Contemporary management of lymph node metastases from an unknown primary to the neck: II. A review of therapeutic options

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Accepted 1 July 2011
Published online 27 October 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/hed.21899

ABSTRACT: Although uncommon, cancer of an unknown primary (CUP) metastatic to cervical lymph nodes poses a range of dilemmas relating to optimal treatment. The ideal resolution would be a properly designed prospective randomized trial, but it is unlikely that this will ever be conducted in this group of patients. Accordingly, knowledge gained from retrospective studies and experience from treating patients with known head and neck primary tumors form the basis of therapeutic strategies in CUP. This review provides a critical appraisal of various treatment approaches described in the literature. Emerging treatment options for CUP with metastases to cervical lymph nodes are discussed in view of recent innovations in the field of head and neck oncology and suitable therapeutic strategies for particular clinical scenarios are presented. For pN1 or cN1 disease without extracapsular extension (ECE), selective neck dissection or radiotherapy offer high rates of regional control. For more advanced neck disease, intensive combined treatment is required, either a combination of neck dissection and radiotherapy, or initial (chemo)radiotherapy followed by neck dissection if a complete response is not recorded on imaging. Each of these approaches seems to be equally effective. Use of extensive bilateral neck/mucosal irradiation must be weighed against toxicity, availability of close follow-up with elective neck imaging and guided fine-needle aspiration biopsy (FNAB) when appropriate, the human papillomavirus (HPV) status of the tumor, and particularly against the distribution pattern (oropharynx in the majority of cases) and the emergence rate of hidden primary lesions (<10% after comprehensive workup). The addition of systemic agents is expected to yield similar improvement in outcome as has been observed for known head and neck primary tumors. © 2012 Wiley Periodicals, Inc. *Head Neck* **35:** 286–293, 2013

KEY WORDS: cervical lymph node metastases, unknown primary tumor, squamous cell carcinoma, (chemo)radiotherapy, neck dissection

Cancer of unknown primary (CUP) metastatic to cervical lymph nodes is uncommon. After a comprehensive diagnostic workup, the expected incidence of CUP in the head and neck is around 3% of patients with cervical lymph node malignancy, with squamous cell carcinoma (SCC) accounting for up to two thirds of cases.[1–4] The diagnostic approaches for patients with cervical lymph

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This article was written by members and invitees of the International Head and Neck Scientific Group.

node metastasis from an occult primary tumor were reviewed recently and an optimal diagnostic workup was proposed.[5]

Historically, treatment of CUP metastatic to cervical lymph nodes was aimed at eradicating existing nodal disease as well as the hidden focus of the potential index cancer that was not discovered during the diagnostic workup. In this context, the choice of a particular treatment approach should be based on the accuracy of the diagnostic workup for assessment of: (1) extent of disease in the neck; and (2) probability that a particular part of the upper aerodigestive tract is not the origin of the occult primary. However, according to a comprehensive literature review of studies published before 2000 by Nieder et al,[6] the risk of nodal recurrence and distant metastases is at least twice higher than the subsequent appearance of a mucosal primary tumor. This should also be taken into account when planning therapy.

As diagnostic facilities and levels of expertise vary considerably across hospitals and countries, several treatment approaches have been implemented. Furthermore, the efficacy of an individual treatment approach should be assessed separately for neck control and for mucosal control and weighed against treatment-related morbidity as a consequence of a particular therapy. The issue of optimal therapy for CUP with cervical lymph node metastases is further complicated by its uncommon occurrence and the variable rate of subsequent evolution of a mucosal primary across international centers; these factors have precluded the execution of properly designed multicenter randomized trials. The questions asked most frequently in the relevant literature are as follows: when is single-modality therapy sufficient; what is the optimal extent of neck surgery or radiation fields; what is the treatment efficacy of radiotherapy (RT) versus the combination of surgery and irradiation, particularly in view of human papillomavirus (HPV) status of biopsied neck nodes; is there a place for systemic therapy; and what is the role for intensity-modulated radiation therapy (IMRT)?

For cervical lymph node metastases of tissue types other than SCC, the treatment recommendations follow those for cases with a known primary tumor of a pertinent histology. The following discussion refers to SCC metastatic to cervical lymph node from an unknown primary.

EARLY-STAGE NECK DISEASE

In low-volume neck disease, pN1 and early pN2a cases without extracapsular extension (ECE) on histopathological examination, several studies have reported excellent regional control with either surgery or RT alone. Whenever surgery is an option, the surgeon must include the previous scar of open biopsies, dissect, and carefully include all the area of the previous operation. Although these studies were small and retrospective, clearance of the appropriate cervical lymph node levels with either of these 2 modalities seems adequate. Colletier et al[7] found no neck recurrence in a group of 16 patients with cN1 disease and no ECE, in whom an excisional biopsy preceded RT. Similarly, Aslani et al[8] reported no failure in the neck in 12 patients who had fine-needle aspiration biopsy (FNAB) or excisional biopsy followed by RT alone. After a standard radical neck dissection or some of its modifications, Coster et al[9] reported recurrence in the dissected necks in 2 of 13 patients with pN1 disease, both of whom had ECE. In the series of Miller et al,[10] no neck recurrence was observed in 6 of 7 patients with pN1 disease and no ECE, treated solely with a selective neck dissection; the 1 patient who developed neck recurrence had ECE. According to Patel et al,[11] none of the 4 patients with pN1 disease without ECE treated by single modality therapy experienced neck recurrence, whereas Iganej et al[12] reported ultimate tumor control above the clavicles in 81% (13 of 16) of surgically treated patients with pN1/pN2a disease without ECE and in 89% (8 of 9) treated with combined modality approaches.

Based on these results derived from small numbers of patients, it is clear that the enrollment of candidates for single-modality therapy should be selective. However, simple excision of an enlarged lymph node even in patients with a single metastatic lymph node without ECE is inadequate. It must be followed by clearance of further neck levels as appropriate or RT of the involved neck. The latter may have the advantage that, depending on the radiation volumes, an occult primary tumor located laterally in the oropharynx may also receive a sufficiently high dose to be eliminated. However, if a thorough examination and appropriate imaging and biopsy/tonsillectomy looking for a primary tumor are all negative, then the chance of a primary tumor becoming evident is low, making neck dissection a highly effective and cost-effective form of treatment.

As in the case of N1 neck without ECE that occurs in the context of the known primary, single modality treatment may suffice and give good control rates. Although this practice is not backed by high level evidence, very few centers offer combined modality therapy in this scenario.[13] However, only surgery reliably allows the diagnosis of ECE. In the case of ECE, postoperative RT, usually with concomitant chemotherapy, is mandatory in order to increase local control rates. Nevertheless, it has been shown that postoperative RT does not increase locoregional control or survival in patients with completely resected head and neck SCC with pN1 or pN2 without ECE,[14,15] which in turn causes additional morbidity (eg., xerostomia). Conversely, a selective neck dissection has a very low rate of postoperative complications and is less expensive than RT.

ADVANCED-STAGE NECK DISEASE AND MUCOSAL PRIMARY

Single-modality therapy or combined treatment approach?

For patients with advanced neck disease, combined-modality therapy is more strongly indicated, although there are exceptions. For example, Grau et al[3] reported a 5-year neck control of 50%, an overall survival rate of 37% and a crude emergence rate of head and neck mucosal primary tumors of 12% in a series of 224 patients treated only with RT during the period 1975 to 1995. The results of 2 recent but smaller series demonstrated more encouraging figures, most probably due to improvements in diagnostics and RT techniques, with 5-year neck control rates of 76.3% and 65.6%; an overall survival rate of

77.8% and 68.5%; and crude mucosal primary emergence rates of 7.5% and 16.7%; 40 patients from 1987 to 2002[8]; and 60 patients from 1989 to 2003.[16] In none[3,8] or in only a negligible proportion[16] of patients from 3 series, was chemotherapy added to RT; and in the majority of cases, both sides of the neck[3,8,16] and putative mucosal primary sites were also irradiated.[3,16] However, according to literature for the period from 1990 to 2003, as summarized by Jereczek–Fossa et al,[17] nodal relapse rates between 0% and 20% and an overall survival at 5 years between 22% and 67% can be expected with a more intensive combination of comprehensive neck dissection and RT (involved field RT or bilateral neck/mucosal RT). Figures from more recent series also show some improvement, ranging from 67.3% to 93% for neck control and from 40.9% to 78.9% for overall survival at 5 years.[8,18–20] When combined therapy was directly compared to RT alone (111 vs 70 patients), Wallace et al[20] reported significantly better 5-year neck control rates in patients who underwent neck dissection: pre-RT neck dissection, 93%; post-RT neck dissection, 82%; and no neck dissection, 73%. In a smaller group of patients (surgery and RT, 21, vs RT alone, 40 patients), no advantage for a combination of neck surgery and postoperative RT was observed by Aslani et al.[8]

It is obvious that aggressive combined therapy is needed for advanced neck disease. However, based on existing evidence, it is not apparent what the optimal therapy is: surgery with postoperative RT or initial (chemo)radiotherapy followed by neck dissection only in those patients who do not achieve a complete clinical or metabolic (positron-emission tomography [PET]) response to irradiation.

Appearance of the Primary Tumor

The mucosal primary emergence rates are comparable when studies are analyzed according to the extent of neck irradiation,[17] with up to 12% (in the series of Reddy and Marks,[21] this figure was 44% but only 16 patients were studied) for ipsilateral versus 2% to 10% for bilateral mucosal irradiation.[17] These results are in line with those presented by Nieder et al[6] (8% after unilateral RT and 9.5% after comprehensive RT). A selective approach regarding the extent of mucosal irradiation was described by Wallace et al.[20] As the majority of unknown primaries are most likely to occur in the tonsillar area and base of tongue, only the oropharynx and nasopharynx were encompassed in their RT portals; the larynx and hypopharynx were only included for patients with level III metastases. Using this criterion, the overall mucosal control rate at 5 years was 92% for the whole group of patients and was 100% for the 28 patients treated with mucosal portals limited to the nasopharynx and oropharynx. Sites of mucosal failure were nasopharynx (1 patient), oral cavity (9 patients), and supraglottic larynx (3 patients).[20]

The emergence rates of mucosal primary tumors after unilateral neck irradiation are similar to the risk of occurrence of metachronous second primary tumors in patients cured of a known head and neck SCC primary.[22] In view of these data, and their own experience, Sinnathamby et al[23] concluded that most emerging primaries are new lesions that are unrelated to the index cancer and that the risk of missing a curable occult primary after a thorough initial workup is too small to justify the morbidity of elective irradiation of potential primary sites. In fact, survival rates are not related to the appearance of the primary tumor.[24] An additional consideration is the potential complexity of adding re-irradiation as a treatment modality for the primary site if and when a primary cancer emerges.

Should Irradiation be Unilateral or Bilateral?

The majority of single-institution retrospective studies comparing the involved field and elective neck irradiation did not show any advantage for more extensive RT,[3,16,25,26] although the opposite has also been reported.[21] Literature reviews[6,17] suggest improved regional control after nodal resection and bilateral neck irradiation over ipsilateral neck RT. Consequently, no firm conclusions can be drawn on this issue. The results from different studies might also be biased by inclusion of patients with more advanced/inoperable neck disease or those in poor general condition into the involved neck RT group. In clinical practice, candidates for bilateral neck RT are patients with suspected primary tumors located close to the midline (ie, base of tongue in HPV-positive cases after tonsillectomy not disclosing the primary; nasopharynx in Epstein–Barr virus–positive cases, and/or suggestive imaging studies but negative biopsy) or those with extensive nodal disease putting the contralateral neck at increased risk for occult nodal metastases, or with bilateral nodes. However, any putative advantage of bilateral RT, particularly when potential sites of the occult mucosal primary are also irradiated, must be weighed against close observation during follow-up, with elective ultrasound and guided FNAB, the morbidity induced and the limitations of salvage surgery with or without postoperative curative re-irradiation in the event of a subsequently manifesting primary tumor or second primary.

Intensity-Modulated Radiotherapy

Three-dimensional (3D) conformal RT and IMRT (vs 2D-RT), have been found to be a strong independent prognostic factors for locoregional control and survival in a recent study.[25] The introduction of IMRT during the last 15 years seemingly abolishes many of the dilemmas related to irradiation in an unknown primary setting. However, one must be aware that even with IMRT the acute and late toxicity of extensive elective irradiation of potential primary sites and both sides of the neck is significantly more pronounced than when RT is limited to the involved neck. Furthermore, when only the involved neck is irradiated, IMRT offers no real advantage over 3D conformal RT.

As summarized in Table 1, after a relatively short follow-up time of a median of 2 years in the majority of studies, an average crude mucosal and neck failure rate of $<5\%$ and 10% (range, 0% to 14.3%), respectively, and overall survival at 2 years of well above 70% (range, 74.2% to 92%) can be expected after IMRT.[27–32] In 2 studies comparing conventional 3-field RT and IMRT, there were no discernable differences in any relevant

TABLE 1. Intensity-modulated radiotherapy for head and neck cancer of unknown primary: review of published series.

Author, (Ref)	Time span	No. of patients	Therapy	Chemotherapy	RT volume	Neck failure	Mucosal site primary	Locoregional control	Distant metastases	Overall survival
Klem et al[27]	2000–2005	21	IBx/FNA+RT 5, EBx+RT, 3 ND+RT, 13	Concurrent, 14	bN+PMPS	3/21, 14.3%	0/21	At 2 y., 90%	At 2 y, 90% (2/21, 9.5%)	At 2 y, 85%
Medani et al[28]	2003–2006	IMRT, 23 CRT, 18	ND+IMRT,19 ND+CRT, 16	IMRT, 3 CRT, 1	bN+PMPS	IMRT, 5/23 (21.7%, median FUP 17 mo)* CRT, 2/18 (11.1%, median FUP 37 mo)	IMRT, 0/23 (median FUP 17 mo) CRT, 4/18 (11.1%, median FUP 37 mo)	–	At 2 y: - IMRT, 76.3% - CRT, 68.4% ($p = .99$) IMRT, 4/23 (17.4%, median FUP 17 mo) CRT, 6/18 (33.3%, median FUP 37 mo) ($p = .42$)	At 2 y: - IMRT, 74.8% - CRT, 61.1% ($p = .97$)
Lu et al[29]	2000–2006	18	FNAB+RT, 5 EBx+RT, 4 ND+RT, 8	Concurrent, 6	bN+PMPS, 17 iN, 1	At 2 y, 88.5% (2/18, 11.1%)	1/18, 5.6%†	–	At 2 y, 88.2% (2/18, 11.1%)	At 2 y, 74.2%
Frank et al[30]	1998–2005	52	FNAB+IMRT, 8 EBx+IMRT, 2 ND+IMRT, 17 FNAB+CRT, 4 EBx+CRT, 3 ND+CRT, 17	Induction, 8 Concurrent, 8	bN+PMPS	At 5 y, 94.2% (3/52, 5.8%)	At 5 y, 98.1% (1/52, 1.9%)	–	At 5 y, 91.7% (5/52, 9.6%)	At 5 y, 81%
Sher et al[31]	2004–2009	24	Bx+RT, 13 LE+RT, 8 mRND+RT, 3 RT+ND, 3	Induction, 7 Concurrent, 22	bN+PMPS	0/24	0/24	At 2 y, 100%	At 2 y, 96% (1/24, 4.2%)	At 2 y, 92%
Chen et al[32]	2001–2009	IMRT, 27 CRT, 24	FNAB+RT, 12 EBx+RT, 5 SND+RT, 7 mRND+RT, 27	Concurrent, 30	bN+PMPS	4/51, 7.8%	2/51, 3.9%	At 2 y, 89% - IMRT, 92% - CRT, 87% ($p = .44$)	8/51, 15.7%	At 2 y, 86% - IMRT, 87% - CRT, 86% ($p = .43$)

Abbreviations: RT, radiotherapy, IBx, incisional biopsy; FNA, fine-needle aspiration; bN, bilateral neck; PMPS, potential mucosal primary site; EBx, excisional biopsy; ND, neck dissection; IMRT, intensity-modulated radiotherapy; CRT, Conventional radiotherapy; FUP, follow-up; FNAB, fine-needle aspiration biopsy; iN, ipsilateral neck; LE, local excision, SND, selective neck dissection; mRND, modified radical neck dissection.

* Included are also 3 patients in whom treatment was stopped because of early lung metastasis, aspiration pneumonia after PEG and sepsis after concomitant chemotherapy.

† The patient who was diagnosed during carotid endarterectomy had RT to the ipsilateral neck only.

efficacy endpoints between the 2 irradiation techniques.[28,32] Importantly, in both studies, an improved therapeutic ratio was found with IMRT when compared to conventional irradiation, particularly when a dose to the contralateral (spared) parotid gland and the ipsilateral inner and middle ear structures was considered.[32] For patients treated by conventional RT and IMRT, the incidence of severe late xerostomia (complete dryness of mouth) of 58% versus 11%, grade 3+ esophageal toxicity (liquid diet only) of 42% versus 17%, gastroscopy tube-dependence at 6 months after treatment of 42% versus 11% (after 1 year 33% vs 0%), and overall grade 3+ late toxicity of 63% versus 29%, respectively, were reported by Chen et al.[32] Also, in a comparative study by Madani et al,[28] no difference in grade 3 acute mucosal toxicity was observed between both RT techniques, whereas grade 3 xerostomia (53.4% vs 11.8%), dysphagia (26.7% vs 0%), and skin fibrosis (26.7% vs 0%) at 6 months of follow-up were significantly more common in the historical group than in the IMRT group. These observations are in line with the results of a prospective although non-randomized study conducted in patients with known primary tumors: patient-rated xerostomia and sticky saliva were significantly lower among patients treated with IMRT compared to a historical control group, as were several other head and neck symptoms. Moreover, the differences in patient-rated head and neck symptoms also translated into higher scores in health-related quality of life in favor of those treated with IMRT.[33]

Neck surgery

The decision regarding the type of neck dissection should be individualized and based on the extent of nodal disease. Selective neck dissection is usually preferred as all 5 levels of the neck are rarely at risk: there is no primary SCC in the head and neck region simultaneously exposing the sublevels IA/IB and VB at sufficiently high risk. Furthermore, when there is extensive involvement along the jugular chain, which is usually the case in an unknown primary setting, the dissection of sublevel IA may be omitted.[34,35] Therefore, classical radical neck dissection is rarely indicated as is—for the same reasons—comprehensive (levels I–V) neck dissection.

Systemic therapy

Experience with systemic therapy in patients with a CUP metastatic to cervical lymph nodes is limited. Generally, there are 2 clinical scenarios in which systemic drugs might be recommended: the intensification of (loco)regional treatment, for the purpose of improving neck control, or to palliate the symptoms of regionally advanced disease or systemic metastases.

Chemotherapy has been used since the 1980s and first adapted to unknown primary disease by de Braud et al[36] who treated 16 patients with a combination of RT and chemotherapy. Although 12 of 16 patients had N3 disease, the complete response rate was 81% and 11 patients showed no evidence of disease after a median survival time of 37+ months. In the second group, 28% of the 25 patients treated with surgery and/or RT (9 of 25 with N3 disease) were free of disease after a median follow-up of 24 months. The heterogeneity of the chemotherapy regimens and schedules used, the small sample size and/or the lack of a control group in de Braud's and several other series preclude any relevant final conclusions.[16,27,30,31,36–39] Recently, Beldì et al[19] and Ligey et al[25] reported no advantage in supplementing locoregional treatment with chemotherapy: 18% and 45% of patients from these 2 series, respectively, were treated with a variety of platinum-based regimens.

The only studies primarily focused on chemotherapy in an unknown primary setting were those of Shehadeh et al[40] and Chen et al.[41] In the first study, 37 patients (with N2b–N3 disease in 71% of cases) were treated with neck dissection, bilateral neck/mucosal sites RT, and 3 cycles of concurrent cisplatin (100 mg/m^2 every 3 weeks). The neck control and distant failure rates were 95% and 11%, respectively, and 89% of patients were alive after a median follow-up time of 42 months for survivors. Both patients with recurrence had N3 disease with ECE and died as a result of their disease in less than 1 year.[40] Recently, Chen et al[41] reported on 60 patients, of whom the majority (75%) were initially operated on and all patients had bilateral neck/mucosal axis RT (IMRT in 58%). Concurrent cisplatin was administered in 53% of patients, mainly with a dose of 100 mg/m^2 every 3 weeks and, in selected cases, weekly cisplatin with a dose of 50 mg/m^2 was delivered for a median of 4 cycles (range, 3–6 cycles). At 2 years, no advantage of treatment intensification was noted with regard to locoregional control, progression-free or overall survival, and no subset of patients who would benefit from chemoradiotherapy could be identified. A significant increase in grade 3+ acute (59% vs 25%) and late (47% vs 14%) toxicity was associated with concurrent cisplatin. The authors concluded that although selection bias cannot be excluded, prospective data are needed to further address this question.[41]

With improved neck control and the diminished incidence of a subsequent mucosal primary, the problem of systemic dissemination as a crucial factor that determines the survival outcome becomes more prominent. The incidence of distant metastases ranges between 11% and 38% and correlates with advanced N-staging and ECE.[6,17] No study specifically addresses this issue. However, Rödel et al[18] found that in patients with advanced nodal disease (N2b–N3) the incidence of distant metastases diagnosed on follow-up was lower when postoperative RT was combined with cisplatin-based chemotherapy (36% vs 59%). This resulted in a trend of improved overall survival in the latter group ($p = .10$). There was no beneficial effect on neck control observed by adding chemotherapy.[18]

What can we learn from patients with head and neck cancer with known primary tumors?

Due to the low incidence of the disease, the studies dealing with CUP metastatic to the cervical lymph nodes usually cover long time periods which limits their current applicability. So, the experiences collected through the management of neck disease in patients with known primary tumors could be instructive.

Systemic therapy

In clinical practice, the application of chemotherapy in patients with CUPs most often reflects its use with known primary tumors. Concurrent application of chemotherapy and RT can be justified with the highest level of scientific evidence[42] compared to mainly negative conclusions regarding chemoradiation from small and retrospective CUP series. Accordingly, ECE and residual disease after neck surgery are usual indications for combining platinum-based chemotherapy with RT in postoperative setting,[43] whereas in the presence of unresectable or high volume (N2–N3) nodal metastases, the efficacy of concurrent chemoradiation as an initial therapy has also been demonstrated.[44,45]

Given the relatively high incidence of distant metastases after advanced neck disease in known and unknown primary tumor settings an effective systemic therapy is urgently needed. Encouraging results are emanating from studies using induction chemotherapy, showing the reduction in distant metastasis rates for approximately 50% compared to concurrent chemoradiation series (from around 20% to around 10%). Thus, induction chemotherapy is another promising area for clinical research that is highly relevant also for patients with CUPs with advanced neck disease.[46]

Human papillomavirus

The HPV status of the tumor can be used as a marker of intrinsic sensitivity to irradiation. Several retrospective studies[47,48] and a prospective analysis of data from a clinical trial[49] confirmed that HPV-positivity confers a 60% to 80% reduction in risk of death from cancer relative to similarly treated HPV-negative tumors. Recently, Ang et al[50] retrospectively analyzed the association between tumor HPV status and survival among stage III and IV oropharyngeal SCC treated in the Radiation Therapy Oncology Group 0129 trial, sufficiently powered to account for potentially confounding factors, including smoking status of the patients. Using recursive-partitioning analysis, tumor HPV status was identified as a major determinant of overall survival, followed by the number of pack-years of tobacco smoking ($\leq$10 vs $>$10) and then N classification stage of the disease (N0–N2a vs N2b–N3) for HPV-positive tumors, or T classification of primary tumor (T2–T3 vs T4) for HPV-negative tumors. Accordingly, patients were classified into 3 prognostic categories with respect to the risk of death; patients with HPV-positive tumors were classified into the low-risk group with the exception of smokers with N2b-N3 neck disease who were considered to be at intermediate risk.[50]

In many centers, HPV positivity, particularly in nonsmokers, is nowadays considered a good indication for irradiation alone or in combination with concurrent chemotherapy. Surgery is then reserved only for those patients not achieving a complete clinical or metabolic response on posttreatment PET scanning.[51] Additional arguments for selecting RT over surgery in patients with CUPs with early-stage as well as advanced-stage HPV-positive neck disease include the relatively lower morbidity as well as the reduced risk of smoking-related metachronous primary tumors when only the ipsilateral tonsil and base of tongue are encompassed by the prophylactic RT. In view of significantly improved survival results in HPV-positive patients and substantial toxicity associated with combined modality therapy, questions emerge as to whether aggressive concurrent chemotherapy schedules can be replaced with less intensive regimens (eg, low-dose weekly platinum) or epidermal growth factor receptor inhibitor or whether RT alone or even with a modest dose reduction would be equally effective.[52]

HPV status is also a favorable prognostic sign for patients treated primarily with surgery[53] and it remains to be seen through the results of prospective randomized trials whether surgery alone or less intensive nonsurgical treatment for HPV-positive lymph nodes is effective enough to be recommended for routine use. Of note, proper evaluation of functional outcomes and quality of life should be an integral part of such trials.

CONCLUSIONS

When no primary tumor has been detected after meticulous examination and investigations, the treatment approach should be individualized and must be adapted to the pertinent clinical scenario. The few principles and recommendations that have been gained through retrospective data analyses and should be considered when planning a treatment strategy include the following. First, only patients whose neck disease is controlled benefit from sterilization of an occult primary tumor.

Second, the emergence rate of occult primary lesions in patients with CUPs is comparable to the risk of developing metachronous second primary tumors seen in patients cured of known primary head and neck SCC.

Third, after a complete diagnostic workup, including immunostaining, MRI or CT and/or fluorodeoxyglucose-PET, the risk of missing an occult primary tumor is small and must be weighed against the morbidity associated with treatment of suspected primary tumor sites.

Fourth, all 5 neck levels are rarely at risk and, therefore, selective neck dissections are preferred over more extensive comprehensive or radical neck dissections in the majority of patients.

Fifth, modern RT techniques, particularly IMRT, ensure an improved therapeutic ratio over conventional 2D RT when elective irradiation is intended, although they are not without long-term toxic side-effects.

Sixth. at present, there is no convincing evidence that the addition of systemic agents to irradiation improves treatment efficacy in CUP. However, it may be likely that it will give similar improvements in outcome as have been seen in known primary tumors of the head and neck.

Seventh, HPV-positive tumors seem more sensitive to irradiation than HPV-negative tumors.

Recommendations for early-stage and advanced neck disease are as follows: (1) pN1 or cN1 disease, without ECE found on histopathological or radiological studies: single-modality therapy is indicated (ie, selective neck dissection or involved field RT alone); (2) N1/ECE-positive, N2-N3 disease: a combined approach is justified. Both established therapies seem equally effective (ie, combination of neck dissection with postoperative RT and initial chemoradiation with surgery planned only for

those patients not achieving a clinical or metabolic complete response on posttreatment imaging). Whether less intensive or even single modality therapy could be adequate in patients who are HPV-positive, particularly nonsmokers, has yet to be determined. In view of the distribution pattern (almost 90% of primaries are located in the oropharynx) and the low emergence rate of hidden primary lesions which is comparable to the incidence of metachronous primaries in patients cured of known index cancer (<10% after comprehensive initial diagnostic assessment and ipsilateral neck irradiation), extensive bilateral/mucosal RT seems not to be indicated for all patients, particularly if close follow-up is provided with elective neck imaging and guided FNAB when appropriate and if HPV-positive status is determined. At present, it is unreasonable to suggest that a radical neck dissection should be performed in all patients with N2 or N3 neck disease.

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