation or radiation alone. It is not possible to tease out the confounding effect of patient selection on the outcome, as there usually were imbalances in known prognostic variables (e.g., number and size of lymph node metastases, extracapsular spread, and histological grade) among the subgroups. A selected subset of patients with minimal nodal disease (e.g., a single node without extracapsular extension) has favorable outcome after nodal dissection without radiotherapy. The role of chemotherapy in the treatment of patients with nodal metastasis from occult carcinoma has yet to be defined. The current literature contains no data on distant metastases rate after chemotherapy.

A few retrospective single-institution studies suggest that radiation to the ipsilateral cervical nodes is not associated with reduced overall survival or DFS rates or higher mucosal primary emergence rates (no data on distant metastases are available). Given the morbidity induced by radiation to bilateral neck nodes and putative mucosal sites, it seems prudent to determine the relative outcome, including quality of life measures, of unilateral versus comprehensive radiotherapy, at least in a defined subset of patients. A randomized trial is being explored by the European Organization for Research on Treatment of Cancer (EORTC) Radiotherapy Group and the Radiation Therapy Oncology Group (RTOG), in collaboration with other cooperative groups

from Australia, Canada, Denmark, and Germany. The main objective of the proposed trial is to test whether equivalent DFS can be obtained with selective irradiation procedure (ipsilateral neck node areas) compared to an extensive irradiation (nasopharyngeal, oropharyngeal, hypopharyngeal and laryngeal mucosa, and neck node areas on both sides of the neck) in patients with unilateral cervical lymph node metastases of squamous cell carcinoma (Stage pN2a, pN2b, pN3 [pN1 depending on institutional policy] after comprehensive neck dissection). A minimum prophylactic dose of 50 Gy will be administered; however, the involved level(s) will receive 60 Gy. Regarding extended boost to 66 Gy as well as details of two-dimensional or three-dimensional irradiation technique, each institution will have to declare its own policy and respect it throughout the entire study period. Of course, ipsilateral neck irradiation will result in some dose to the pharyngeal mucosa. Therefore, the primary endpoint will be DFS. Secondary endpoints will include control of the neck, incidence of subsequent mucosal primary emergence, overall survival, incidence of late effects including xerostomia (EORTC/RTOG scale for late toxicity), and quality of life (EORTC QLQ-H&N35). The protocol will be designed as an equivalence trial, with an absolute difference of 9.62% in DFS between the experimental arm (ipsilateral irradiation) and the control arm being accepted as the definition of "equivalence." Assuming a 5-year DFS of 40% in the control group, a total number of 368 events (600 patients) will be required (one-sided modified log–rank test with an α of 0.05 and a power of 0.8). This number of patients will provide 98% power to test for a 20% difference in the incidence of Grade 3–4 xerostomia between the 2 groups (50% in control arm and 30% in experimental arm). The design assumes a recruitment of 7 years and a further follow-up of 1.5 years. This protocol represents a unique opportunity to demonstrate the importance of adequate selection of target volumes for optimal treatment of patients with cervical lymph node metastases of squamous cell carcinoma from unknown primary.

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