

ORIGINAL ARTICLE

## HPV-related oropharyngeal carcinoma with Overt Level II and/or III metastases at presentation: The risk of subclinical disease in ipsilateral levels IB, IV and V

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### Abstract

**Background.** To assess the risk of subclinical neck nodal involvement of levels IB, IV and V for early T-stage, node positive, human papilloma virus (HPV)-related oropharyngeal carcinoma. **Material and methods.** We retrospectively identified the patients with clinically positive and un-violated neck that underwent upfront ipsilateral neck dissection for HPV-related oropharyngeal cancer between 1998 and 2010. From the pathology report we extracted the prevalence rate of involvement of each selected level and then estimated the risk that a level that does not contain any node larger than 10 mm at computed tomography (CT) harbors subclinical disease. Predictors of involvement were investigated as well. **Results.** Ninety-one patients were analyzed. The risk of subclinical disease in both levels IB and V is < 5%, while it is 6.5% (95% CI 3.1–9.9%) for level IV. Level IB subclinical involvement slightly exceeds 5% when 2 + ipsilateral levels besides IB are involved. The risk of occult disease in level IV tends to be < 5% when level III is not involved. **Conclusion.** These data support the exclusion from the elective nodal volume of level V and level IB but when 2 + other levels are involved. Level IV might also be spared when level III is negative. Clinical implementation within a prospective study is justified.

Over the past decade, a rise in the incidence of oropharyngeal squamous cell cancer (SCC) has been detected in white men younger than 50 years of age and who have no or limited history of alcohol or tobacco use [1]. It has been later recognized that most of these cancers are associated with infection by human papilloma virus (HPV) 16 or other less common strains and, besides a different epidemiology, they show several other distinct features compared to the ‘classical’ tobacco and alcohol-related counterparts [2]. From a clinical standpoint, HPV-related SCC of the oropharynx often presents with an early or undetectable primary tumor (clinical primary tumor stages cT0–2) and multiple/bulky regional nodes (clinical nodal stages cN2–3) [3]. Given the facts that this represents a relatively young

subgroup of patients with a good prognosis and that the extent of both surgery and radiotherapy will drive the risk of long-term morbidity (xerostomia, dysphagia, hypothyroidism, ...), it would be desirable to avoid unnecessary irradiation of regions at very low risk (< 5%) of subclinical involvement. However, due to the lack of specific data on the pattern of regional tumor spread, they are currently treated following the principles and tenets of their non-HPV counterparts [4–6] and the treatment approach is often ‘comprehensive’ (at least on the side of overt neck disease). In a previous study, we have shown that the risk of subclinical involvement tends to be < 5% for levels IB and V and < 10% for level IV, but results were not stratified by HPV status [6]. Moreover, predictors of involvement of selected levels were not

investigated systematically and confidence intervals for estimates were not reported [6]. In the present study, that was approved by the local IRB, we tried to clarify the risk of involvement (and thus the need to be electively treated) of selected nodal levels ipsilateral to known nodal disease along with their predictors in patients with HPV-positive, early T stage (cT1-2) oropharyngeal SCC.

## Material and methods

Patients who underwent neck dissection (ND) for oropharyngeal SCC at Johns Hopkins Institutions (JHI) from January 1998 to December 2010 were retrospectively identified. Patients were further selected who fulfilled all of the following criteria: 1) 'upfront' ND, i.e. before definitive radiotherapy  $\pm$  chemotherapy; 2) early clinical primary tumor stage (cT1 or cT2); 3) neck nodes that were clinically palpable or detectable on imaging at presentation in levels II and/or III; 4) no previous/synchronous tumors; 5) no previous neck surgery or 'neck violation' such as excisional nodal biopsy; fine needle aspiration or incisional biopsy with macroscopic/palpable tumor residual were allowed; 6) dissection of at least three contiguous neck nodal levels; 7) ND surgery performed at JHI; 8) neck specimen processed by surgical levels in the standard manner [7]; 9) tumor positive for HPV at in situ hybridization and/or for p16 at immunohistochemistry.

The strategy to perform upfront ND in patients with early T stage disease has been previously reported [8]. In most recent years, patients could also undergo ND along with the transoral robotic resection of the primary lesion, as an attempt to reduce the dose of radiation and/or skip concomitant chemotherapy [9].

If the patient had undergone bilateral ND, only the side of dominant neck disease, defined as the one that drew medical attention and/or contained the largest adenopathy, was considered.

Tumors were evaluated for the presence of HPV16 DNA by use of the in situ hybridization – catalyzed signal amplification method for biotinylated probes (GenPoint; Dako, Carpinteria, CA, USA) [10]. The expression status of p16 is strongly correlated with tumor HPV status and therefore it was evaluated by immunohistochemistry, as previously described [11]. For tumors positive at p16 but negative for HPV16, a wide spectrum in situ hybridization test was run to exclude infection by less frequent subtypes of HPV (30, 31...) [2]. Since 2007, oropharyngeal SCC have been routinely and prospectively tested for both HPV and p16 at JHI. Regarding older cases, a retrospective analysis was performed, provided the paraffin block of the neck specimen had been available.

The pathology reports of all eligible patients were reviewed and the prevalence ( $\pm$  standard error, SE) of pathological involvement of nodal levels IB throughout V was determined. Patients were considered to have a positive nodal level when one or more nodes within that level were reported to contain tumor.

The association between selected covariates and the pathological involvement of nodal levels was investigated with logistic regression [12].

Covariates (and their stratification) were as follows: presenting symptom (neck mass vs. other); primary tumor site (tonsil vs. other); age (continuum); sex (male vs. female); clinical primary tumor stage (T1 vs. T2); clinical nodal stage (N1-2a vs. N2b-3); pathological involvement of each other level (no vs. yes); number of pathologically positive levels besides the one being considered (0-1 vs. > 1); number of pathologically involved lymph nodes besides those belonging to the level being considered (0-1 vs. > 1); presence of extracapsular extension (no vs. yes).

The risk of subclinical involvement of each level was estimated from the observed prevalence rates assuming that that level had been found to be negative on computed tomography (CT) [6].

First, the negative-predictive value (NPV) was computed as follows:

$$\text{NPV} = \frac{(\text{specificity}) (1 - \text{prevalence})}{(\text{specificity}) (1 - \text{prevalence}) + (1 - \text{sensitivity}) (\text{prevalence})}$$

The NPV represents the probability that the patient will not have the disease when restricted to all patients who test negative, and equals the number of true negatives divided by the sum of all (true and false) negatives. The calculation of 1-NPV provides the probability that a neck nodal level that is negative on imaging harbors subclinical disease. The standard error of NPV was estimated by propagation of errors using the observed SE of the prevalence of each nodal level [13].

As stated above, prevalence rates were determined from Johns Hopkins pathology data. Unfortunately, we did not have in-house data for sensitivity and specificity of diagnostic imaging, since images at diagnosis were available for review only for a minority of patients as the remaining ones had their initial work up performed outside. Therefore, we used values from a multi-center prospective trial evaluating the sensitivity and specificity of CT for detecting pathologically positive lymph node metastases of head and neck SCCs [14]. Sensitivity and specificity vary in relationships with the nodal size cut-off used to define a 'negative' scan and they have been reported to be 0.88 and 0.39, respectively, for nodal sizes up

to 10 mm in largest axial diameter [14]. While a neck level that does not contain any lymph node exceeding 10 mm is usually considered 'negative' [15], we investigated also more restrictive cut-offs: 9 mm (sensitivity: 0.92, specificity: 0.31); 8 mm (sensitivity: 0.95, specificity: 0.22); 7 mm (sensitivity: 0.97, specificity: 0.17); 5 mm (sensitivity: 0.98, specificity: 0.13) [14].

The risk of subclinical nodal disease was also estimated for selected subgroups of patients for whom radiological (CT) staging of the neck was negative. For example, in order to assess the risk of subclinical disease of level x when level y is negative on CT, we first extracted from pathological data the prevalence of disease in level x when level y is clinically negative and then we estimated the risk of subclinical disease (1-NPV) for a given level of sensitivity and specificity as reported above. A cohort of patients with a clinically negative test for level y actually includes both true negatives (patients who do not have disease in level y) and false negatives (patients who actually harbor subclinical disease in level y). Each subgroup has its own prevalence of pathological involvement of level x. The former is estimated multiplying the observed rate of pathological involvement of level x in patients without pathological involvement of level y by the NPV of level y; the latter by multiplying the observed pathological involvement of level x in patients with pathological involvement of level y by 1-NPV of level y. Since these are mutually exclusive events, the probability of either occurring is the sum of the probabilities of each occurring. Therefore, the prevalence pathological involvement of level x when level y is radiologically negative is the sum of the two.

A level is considered to be at risk of involvement when its estimated value for 1-NPV, including 95% confidence intervals, exceeds 5%.

## Results

### Patients and treatment

Of 103 patients identified up to December 2007 and previously analyzed [6], two patients were excluded because they had isolated involvement of level IB or level IV (criterion #3). Seventy-eight patients (77.2%) had HPV positive and/or p16 positive tumors. Of 23 specimens that were labeled as 'not positive', only 13 (56.5%) were truly negative after being tested for both HPV and p16; 10 specimens were not tested for two main reasons, insufficient tissue in the paraffin block or the block could not be localized. In more recent years, 13 additional patients with both HPV and p16 positive oropharyngeal SCC

Table I. Selected patient, tumor and treatment characteristics of patients with oropharyngeal SCC seen at Johns Hopkins Hospital from 1998 to 2010.

Variable	Stratification	# pts/mean	%/SD
Age (years)		55.7	9.1
Sex	Male	85	93.4%
	Female	6	6.6%
Presenting symptom	Neck mass	75	82.4%
	Other*	16	17.6%
Duration (months)		3.7	3.4
T site	TON	63	69.2%
	BOT	24	26.4%
	PW	4	4.4%
cT stage	T1	56	61.5%
	T2	35	38.5%
cN stage	N1	16	17.6%
	N2a	29	31.9%
	N2b	39	42.9%
	N2c	4	4.4%
	N3	3	3.3%
Neck dissection	SND	22	24.2%
	MRND	59	64.8%
	RND	10	11.0%

BOT, base of tongue; cN, clinical nodal stage; cT, clinical T stage; MRND, modified radical ND; ND, neck dissection; PW, pharyngeal wall; RND, radical ND; SD, standard deviation; SND, selective ND; SP, soft palate; T, primary tumor; TON, tonsil.

\*other includes: otalgia. pain. sore throat. bleeding.

underwent upfront ND for a final number of 91 analyzed patients.

Selected patient, tumor and surgical treatment characteristics are reported in Table I. Of the four patients with cN2c disease, the stage of the dominant dissected neck was cN1, cN2a and cN2b in 2, 1, 1 patients, respectively.

Radical and modified radical ND always included levels IB through V; a selective ND included four levels in 11 patients and three levels in 11 patients. As a result, levels II and III had been dissected in all of the patients; approximately 85% of patients had levels IB and V dissected as well (Table II).

For 87 (95.6%) patients undergoing ND, the exact count of pathologically examined/involved nodes was reported, with an average of 41.9/2.9 per patient (standard deviations: 17.1/2.4). In the remaining patients, lymph node counts were reported as 'matted' or 'multiple' for one or more levels.

Table II. Prevalence of disease in dissected levels.

	Dissected		Positive at pathology		
	#	%	#	%	95% CI
level IB	80/91	87.9%	6/80	7.5%	1.7–13.3%
level II	91/91	100.0%	84/91	92.3%	86.8–97.8%
level III	91/91	100.0%	36/91	39.6%	29.5–49.6%
level IV	87/91	98.9%	16/87	17.8%	10.3–26.5%
level V	73/91	83.5%	2/73	2.6%	0–6.5%

*Observed pathological rates*

Overall, 56 patients (61.5%) had involvement of a single nodal level; 19 (20.9%), 14 (15.4%) and two (2.2%) patients had two, three or four levels pathologically involved, respectively.

The rate of involvement of each neck level is reported in Table II. Levels II and/or III were the only site of neck disease in 71 patients (78.0%).

*Predictors of subclinical involvement*

The only factor that showed an association with pathological involvement of level IB was the number of pathologically involved neck levels besides IB: none of the 47 patients with only one (other) level involved was found to harbor disease in ipsilateral level IB as opposed to 6/33 (18.2%) with two or more other levels involved (OR 22.4, 95% CI 2.5–2980,  $p = 0.0026$ ).

Both the number of pathologically involved levels beyond level IV (1 vs. >1, 4/57, 7.0% vs. 12/30, 40.0%, OR 8.8, 95% CI 2.5–30.9,  $p < 0.001$ ) and level III involvement (no vs. yes, 4/52, 7.7% vs. 12/35, 34.3%, OR 6.2, 95% CI 1.8–21.5,  $p = 0.004$ ) predicted the presence of disease in level IV at univariate logistic regression. The two covariates were highly correlated (Spearman's  $\rho = 0.79$ ,  $p < 0.001$ ).

The low number (N = 2) of events for level V did not allow us to investigate predictors of involvement.

*Estimated subclinical rates*

Figure 1 shows the estimated risk of subclinical involvement of each level for a cut-off of the largest axial diameter of the largest node of 10 mm. Overall, the risk of subclinical disease is < 5% for both levels IB and V, while it is slightly higher for level IV. While a lower cut-off to define a negative CT scan reduces the risk of subclinical involvement, this does not change the categorization of the risk (< or  $\geq 5\%$ ) of occult disease of any level (data not shown).

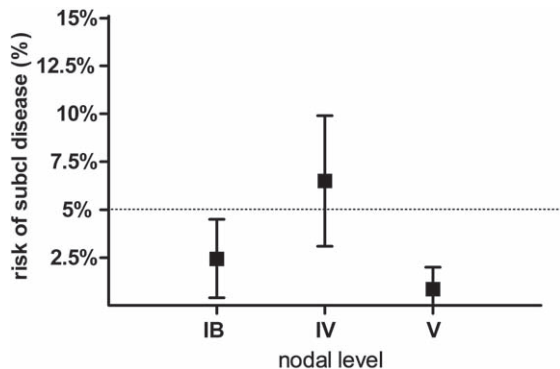


Figure 1. Estimated risk (mean and 95% CI) of subclinical involvement of levels IB, IV and V.

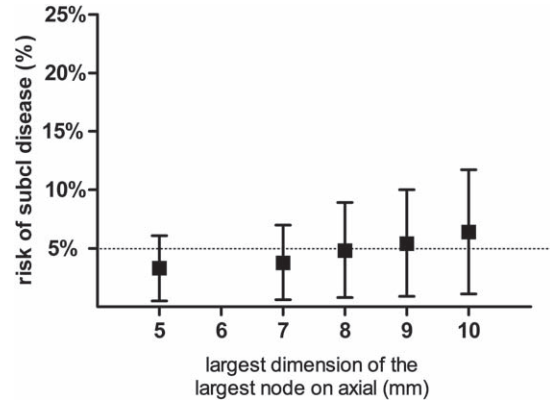


Figure 2. Estimated risk (mean and 95% CI) of subclinical involvement of level IB by the largest size of the largest node on axial slices when two or more ipsilateral levels besides IB are pathologically involved.

When two or more ipsilateral levels besides IB are pathologically involved, the risk of subclinical nodal involvement of level IB exceeds 5% regardless the cut point used to define a negative scan (Figure 2). Conversely, if the neck is staged with CT without pathologic confirmation, the risk of subclinical disease in level IB for an ipsilateral neck that does not contain any node exceeding 10 mm in two or more other (II–V) levels is extremely low ( $\approx 0.14\%$ , 95% CI 0.03–0.25%).

Figure 3 shows the risk of occult disease in level IV when level III is pathologically or clinically negative. In both circumstances, the risk of subclinical level IV involvement tends to be < 5% especially when the cut-off to define a negative CT scan is 8 mm or lower.

*Impact of diagnostic accuracy*

Since a cut-off size has been associated to a given level of specificity and sensitivity, this raises the

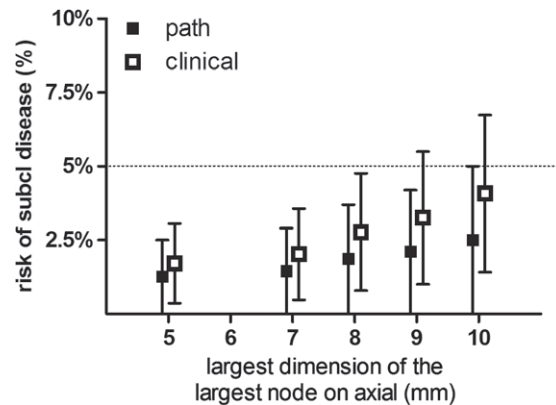


Figure 3. Estimated risk (mean and 95% CI) of subclinical involvement of level IV by the largest size of the largest node on axial slices when ipsilateral level III is either pathologically ('path') or radiologically ('clinical') uninvolved.

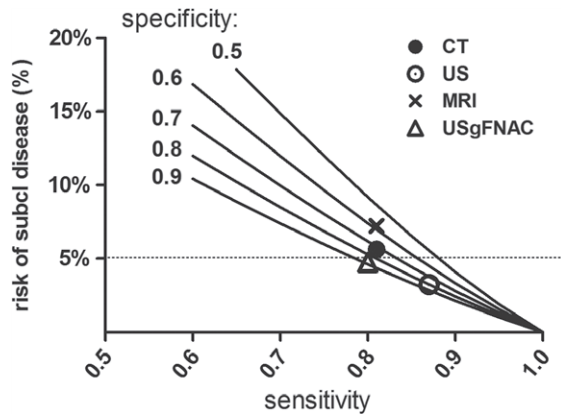


Figure 4. Estimated upper 95% interval for the risk of subclinical involvement of level IV when ipsilateral level III is radiologically negative according to different values of both sensitivity and specificity. Values for sensitivity (SD) and specificity (SD) are 0.81 (0.06) and 0.76 (0.06) for CT, 0.81 (0.07) and 0.63 (0.09) for MRI, 0.87 (0.04) and 0.86 (0.05) for Ultrasonography (US), 0.80 (0.09) and 0.98 (0.02) for US-guided Fine Needle Aspiration Cytology (USgFNAC) [16].

question on how the results reported in Figure 3 would be impacted by different values of these parameters. Figure 4 shows the upper 95% confidence interval for different combinations of sensitivity/specificity. If a test has a high sensitivity ( $\geq 0.9$ ) the upper 95% interval for subclinical disease in level IV would be less than 5% when level III is radiologically negative, regardless specificity. Figure 4 also shows the performance of various imaging techniques according to the average (SD) values of both sensitivity and specificity reported in the meta-analysis of de Bondt et al. [16]. Magnetic resonance imaging (MRI) does not provide better results than CT in ruling out disease in level IV when level III is negative, while US with or without fine needle aspiration performs better than both CT and MRI due to its higher average sensitivity and provides values  $< 5\%$ .

## Discussion

The present paper reports the prevalence of pathological involvement of levels IB, IV and V in a contemporary series of patients with clinically positive level II and/or III disease, early primary tumor stage and HPV-related oropharyngeal carcinoma. Overall, a relevant proportion of patients (slightly more than 20%) were found to harbor disease in the ipsilateral neck outside levels II and III.

Regarding the estimated pattern of distribution of occult disease (Figure 1), level V is at very low risk ( $< 5\%$ ) of involvement and it should be always omitted from the elective nodal volume when negative on diagnostic CT (any cut-off). As previously discussed [17] the advantages to skip level V are mainly surgical ones though one cannot exclude that also beam-

path toxicities such as alopecia in the occipital region could be impacted as well [18,19].

Regarding level IB, our data show that it should be electively covered when multiple ipsilateral levels are positive (Figure 2). Since our results relate to *pathologically* involved nodes this seems prudent also in case of *clinically* positive nodes. We have previously discussed the option to contour only the posterior part of level IB (or the part around the submandibular gland) that is supposed to contain the highest concentration of lymph nodes, minimizing the risk of incidental irradiation of the oral cavity [6]. However, the present data show that level IB can be completely excluded when two or more other (II–V) levels do not contain any node exceeding 10 mm.

Ipsilateral level IV should be routinely included in the elective nodal volume. However, its exclusion might be considered when level III is pathologically negative (or alternatively when the number of pathologically involved ipsilateral nodal levels is only one). When pathology confirmation of level III involvement is not available, Figure 3 shows that, using a cut-off of 8 mm to define a negative CT scan, level IV might be skipped when level III is radiologically negative. The fact that level IV involvement follows level III one suggests an orderly craniocaudal spread for oropharyngeal HPV-positive carcinoma and a low risk of skip metastases to level IV similarly to nasopharyngeal carcinoma [20], but differently from oral tongue cancer [21]. Since in a craniocaudal direction the upper border of level IV is at the level of the cricoid cartilage [19], the exclusion of level IV would spare from the irradiated volume most (if not all) of the cervical esophagus (in case of whole-field IMRT) and the (ipsilateral) brachial plexus other than a major part of the thyroid gland.

CT is currently considered part of the work up for oropharyngeal SCC [22] and is routinely obtained for IMRT planning. Though in a meta-analysis the accuracy of CT to detect cervical node metastases was lower than both ultrasonography (US) and US-guided FNAC [16], CT use is still widespread in daily clinical practice for several reasons, including its accessibility and its relatively straightforward interpretation with low inter-observer variability [16]. Positive cervical nodes on CT are usually defined those with a maximum axial diameter  $> 10$  mm ( $> 5$  mm if retropharyngeal) and/or with internal focal defects, such as irregular enhancement pattern [15]. However, a prospective multi-institutional study on 213 patients failed to show a benefit on both sensitivity and specificity from adding information on internal abnormality to the one on size for nodes 10 mm or smaller in largest axial dimension on CT [14]. Therefore, for nodes  $< 10$  mm, axial size seems to be the main criterion that drives the

risk of containing subclinical disease on CT. Moreover, provided that blood vessels are distinguishable from lymph nodes, nodal size can also be estimated by a non-contrasted, high quality (3–4 mm axial cuts) CT used for planning purposes. While cervical nodal levels that do not contain nodes larger than 10 mm are usually regarded as ‘negative’ on imaging, their risk of containing subclinical disease varies with the cut-off size used, the lower the size the higher the NPV [14].

We found that nodal cut-off size has limited implications on the risk categorization of both levels IB and V, but it may be critical for level IV relatively to level III status (Figure 3). If a test has high sensitivity, a negative result would then suggest the absence of disease, ruling out the presence of disease, but if sensitivity decreases the risk of false negatives increases. Figure 4 shows that unless CT (and MRI) have a high sensitivity or, in addition, US with or without fine needle aspiration is part of the diagnostic workup, it would be cautionary to cover electively level IV even when level III is ‘negative’ on CT (or MRI).

Several methodological aspects of the present study (retrospective analysis, nodal level definition, time span > 10 years, ...) have been discussed previously in details [6]. Most of HPV testing was done retrospectively though it is remarkable that only 10 of 103 specimens (9.7%) were not available for analysis. Ultimately the estimated risk of subclinical involvement will be related to the personal/institutional values of sensitivity and specificity for a given diagnostic modality and we encourage each institution to assess its own values.

Contemporary locoregional control rates obtained with IMRT ± chemotherapy for oropharyngeal SCC are consistently > 85% (summarized by Setton et al.) [23]. In order to effectively improve the therapeutic index in selected patients with HPV-related disease, strategies to de-intensify treatment are being developed for selected patient subgroups [24,25]. One strategy is to avoid the unnecessary inclusion of neck levels at low risk (< 5%) of involvement. It has been already shown that, for well-lateralized primary oropharyngeal lesions with limited nodal involvement, ipsilateral nodal treatment is feasible in terms of tumor control and is associated with a lower risk of permanent gastrostomy [26]. There has been increasing interest in estimating the risk of containing disease of levels that are considered at borderline risk of involvement in oropharyngeal cancer, such as level V and retropharyngeal [17,27,28]. The present paper, that is the first one to focus on HPV positive patients only, provides the rationale for avoiding treatment of ipsilateral ‘very low risk’ (< 5%) levels, that would

include levels V and IB. The latter may qualify for elective irradiation only when two or more other levels are involved. Level IV might also be spared when level III is negative on a ‘reliable’ imaging study or when the negativity of level III is pathologically assessed. With this background, clinical implementation within a prospective study seems justified.

**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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