Supplementary material

Appendix 1. Search strategy for each question

Question 1:
PubMed: (("Mouth Neoplasms"[Mesh]) AND "Young Adult"[Mesh]) AND "Prognosis"[Mesh]
Embase: 'mouth cancer'/exp AND 'young adult'/exp AND 'prognosis'/exp

Question 2:
Pubmed: (“mouth neoplams radiotherapy adjuvant size tumor”) (“oral cavity cancer size pronostic factor”)

Question 3:
Pubmed: SEARCH CONDUCTED UP TO december 2021Search: ((oral cancer)) AND (adjuvant radiotherapy) Filters: from 2000 - 2021 Sort by: Publication Date (("mouth neoplasms"[MeSH Terms] OR ("mouth"[All Fields] AND "neoplasms"[All Fields]) OR "mouth neoplasms"[All Fields] OR ("oral"[All Fields] AND "cancer"[All Fields]) OR "oral cancer"[All Fields]) AND ("radiotherapy, adjuvant"[MeSH Terms] OR ("radiotherapy"[All Fields] AND "adjuvant"[All Fields]) OR "adjuvant radiotherapy"[All Fields] OR ("adjuvant"[All Fields] AND "radiotherapy"[All Fields]))) AND (2000:2021[pdat]) Translations oral cancer: "mouth neoplasms"[MeSH Terms] OR ("mouth"[All Fields] AND "neoplasms"[All Fields]) OR "mouth neoplasms"[All Fields] OR ("oral"[All Fields] AND "cancer"[All Fields]) OR "oral cancer"[All Fields] adjuvant radiotherapy: "radiotherapy, adjuvant"[MeSH Terms] OR ("radiotherapy"[All Fields] AND "adjuvant"[All Fields]) OR "adjuvant radiotherapy"[All Fields] OR ("adjuvant"[All Fields] AND "radiotherapy"[All Fields])
Search: contralateral neck AND oral carcinoma Filters: from 2000 - 2021 Sort by: Publication Date (("contralateral"[All Fields] OR "contralaterality"[All Fields] OR "contralaterally"[All Fields] OR "contralaterals"[All Fields]) AND ("neck"[MeSH Terms] OR "neck"[All Fields]) AND (("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields] OR "carcinomas"[All Fields] OR "carcinoma s"[All Fields]))) AND (2000:2021[pdat]) Translationscontralateral: "contralateral"[All Fields] OR "contralaterality"[All Fields] OR "contralaterally"[All Fields] OR "contralaterals"[All Fields]neck: "neck"[MeSH Terms] OR "neck"[All Fields]oral: "mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]carcinoma: "carcinoma"[MeSH Terms] OR "carcinoma"[All Fields] OR "carcinomas"[All Fields]

Question 4:
Pubmed: (“postoperative radiotherapy and Oral Cancer”), (“Lymphovascular and oral cancer”), (“perineural invasion and oral cancer”), (“early oral cavity cancer AND radiotherapy”) (“adjuvant radiotherapy AND early oral cancer”)

Question 5:
Pubmed: (“perineural invasion and oral cancer”)

Question 6:
Embase: positive AND margins AND oral AND cavity AND squamous AND cell AND cancer AND postoperative AND radiotherapy AND prognosis

Pubmed: (("oral squamous cell carcinoma"[All Fields]) AND ("intraoperative margins"[All Fields])) AND ("fresh resection specimens"[All Fields])"squamous cell carcinoma of head and neck"[MeSH Terms] OR ("squamous"[All Fields] AND "cell"[All Fields] AND "carcinoma"[All

Fields] AND "head"[All Fields] AND "neck"[All Fields]) OR "squamous cell carcinoma of head and neck"[All Fields] OR ("oral"[All Fields] AND "squamous"[All Fields] AND "cell"[All Fields] AND "carcinoma"[All Fields]) OR "oral squamous cell carcinoma"[All Fields] "margins of excision"[MeSH Terms] OR ("margins"[All Fields] AND "excision"[All Fields]) OR "margins of excision"[All Fields] OR ("surgical"[All Fields] AND "margin"[All Fields]) OR "surgical margin"[All Fields] Filters: from 1998 – 2022

Question 7:
Embase: ('mouth cancer'/exp OR 'cancer, mouth' OR 'intraoral cancer' OR 'mouth cancer' OR 'mouth mucosa cancer' OR 'oral cancer' OR 'oral cavity cancer') AND 'early stage' AND 'adjuvant therapy'/exp AND 'surgical margin'/exp
PubMed: (("oral cavity cancer"[All Fields] AND "postoperative radiotherapy"[All Fields]) OR ("margins of excision"[MeSH Terms] OR ("margins"[All Fields] AND "excision"[All Fields]) OR "margins of excision"[All Fields] OR ("surgical"[All Fields] AND "margins"[All Fields]) OR "surgical margins"[All Fields])) AND ("squamous cell"[All Fields])

Question 8:
Pubmed: ((depth of invasion) AND (oral cancer)) AND (adjuvant neck radiotherapy)

Question 9:
PubMed: (("Radiotherapy, Adjuvant"[Mesh]) AND "Oral cancer"[Mesh])

Question 10:
Pubmed: PubMed (("oral cancer"[All Fields]) AND ("postoperative radiotherapy"[All Fields])) OR ("depth of invasion"[All Fields])

Question 11:
PubMed: Oral cavity (OSCC+/- oropharynx) AND neck dissection and sentinel

Question 12:
Pubmed: "oral cancer"[All Fields] AND ("neck dissection"[All Fields] OR "t n tract"[All Fields] OR "discontinuous"[All Fields] OR "en-block"[All Fields])

Question 13:
PubMed: (("Radiotherapy, Adjuvant"[Mesh]) AND "Mouth Neoplasms"[Mesh]) AND "Surgical Flaps"[Mesh]

Embase: ('adjuvant radiotherapy'/exp OR 'adjuvant radiotherapy') AND ('mouth tumor'/exp OR 'mouth tumor') AND ('surgical flaps'/exp OR 'surgical flaps')

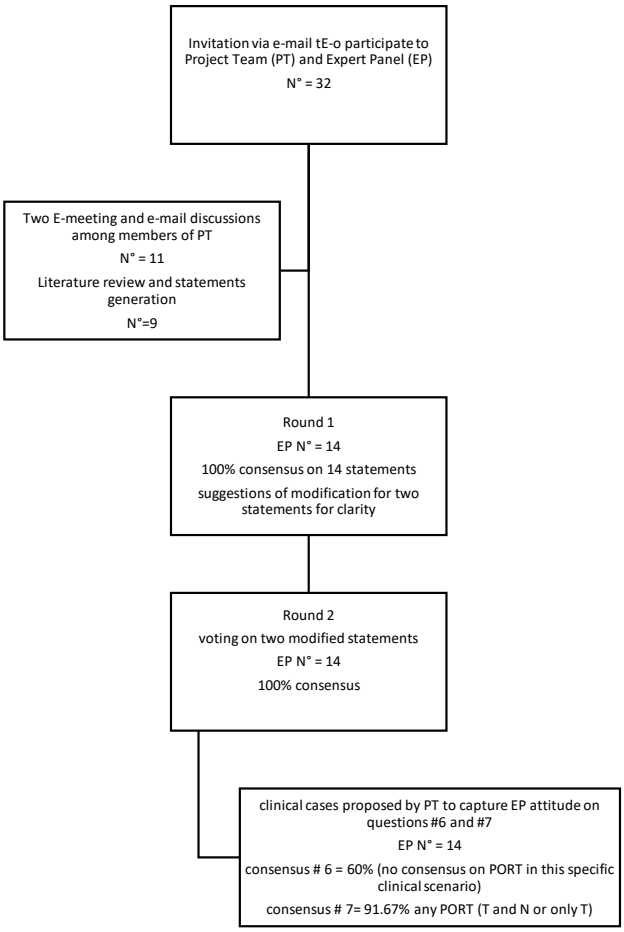
Question 14:
Pubmed: (“oral cavity and tumor bed and radiotherapy omission”)

Appendix 2. Description of Modified Delphi method.

Radiation oncologists who had published relevant articles about radiotherapy in head and neck cancer or were considered to be international experts in the field through their international profile, publications, academic collaborations, and educational activity in the two national Scientific Societies were approached by e-mail. They were invited to participate to Project Team (PT) or Expert Panel (EP)

The discussion has been developed in two rounds. The Round 1 questionnaire was developed in SurveyMonkey (Survey Monkey Inc., San Mateo, California, USA). The PT tested a pilot questionnaire and modified it if necessary to obtain the final questionnaire.
In Round 1, the questionnaire was distributed by e-mail to the EP, with the evidence presented in a brief narrative review. A cover letter reiterated the goals of the project. A three-week deadline has been set for the statement's rating. A comments box has been included, allowing justification of responses and the opportunity to propose new statements, and has been sent a reminder e-mail at weekly intervals.
In Round 2, collective feedback of all responses has been provided, highlighting levels of consensus achieved and comments for each statement. The Round 2 questionnaire required participants to rate only statements that met a low agreement and were reformulated, considering the comments from Round 1. As in Round 1, a two-week deadline has been given for completion and return. To better illustrate the Experts' attitude toward specific statements, we proposed clinical cases for questions #6 and #7.
At the end of Round 2, a Consensus summary document was produced.

Diagram of Delphi's method in this study



Appendix 3. Narrative reviews for each question.

Question 1: in the absence of other risk factors, young age (<40-45 years) and a smoking history of <10 pack-years are risk factors requiring PORT?

Synthesis of evidence and discussion:
Unequivocal definition of "young population" has not been established yet. Most authors refer to age cutoffs ranging from 20 to 30, 40, 45 years.
There seems to be a general trend of increasing incidence in oral tongue cancer in young patients while SCCs in the other oral subsites are on the decline [1]. In particular, the incidence in patients not exposed to traditional risk factors for H&N tumors seems to be increasing. For this reason, some authors hypothesize that OSCC (in particular the tumors of the tongue) which arise at a young age are a different biological entity than its older counterpart and may have different prognosis.
In support of this thesis a retrospective analysis of 425 patients with oral tongue tumors, patients with < 45 years had a higher incidence of several adverse pathological features (perineural invasion, moderate/poor differentiation, nodal spread and extranodal extension spread) with comparable stage, tobacco exposure and treatment between younger and older patients [2].
Also in early-stages, features of increased aggressivity in young patients is suggested, although not statistically significant: 42 patients aged ≤45 years with early-stage OSCC were matched according to the clinical tumor stage (stage I or II), gender, and centers of management with patients >60 years old. Young patients appeared to have marginally higher intensity of tumor budding, histologic risk score, infiltrative pattern of invasion and tumor-stroma ratio [3].
In another matched-pair analysis of patients with oral tongue tumors, the majority having T1-T2 N0-N1 tumors, younger patients (< 40 years) were more likely to have lymph-vascular invasion (LVI) or perineural-invasion (PNI), as well as recurrent cancer [4].
However, no evidence of differences in histopathological features has been reported in another study between younger (< 40 years) and older OSCC patients [5].
Also considering genomics, SCC of the oral tongue in nonsmoking patients 45 years or younger are similar to tumors of older patients who had a smoking history [6].
Considering survival, OTSCC in young patients (< 45 years) was better than in older patients in a recent metanalysis with 28,288 patients [7]. Still, estimations were not adjusted for confounders and other prognostic factors.
Also in a recent SEER database analysis of 16,423 patients with OTSCC, young patients (< 40 years) of either gender had improved OS and DSS compared to older patients [8]. Younger patients were also more likely to receive multimodality therapy. Radiation treatment was associated with improved OS in older patients but not in the younger cohort.
Otherwise, there was no statistically significant difference in CSS between age groups (< 44 years and older) of patients with OTSCC in another SEER database analysis with 32,776 patients [9].
In a retrospective analysis of 395 patients having stage I-II disease in 59.5% of cases (AJCC 6th and 7th editions) [10], patients < 50 years old had better overall survival, particularly in never-tobacco users. But young patients received more aggressive treatment than their counterparts, despite no difference in overall clinical staging.
In a series of 479 patients with early-stage (cT1-2N0 7th ed.) OTSCC, evaluating the prognostic role of age, gender, stage, grade, lymphocytic host response (LHR), PNI, worst pattern of invasion (WPOI), and DOI, OS was significantly better for younger patients (< 45 years) [11]. DOI and WPOI were also factors significantly associated with OS.
In another metanalysis with 23,382 patients with OCSCC, younger patients with < 40 years had the same survival outcomes than older patients (hazard ratio = 0.97, 95% confidence interval = 0.66–1.41) [12]. The vast majority were either T1 or T2 (6^{th} and 7^{th} ed.), accounting for 859 (80%) malignancies in younger patients and 8,126 (77%) malignancies in older patients.

In a series of 397 oral tongue tumors, despite the increased recurrence, there was no significant difference in disease-specific or overall survival between young (< 45 years) and older patients at 3 years in both adjusted and unadjusted models [4].
In a matched analysis of OTSCC with 100 patients, 58% having stage I-II tumors (7th ed.), no difference was observed in OS and DSS [13].
However, in a retrospective series on 247 patients [14], in a subgroup analysis of younger patients (n = 49, age < 45 years), survival was worse in non-/lighter smokers young patients. The cutoff value was 10 p/y.
In another study of 291 patients with OTSCC, patients aged <40 years at diagnosis had a worse overall (p = 0.015) and disease-free survival (p = 0.038) in those without risk factors [15].
Considering recurrence risk, in the metanalysis by Tagliabue et al. [7], youngs had a greater risk of recurrence than older patients.
In a series of locally advanced OSCC staged with TNM 8th ed., looking at disease recurrence within 12 months, TNM 8 stage IVB, LVI, younger age (< 60 years) and lesser smoking history were predictive factors on multivariable analysis [16].
Subramaniam et al. [2] report that patients below 45 years had a significantly higher risk of local recurrence. At 5 years, the local control rate was 65% for the younger group and 78% for the older group (p = 0.008). Still, younger age was not an independent predictor of reduced DSS, possibly because of an improved likelihood of tolerating more radical salvage therapies. The regional and distal recurrence rates were 5% and 13% in the younger age group, 11% and 9% in the older age group, respectively, which was not statistically significant.
In a large Chinese study on OSCC with a retrospective analysis of 2,443 patients and a prospective population (validation set) of 339 patients, age (< 40 years) was not an independent risk factor for either DFS or DSS. The total consumption of cigarettes or alcohol has no significant difference between young, moderate, and advanced age-group [17].
In another study focusing on OTSCC, the young population was significantly more likely to recur, with a hazard ratio of 3.0 (95% Confidence Interval (CI) 1.2–7.3) for 3-year recurrence relative to older patients. The hazard ratio was 3.9 (95% CI 1.4–10.5) after adjusting for alcohol and tobacco use [4].
In a matched-pair analysis of OTSCC with 138 patients, the frequency of recurrences was found to be significantly higher in younger patients (< 40 years) with a lower median time to relapse (18 months in the younger and 23 months in the older ones) [18].
Also, in the previously cited matched analysis of Blanchard et al. [13] in OTSCC, the vast majority of PFS events in cases occurred during the first year in the young group but without significant differences in PFS at 5 and 8 years.
However, the increased recurrence rates in younger patients may be explained by higher non-cancer-related mortality in older patients before relapse occurs [19].
Based on the available data, it is not possible to establish whether young patients not- or light-smokers are at increased risk of relapse and death with the same other prognostic factors, especially in early-stages. Several confounding factors can justify the heterogeneity of the reported results: the different definition of young age, the correlation with different risk factors, the analysis of endpoints such as OS that does not consider the higher mortality related to the comorbidities most present in older patients. Furthermore, in the elderly, the treatments can be less aggressive, while younger patients benefit from a higher number of available therapeutic options, such as major surgery. It is not possible to draw information on the risk-benefit of more intensified treatment for young non- or light-smoking patients with early stage cancers. There is a lack of data on toxicity or patient-reported outcomes in the examined series, which would be necessary for balancing treatment to long-term functional or toxicity effects. For example, in a long-term analysis of QoL in 62 patients treated for OSCC, radiotherapy and tumor stage correlated with swallowing outcomes. Only radiotherapy seemed to adversely affect the overall QoL [20].

Codice campo modificato

One possible recommendation is that young non- or light-smoking patients should receive personalized follow-up plans.

Question 2: is the size of T (< 3 cm versus ≥ 3 cm ≤ 4 cm), in tumors with depth of invasion (DOI) > 5 mm ≤ 10 mm (pT2 TNM 8th ed.), an independent prognostic factor?

Synthesis of evidence and discussion:

Historically, the size of the tumor defined the TNM classification, but in the oral cavity, the thickness of the tumor, has been recognized as an important prognostic factor as the risk of nodal metastases and death was in relation to thickness in tongue and flour mouth tumors [21] [22].
The eighth edition of the AJCC-TNM staging system for OCSCC recognized the depth of infiltration (DOI) as an independent predictor of both recurrence and survival [23].
Nonetheless, discrimination between pT1 and pT2 categories remained scarce [24] [25]
Few studies analyzed size among other risk factors.
Grimm et al. found that the tumor size and microvascular invasion are independent factors in predictor overall survival but in this retrospective study, the size of the tumor was between 9.6 and 12.3 mm [26].
Jan et al. studied retrospectively 394 patients who received surgical intervention. Multivariate analysis identified the factors that independently influenced the survival rate as advanced stage disease (stage III: relative risk [RR], 3.09; P = .006; stage IV: RR, 4.64; P < .001), positive surgical margin (RR, 2.02; P = .001), and extracapsular spread of cervical lymph node metastasis (RR, 6.89; P < .001). The size (< 3 cm or > 3 cm) was not an independently factor of survival rate [27].
Shim et al. published a retrospective analysis of 86 patients with T1-2 N0 oral tongue squamous cell carcinoma who received surgery. The two prognostic factors affecting five-year overall survival and disease-free survival were invasion depth > 0.5 cm and higher tumor grade [28].
Bobdey et al. published the results of retrospective analysis of prognostic factors in surgically treated buccal mucosa squamous cell carcinoma patients. The overall 5-year survival was quite the same for stage 1 and 2. On multivariate analysis, the factors associated with overall survival are the presence of comorbidity, histological tumor size, pathological lymph node status, tumor differentiation, perineural invasion, and extracapsular spread. For histopathological size, it was divided in < 2 cm, between 2 and 4 cm and > 4 cm. The survival is better if the size is under 2 cm [29].
The presence of two or more adverse features may better predict prognosis. In fact also DOI alone (ie, in absence of other risk factors such as nodal metastasis or close margin) should not be used as an indication of postoperative radiotherapy in patients with a small OSCC [30].
This consideration is supported by the finding from another recent study [31], concluding that in the case of small oral tongue cancer (≤2 cm) with DOI > 4 mm, the presence of at least two adverse features (eg, perineural invasion and lymph-vascular invasion) will warrant the consideration of adjuvant therapy [31].

Question 3: in tumors ≤ 4 cm with DOI > 3 mm ≤ 10 mm, pN0, when PORT is considered, is contralateral neck radiotherapy indicated?

Synthesis of evidence and discussion:

Indication for PORT to the neck is based on the risk of microscopic disease remaining in the surgical bed. Regional recurrence rate in pN0 patients is low (<10-15%), hence, it could be reasonable to omit neck RT [32] [33] [34].
There is growing interest in the omission of the PORT in contralateral neck also in more advanced stages when pathologically staged as negative.
However, the decision to treat the contralateral neck is strongly related to the proximity of the tumor to the midline.
A clear definition of tumor "approaching midline" is lacking, especially for the tip of the tongue, where contralateral lymphatic flow is more likely. Also the impact of TT or depth of invasion (DOI) to determine the management of the contralateral neck is controversial.
A contralateral positive sentinel lymph node has been identified in 12.4% of patients with lateralized oral cancer [35].
Occult contralateral lymph node involvement has been identified in 11% of cN0 oral cavity tumors when bilateral neck dissection has been performed [36]. Rates of contralateral neck failure (CNF) have been reported to be 3%–17% in multiple case series [37] [38] [39] [40].
In a recent case series by Liu, most of patients had T1 (68%, 7 ed. AJCC) well-lateralized oral carcinoma, and 15% of patients received PORT: the 5-year incidence of CNF was 4.3% (95% CI 1.2-7.4%). Only DOI>10 mm remained a significantly associated factor to MVA, and 5-year OS was 80.6% (95% CI 74.5-86.8%) [41].
In a study comparing END versus sentinel lymph node biopsy, only 3.7% (30/816) showed occult contralateral nodal metastasis. Tumors near the midline had a higher risk of contralateral nodal occult metastasis than those with lateralized tumors ($p = 0.018$). The contralateral relapse rate incidence (CRR) was 2.5% (20/816) in the series. Tumor depth of invasion was predictive for developing contralateral relapse (HR = 1.922; $p = 0.009$). The END cohort presented higher T-stages, DOI (>4mm), and pN stage, and only 7.7 % of bilateral END.
In their analysis of 164 patients with T1-T2N0 oral tongue SCC treated with surgery alone, Ganly et al. [37] reported that 8% and 6% of patients developed isolated ipsilateral and contralateral neck recurrences, respectively. On multivariate analysis, TT ≥ 4 mm was a significant predictor of regional failure, and nearly 40% of regional failures were in the contralateral neck. Hence, the authors suggest contralateral neck irradiation in patients with tumor thickness >=4 mm, regardless of the tumor location relative to the midline. These results are controversial because this study did not evaluate tumor position regarding the midline.
Some authors [42] argue that the risk of contralateral nodal recurrence is associated more with crossing the midline than other risk factors.
In their study, Sridharan et al. [43] analyzed 494 patients with surgically treated, early-stage pN0 tongue cancers. The rate of contralateral neck failure was low (13 patients), suggesting bilateral elective neck dissection or PORT can be unnecessary.
This conclusion does not apply to patients with tumors that cross the tongue's midline or extend to adjacent subsites.
Koo et al. [36] similarly demonstrated the rate of contralateral occult neck metastasis was significantly higher in cases in which the primary lesion showed extension across the midline, compared with early-stage or unilateral lesions. In a series including 513 consecutive patients, Kowalski et al. showed that the risk of contralateral metastases were significantly higher in cases of tumors crossing or extending to 1 cm or less from the midline (relative risk from 2.8 to 12.7) [39].
Patients with floor of the mouth or oral tongue tumors have a rich and bilateral lymphatic drainage pattern and, thus, a higher risk of contralateral metastases. ASCO guidelines recommend contralateral END for these tumors, even at an earlier T stage.
A SEER database analysis showed that the floor of the mouth and oral tongue tumors were the most common subsites, and 5-years cause-specific mortality was lower in the first than in the second [44]. Rusthoven reported similar results: 5-year relative survival for oral tongue cancer is approximately 67% [45].

In the meta-analysis conducted by Kao in 2021 [46], studies including patients affected by oral carcinoma and addressed to PORT (with or without ipsilateral irradiation) were eight for a total of 524 patients. The authors found a low rate of contralateral failure, 3.4% (95% [CI]: 2.2%–5.4%). The rate of contralateral neck failure rate in N0–1 group was 1.5% (95% CI = 0.5%–4.6%); in the N2–3 group, the corresponding rate was 14.4% (95% CI = 5.5%–32.7%). In addition, the contralateral neck recurrence rate was 6.3% (95% CI = 2.3%–13.1%) and 2.8% (95% CI = 1.5%–4.8%), in the tongue cancer patient group and the non-tongue cancer patient group, respectively. Meta-regression showed that the rate of contralateral recurrence was not different between both groups (p = 0.08). Only 2 exhibited isolated contralateral neck recurrence (5.1%) in pN0–1 tongue cancer patients (most of them well lateralized).
The authors concluded that it is safe to omit contralateral neck irradiation in well-lateralized oral cavity cancer with pathological stage N0–1, regardless of whether the tumor is of the tongue or not.
The limitations of the reported studies are the retrospective design and the heterogeneity of approach to the elective contralateral neck treatment (surgery, radiotherapy, observation). Moreover, occult contralateral nodal metastases are uncommon in early-stage oral carcinoma, making statistical analyses inadequate.

Question 4: in tumors ≤ 4 cm and DOI ≤ 10 mm pN0, does the presence of one single minor risk factor mandate per se PORT or do we need the presence of at least two or more concurrent minor risk factors?

Synthesis of evidence and discussion:
In a study published by Lin et al., PORT was administered in patients with two minor risk factors (i.e., pN1, DOI ≥10 mm, 3-4 mm close margins, poor differentiation, perineural lymphatic invasion, and vascular invasion). Compared with patients who underwent surgery alone (n = 6), those who received adjuvant RT (n = 8) had a higher neck control rate (100% vs. 83%, respectively, P = 0.248) [47]. The small sample size and pooling together different risk factors are the limits of this study.
Chen et al., in their study, analyzed the prognostic impact of PNI and LVI in early-stage OSCC patients. They enrolled 360 patients in group A (without PNI or LVI) and 82 patients in group B (with PNI and/or LVI). Between these groups, there were no significant differences in the 5-year disease-free survival (73.8 vs 68.7 %, p = 0.48) and overall survival (90.9 vs 86.1 %, p = 0.25) irrespective to PORT. Multivariate analyses revealed that PNI, LVI, and PORT could not significantly improve treatment outcomes [48].
In the current last update of NCCN guidelines, adverse features in OSCC for PORT include three minor risk factors: close margins, perineural invasion, and lymph vascular invasion. They do not consider poor differentiation [49]. On the contrary, Katz et al., in a study focused on tongue carcinoma, showed a significant improvement in DFS among 12 patients (25% of the cohort study) with histopathological risk factors, included poor degree differentiation, treated by surgery plus PORT compared to surgery alone [50]. However, there is a lack of evidence to support poor cell differentiation as a sole risk factor per PORT.
On the other hand, depth of invasion (DOI) is an strong prognostic factor, and it has been added in TNM staging (VIII edition). Liao et al. studied 1250 patients treated by primary excision and neck dissection and showed that DOI > 4mm led to worse outcomes. They hypothesized that such patients might benefit from PORT [51]. Recognizing this prognostic value, the AREST Trial (Adjuvant Radiotherapy in Early Stage Oral Cavity Cancers) (NCT03853655) is currently open for recruitment in India to assess the benefit of postoperative IMRT (60 Gy/30f/6w) in patients with a ≤4 cm OSCC primary with DOI ≥ 0.5 cm (i.e., approximating T2 lesions in TNM 8).

On the contrary, Gokavarapu and others investigated the impact of PORT in 103 pT1-2 N0 oral tongue SCC with DOI> 4mm, suggesting similar locoregional recurrence and survival rates between patients who received PORT and those who did not [52].
Another recently published study aimed to clarify the role of DOI as an independent prognosticator in early-stage (T1-T2N0M0) oral cavity tumors. DOI seems not to be statistically significant related to either OS ($p = 0.45$), DFS ($p = 0.67$) or LRFS ($p = 0.66$). In this study, only PNI is an independent prognostic factor in early-stage (T < 4 cm and N0) OTSCCs, considering DOI along with other well-known pathological tumor-related risk factors [53].
Lymph vascular invasion (LVI) is related to lymph nodal metastases and poor outcomes (particularly for tongue and floor of mouth). In a retrospective series by Adel et al., although it exhibited significant associations with poorer overall survival ($P < 0.001$), disease-specific survival ($P < 0.001$), and disease-free survival ($P = 0.01$), LVI was not an independent prognostic factor in all multivariate analyses. Based on these results, pathological findings of either lymphatic or vascular invasion might not necessarily indicate postoperative adjuvant therapy [54].
Concerning surgical margins, Dik and others analyzed the results of re-resection, PORT, or watchful waiting in the treatment of early-stage OSCC in the presence of close or involved margins. They found no conclusive evidence to suggest local adjuvant therapy in case of close margins (≥3 mm) with ≤2 pathological risk factors (overall recurrence rate PORT, 13% vs. re-resection, 3% vs. watchful waiting, 2%). PORT did not significantly improve LRC in early-stage OSCC with close margins (surgery alone vs. surgery plus RT; p=0.259) [55]. The close surgical margins were a significant risk factor for local recurrence only in advanced oral cancers, but not in early-stage tumors, where microscopic tumor extension was not beyond 3 mm in T1 tumor [56]. Patients with stage I to II OCSCC and positive/close margins have poor long-term outcomes. For this population, adjuvant treatment improved survival (OS p=0.002 and LRC p=0.03) [57].
Multiple studies show the prognostic impact of PNI with increased locoregional recurrence (LRR) and poorer OS. Perineural invasion should be documented in regular pathological reports for oral cancer patients, significantly affecting treatment decisions. In a recent study published in 2015 by Avaizian et al., multifocal PNI is associated with poor outcomes even with PORT suggesting therapeutic escalation, particularly with involved nerves ≥1 mm. Unifocal PNI did not affect prognosis even in the absence of PORT, which may not be required if this is the sole risk factor. Elective neck dissection could improve neck control in cN0 PNI positive patients with OSCC [58].
Tai et al. proved that PNI represents an adverse prognostic factor for predicting neck node metastasis, neck recurrence and worse 5-year DFS. PORT for isolated PNI without other risk factors is recommended in most treatment algorithms, despite the controversial role in significantly improving survival rates [59].
Chatzistefanou et al. observed that PNI positive patients (without other RFs or lymph node involvement) who underwent neck dissection did not benefit from PORT. PORT did not significantly alter the incidence of local (p=0.763) or regional recurrence (p=0.319) in patients with PNI-positive early OSCC [60].
On the contrary, in the study by Nair et al., PNI in early oral cancer was found to be prognostic, and PORT seemed to offer a better survival outcome [61].
Very few patients with PNI did not receive PORT. Therefore, adjuvant radiotherapy should remain the standard of care [62].
Based on the current evidence, one minor risk factor is insufficient to prescribe PORT in early oral cancer (T1-T2 N0). A combination of adverse minor risk factors is necessary to administer PORT. Shim et al. showed that both higher tumor grade and deep invasion depth over 0.5 cm are related to prognosis in early oral cancer [28]. The decision to administer adjuvant therapy needs considerations individually; patients with >1 adverse pathological risk factors are likely to benefit from PORT, and the use of risk-scoring systems may help in decision making [63]. For early-stage pN0 OSCC, a recent review suggests treating the surgical tumor bed in case of PNI without other adverse tumor features or when at least two minor adverse risk factors are present [64].

Stratification risk models could determine which patient could benefit from PORT best. Almangush et al. introduced a simple histopathological model for the prognostication of survival in patients with early OTSCC (oral tongue squamous cell carcinoma), based on tumor budding and depth of invasion [65]. Risk-tailored approaches are needed [66].

Question 5: in tumors ≤ 4 cm and DOI ≤ 10 mm pN0, is PNI an independent risk factor for local or locoregional recurrence?

Synthesis of evidence and discussion:

Many studies tried to correlate PNI with the increase of local recurrence: Chinn et al. showed a statistically significant improvement in the disease-free interval and locoregional control in patients with pN0 and PNI+ T1-T4 stages underwent postoperative radiotherapy. In this cohort of patients, perineural invasion seems to be an independent adverse risk factor, characterized by a worse DSS, DFI, and LRC. However, the limit of this study is the small sample size [67].
In a study on surgically treated stage I-II OSCC (TNM 8th), none treated with PORT, PNI was a stronger predictor of locoregional failure than DOI in stage II disease [68]. In the subgroup of patients with T1-T2 N0 oral cancer, Nair et al. found that PNI was an independent prognostic factor for OS with the highest HR of 2.54 and DFS with the highest HR of 2.79. OS at 3 years for this subset of patients was 58.5% versus 86.7% in those patients without PNI. The addition of PORT in this setting showed an improvement in survival statistically significant [61].
Similarly, Rajappa et al. performed a retrospective study in node-negative early-stage oral cancer patients. They showed that postoperative radiotherapy in these patients had a significant impact on outcome in terms of disease-free survival, even in patients who have had elective neck dissections. The authors excluded all independent prognostic factors that indicate adjuvant radiotherapy (such as T3/T4, N+, or positive margins) in this study. Locoregional recurrence rates in both arms (PORT or close follow-up) were comparable, although the nodal recurrence rate was higher in the group not given radiotherapy [69].
On the contrary, an analysis by Chatzistefanou et al. concluded that perineural invasion is an important prognostic factor indicating the need for neck dissection. Adjuvant radiotherapy didn't reduce recurrence and didn't provide survival benefits [70]. Similarly, Tai et al. found that cN0 PNI positive patients who underwent neck dissection did not show improved results with PORT (5-year DSS PORT, 81.3% vs. no PORT, 88.5%; 5-year OS PORT, 71.3% vs. no PORT, 83.8%) [59]. END significantly improved regional recurrence and 5years DSS rates in cT1/2 N0 patients with PNI positive oral cancer.
In support of this, a randomized phase III study by D'Cruz et al. showed that elective neck dissection of levels I-III could significantly improve survival rates (overall survival and disease-free survival) and reduce the risk of recurrence for patients with early oral squamous cell cancer (T1-T2 N0) [71].
A recent systematic review and metanalysis published by Li et al. evaluate the prognostic value of PNI in oral tongue squamous carcinoma: the presence of PNI significantly affects the locoregional recurrence and survival outcomes in early OTSCC [72]. In agreement with this, in a recent study by Yang et al., the presence of PNI independently predicted LN metastasis, tongue local relapse, neck relapse, and worse survival outcomes [73].
Moreover, a recently published study by Hughes et al. evaluated the role of PNI as the sole risk factor after surgical resection of head and neck cancer (oral cancer, larynx, and pharynx). Those patients with other pathological risk factors were excluded to minimize confounding factors. PNI was more frequent in oral cancer, young patients, and they were more frequently subject to PORT. Patients with pathologically low-risk HNSCC after surgical resection experience high rates of LRC. However, in this setting of patients, PNI as the sole risk factor was extremely rare, so it is difficult to define the benefit of adjuvant therapy. PORT remains the standard of care for patients with PNI

to reduce the risk of locoregional failure, even if further studies are needed to best define the prognostic impact of PNI alone [62].
How the type of PNI influences the risk of recurrence and how PNI should be quantified is unknown. A high density of PNI foci was predictive of a significantly poorer DSS in a subgroup analysis of T1-2 tumors of oral tongue cancer (n=336) in both univariate and multivariate analysis. Still, it wasn't associated with local or regional control rates [74]. Another study, which investigates how PNI should be quantified, was published by Aivazian et al. It showed that multifocal PNI is associated with poor outcomes even with PORT suggesting consideration of therapeutic escalation, particularly with involved nerves ≥1 mm. Unifocal PNI did not affect prognosis even in the absence of PORT, which may not be required if this is the sole risk factor [58].

Question 6: should we offer PORT for intra-operatively converted R1 to R0 margins without other risk factors?

Synthesis of evidence and discussion:

There are two methods for soft tissue intra-operative resection margin assessment (IOARM): the traditional defect-driven method and the specimen-driven method. In the conventional defect-driven approach, the surgeon samples one or more suspicious pieces of tissue from the tumoral bed for analysis by frozen section (FS). The significant disadvantages of defect-driven IOARM are that it can only indicate the presence of a tumor-positive margin and it cannot provide the exact margin value in millimeters, and relocation of the site of interest in the tumor bed might be off-target by approximately 1 cm in one-third of cases [23].
In the specimen-driven method, the margins are assessed on the oriented tumor specimen by visual inspection and palpation followed by perpendicular incisions with or without tissue sampling for frozen section examination. This approach provides immediate feedback on whether an additional resection is needed and where.
One proposed alternative to FS analysis is Mohs micrographic surgery. Currently, this technique is only commonly practiced by dermatologic surgeons in the treatment of skin neoplasms. The complex geometry oral cavity limits adoption of MMS in oral cancer [24].

The table below shows studies analyzed and results.

Study/Patients	Factors analyzed	Results	Radiotherapy	Comment
Chang 2013 [75] 126 pts pT1-pT2 pN0 oral tongue	Comparison of 3 IOARM workflows: group 1 (margins sampled from the glossectomy specimen only), group 2 (intraoperative evaluation of glossectomy margins was followed by the revision of some margins from the tumor bed.), and group 3 (margins primarily sampled from the tumor bed).	Probability of local recurrence-free survival at 3 years was 0.90 (95% CI = 0.82–.99), 0.76 (.62–.93) and 0.73 (.56–.95) in groups 1, 2, and 3, respectively.	Adjuvant radiotherapy administered to 16 patients	microscopic tumor cut-through represents an adverse prognostic factor regardless of eventual revision to "negative" margin. Not possible to analyze RT impact in this study
Maxwell 2015 [76] 280 patients with pT1-2 pN0 SCC of the oral tongue	Comparison of 3 IOARM workflows: group 1(n=119), tumor bed margins not sampled; group 2 (n = 61), margins examined from the glossectomy specimen, if positive revised with additional tumor bed margins; group 3 (n = 100), margins sampled from the tumor bed	3-year LR-free survival was worse for group 3 compared with that in group 1 (0.8 vs 0.9, respectively; *P* = .03	Adjuvant radiation therapy was similar among all groups (20% on average)	R1 converted R0 margins sampled from tumor bed represents an adverse prognostic factor that could require PORT. Not possible to analyze RT impact in this study
Varvares 2015 [77]	84.3% had IOARM from the	Local recurrence rates	Rate of adjuvant	LRR was similar for initially R1

108 patients (all OSCC except 6 with base of tongue HPV negative tumors), 47% early stage	specimen. The patients were stratified into four groups depending on the status of their margins: 1) >5 mm and negative, 2) <5 mm and negative, 3) initially positive and resected to negative, and 4) initially positive with persistently positive margins after additional resection	was 3.4%, 26.4%, and 28.6%, for groups 1,2, and 3 respectively. On multivariate analysis R1converted to R0 margins were only correlated to local recurrence and not to DFS and OS	radiation therapy was similar among all groups (20% on average) with different methods of IOARM despite the significantly higher rate of positive margins in group 3	converted to R0 and close margins patients even with the "gold standard" method of IOARM. Lack of difference in local recurrence or survival with the addition of postoperative radiation therapy could reflect the presence of risk factors other than margin status that worsened prognosis in the group submitted to PORT.
Brandwein-Gensler 2005 [78] 168 OSCC pts all stages	IOARM from specimen. Four margin groups: group 1 clear (>5 mm) at initial resection; group 2 inadequate intraoperative margins, final clear margins (> 5 mm); group 3 final close (< 5 mm) margins; and group 4 final positive margins.	No significant relationship between margin status and LR, or OS. Worst pattern of invasion, perineural invasion, and lymphocytic response were significant and independent predictors of both LR and OS, even when adjusting for margin status. The authors assigned a score value to these variables and developed a classification of patients into low, intermediate, and high risk. Administration of adjuvant radiation therapy was associated with increased local disease-free survival for high-risk patients only according to the proposed score (P = 0.0296) but not low-risk or intermediate-risk patients irrespective of the status of margins	105 pts received PORT In a subset of T1/T2 tongue carcinomas, the LRR for group 1 margins is 16% (3 of 18) and for group 2 margins is also 16% (5 of 30). In T1 tongue carcinomas (all margin groups), the likelihood of remaining disease free at the primary site is seen as a function of adjuvant RT (0% LRR for 10 RT+ patients, 13% LRR for 22 RT2 patients) (P = 0.0027). For T2 tumors, there was also an impact of RT on LRR: 16% for RT+ versus 40% for RT2 patients (P = 0.001) but no direct association between margin status and LRR.	The majority of patients received PORT The similar LRR in group 1 and 2 in the subset of T1/T2 tongue carcinoma could be in part due to PORT. This study highlights the difficulty of analyzing the impact of the state of intraoperative margins without the influence of other prognostic factors.
Patel 2010 [79] 547 OSCC pts 206 pT1-pT2 pN0 and 41 pT1-pT2pN1	IOARM with tumor bed frozen sections. Group 1 had margins that were clear on frozen and permanent sections (they used the designation of clear >5 mm, close <5 mm but not involved). For group 2, the resection margin was initially positive (cut-through) but then revised to negative on frozen and permanent pathology.	9.5% had one or more margins that were positive on frozen section and revised to negative. Sub- group analysis demonstrated that in the absence of regional nodal disease, patients had similar local, regional, and distant control rates, irrespective of microscopic tumor cut- through; and disease-specific survival was slightly lower in patients with tumor cut-through.	29.2 % received and 2.9% PORT+CHT. In univariate analysis, but not in multivariate analysis, PORT predicted local control , regional control and OS	Group 2 had had a statistically significant higher incidence of extranodal spread and use of adjuvant therapy. The prognostic impact of microscopic tumor cut-through revised to negative margins in the patient population with no other adverse pathologic features cannot be elucidated in this study
Buchakijan 2016 [80] 406 OSCC 45% T1,	IOARM was performed on tumor bed. Comparison of 3	LR for group D was 29% (95% CI, 16%-	PORT was administered in	Effect of PORT cannot be analyzed in this study.

21% T2 71% N0, 10% N1	groups: group A patients with negative margins on both intraoperative and permanent specimens; group B positive intraoperative margins subsequently cleared by additional resection to negative margins; group C included those with negative intraoperative but positive permanent specimen margins, group D positive intraoperative and definitive margins	48%), which was not different from group B or C. Five-year survival of groups 1-4 were 72%, 61%, 43%, and 19%, respectively	41% of patients. 51% of final positive margins patients did not receive PORT.	Prognosis of intraoperatively positive converted to negative margins using tumor bed IOARM is similar to R1 patients. The role of PORT cannot be analyzed in this study
Nentwig 2021 [81] 194 OSCC patients (nearly half early stage)	IOARM was performed with frozen section on tumor bed.	Intraoperative re-resection, resulted in a postoperative R1 in 42.1% of positive margin cases. False negative cases (R0 intraoperative, R1 postoperative) were 10.9%. In cases with intraoperative R1 status local disease recurrence was higher than in R0 status although not statistically significant (26.3%, compared to 21.7% [p = 0.417]). It was observed a lower rate of 2year 4-year OS if close or positive resection margins were diagnosed and revision was conducted (p < 0.05).	51.5% received PORT or PORT+CHT	There was a high percentage of definitive positive margins (42.1%) and false intraoperative negative margins (10.9%). This study confirms that intraoperative positive tumor margins maintain a negative prognostic value even if re-resected when tumor bed IOARM is used. The role of PORT cannot be analyzed in this study
Szewczyk 2018 [82] 151 OSCC patients. pT1 and pT2 tumors 31% and 47% respectively, 59% of patients pN0	IOARM was specimen-driven. Comparison of outcome between positive and negative fresh frozen surgical margins.	On multivariate analysis, only positive fresh frozen surgical margins (P = 0,001) remained significant independent adverse factors for local recurrence. DFS was lower in patients with positive fresh frozen margins, regardless of stage of disease. Regarding OS only PNI had an independent prognostic value.	80% received PORT. There were differences in the percentages of other risk factors (PNI 25%, LVI 25%, and ECS 39% in the group with R1 to R0 margins; PNI 11%, LVI 8%, and ECS 22% in the group with primarily negative margins).	Due to the different risk profile of the two groups no conclusion on the role of PORT when the sole risk factor in intraoperative positive margin can be drown.

From the literature analysis, it is not clear whether the positive margin converted intraoperatively to negative constitutes an independent prognostic factor for local control or survival; probably, its association with other factors confers a greater prognostic value. Some suggest that microscopic tumor cut through might reflect more aggressive biology of the SCC, for example, more infiltrating, less differentiated tumor, with non-cohesive invasion pattern.

Patients with positive tumor specimen margins and negative tumoral bed margins show a reduction in local control compared to patients with negative margins without a history of transiently positive cut-through margin. Yet with different follow-up, local relapse in R1 to R0 patients is around 26% with different methods of IOARM.

Limitations in interpreting the presented data are the potential confounding factors not always considered in these studies: surgical center volume/resources, anatomic tumor site, immune status of the patient, the number of positive margins and location/ tissue type (mucosa, soft tissue, nerve or bone), sampling accuracy of margins, tumor size, and stage, depth of invasion, histologic pattern of invasion, tumor grade, lymphovascular invasion, perineural invasion, pN stage, and extracapsular extension, lymph node ratio, inclusion of patients with prior therapy, setting of positive margin revision (intraoperatively at same setting versus second operation to revise margin), continuing to smoke, time to and total treatment time of adjuvant therapy, length of follow-up, variability in operational definitions of positive, close, clear margins.
What is seems to emerge is the dependency of actual negative margins on the IOARM method. If a fresh frozen section on the tumor bed is used, false-negative cases (R0 intraoperative, R1 postoperative) can be up to 10.9%.
The benefit of PORT in R1 to R0 margin is difficult to prove because it is not always analyzed in published studies focusing on intraoperative margin management. Some patients receive adjuvant therapy for other reasons than an inadequate resection (e.g., extra-capsular spread and perineural involvement).
Indication to adjuvant RT should balance the treatment outcomes with significant additional morbidity. Binahmed et al. [83] observed minor (33.1%) and major morbidity (7.9%) in 127 patients who received adjuvant radiation therapy. The morbidity levels for patients who received radiation therapy were significantly higher than those treated with surgery alone. Radiotherapy may be of no benefit R1 to R0 cases without other risk factors or instead can provide better local control.

Question 7: in tumors ≤ 4 cm and DOI ≤ 10 mm pN0, should we perform PORT in case of close margins (< 5 mm) without other risk factors?

Synthesis of evidence and discussion:

Not all investigators agree that the radial distance of the margin has the most significant impact upon disease control and the ability to eradicate the tumor surgically completely.
Sutton et al. [84] suggest that a positive or close margin indicates a biologically more aggressive tumor. In their series of 200 oral and oropharyngeal cancers, patients with close margins had significantly higher perineural invasion and vascular permeation rates, an aggressive pattern of invasion, greater diameter, and a higher incidence of nodal metastatic disease.
In support of this thesis, Brandwein-Gensler et al. [78] reported on the impact of patterns of tumor invasion. They developed a histological risk assessment score in resected oral cavity cancer compared to the margin status. The pattern of invasion was significantly associated with local recurrence and overall survival, as was perineural invasion involving a large nerve and limited lymphatic response to the primary tumor, and margin status alone was not a predictor of local recurrence.
In a retrospective series, Liu et al. [85] analyzed 432 intermediate-risk OSCC patients (defined by of close margin <5 mm, pN1, depth of invasion/tumor thickness > 5 mm, PNI, and/or lymphovascular invasion). There were significant differences in the characteristics between the PORT and surgery-only groups, thus, limiting the interpretation of their results. Close margin was associated with poorer DFS but not OS and DSS on multivariable analysis. On univariable analysis, PORT was not associated with differences in 5-year OS (81% vs 80%; P = 0.544) or 5-year DSS (89% vs 87%; P = 0.376), while it was associated with improved 5-year DFS (80% vs 71%; P = 0.044). In the surgery-only group, 5- year OS, DSS, and DFS were significantly worse for patients with >4 intermediate-risk factors (IRFs). For patients who received PORT, there was no significant difference in 5-year OS, DSS, or DFS with increasing numbers of concurrent IRFs. That means that PORT has reduced the impact of adverse factors on these endpoints.

Barry et al. [86] explored the significance of resection margin status on local recurrence and survival for early (T1/T2) oral cancer. Local or locoregional recurrence occurred in 28 of 295 patients (9.5%). Factors significantly associated with local recurrence included pT classification, site, nodal status, ECS, and PORT (but this can be a prescription bias). There was a trend toward increased local recurrence with close or involved margins. Margin status did not influence local recurrence for the pN0 cases or the ECS positive cases. However, the surgical margin did seem to correlate with local recurrence in pN1 without ECS cases (p .05). The authors suggest that surgical margins may have the greatest significance for patients with intermediate-risk regarding biological aggressivity.

In a retrospective series of 200 patients with stage I-II OSCC, Dik et al. [55] identified three groups based on resection margin status: pathologically positive margin (PM), close margin (CM), and free margin (FM) group. There were three options for further patient management: re-resection, PORT, or watchful waiting. The author found a similar level of recurrence, OS, and DSS in the CM and FM groups. However, the CM group was inhomogeneous: 34/126 (27%) patients received PORT, 15/ 126 (12%) underwent RR, and 77/126 (61%) received no adjuvant therapy at all. A comparison between the watchful waiting group with CM and FM groups showed a local recurrence of 1.3% and 3.8%, respectively (not significant). The authors conclude that there is no evidence for local adjuvant treatment in the case of resection margins at least 3 mm with less than two unfavorable histological parameters.

Chen et al. [87] reported that close margins were associated with significantly lower survival compared with clear margins for patients with stage 1 and 2 tumors in a series of 407 patients. However, the close margin subgroup is very small (7.6%; n = 31), and none received PORT.

Jang et al. [56] report a series of 325 patients stratified into early-stage (T1–2N0) (n = 176) and resectable advanced-stage (T3–4 or any N) (n = 149). Tumors in the CM group had more advanced T classification, worse differentiation characteristics, and prevalent perineural invasion than those in the FM group CM was a significant risk factor for local recurrence only in advanced oral cancers, but not in early-stage tumors. The addition of postoperative adjuvant radiation to early-stage tumors with CM did not further reduce the local recurrence rate compared to surgery alone. However, there were significant differences in LCR between FM and CM in T2 tumors. Tasche et al. [88], in a retrospective cohort study of 432 patients, reported no difference in LR for margin distances greater than 1 mm. Forty-five percent of patients was T1 (n = 188), 21% T2 (n = 89), and 34% T3/T4 (n = 145). The N-stage distribution was 70% N0 (n = 296), 11% N1/N2a (n = 46), 19% N2b/N2c/N3 (n = 79). Forty-one percent of patients received PORT. For all the specimen margins categories (except positive margins), the LR rate was the same irrespective of PORT.

Zanoni et al. [89] reported that local recurrence-free survival (LRFS) was significantly affected only with surgical margins of less than or equal to 2.2 mm on multivariate analysis in a cohort of 381 patients, primarily early stages. The role of PORT for different margins distances is not analyzed.

In a series of 187 patients [90], 50% with early-stage, surgical margin status was not associated with worsened RFS or DSS on multivariate analysis. The use of adjuvant treatment was also not associated with DSS, but patients with close margins were more likely to receive adjuvant therapy in this cohort.

Varvares et al. [77], in a multivariate analysis on 108 patients (all OSCC except 6 with base of tongue HPV negative tumors, 47% early stage), found that the radial distance of the margin predicted local recurrence, disease-free survival, and mortality There was no difference in local recurrence or survival with the addition of postoperative radiation therapy but the fact that it was administered in 20% of patients of all the margin-status groups, indicate that other prognostic factors could be unbalanced.

Binahmed et al. [83] considered close margin 2 mm or less from ink. In a series of 425 patients (70% T1-T2, 72% N0), CM was associated with a higher probability of treatment failure, similar to positive margins. OS was similar for CM and free margins groups. PORT was performed in 29.9%

of cases (50% in the PM, 30% in the CM, and 25% in the FM group, respectively). PORT did not impact local and regional recurrence or survival in this study. At the same time, it significantly increased morbidity.
Limitations in the interpretation of these studies are the different definitions of "close margin" (some include between 0 and 5mm, others less than 2 mm, others consider margins 1 mm or more as positive); the shrinkage of the surgical specimen that may compromise the measurement after resection; the different intraoperative surgical margins management (in many studies frozen sections were obtained intraoperatively from the tumor bed and not from the surgical specimen). Another limitation is that this question does not account for the vast heterogeneity in biological aggression seen in oral cavity SCC and, therefore, might be an oversimplification. Moreover, patients with close margins are more likely to receive adjuvant treatment, thus confounding the role of CM as a prognostic factor and the impact of PORT.
Close margin seems to confer a lower local control but a not different survival probability. In early-stage tumors without other risk features, this is less certain.

Question 8: can we omit PORT in the neck in patients with tumors ≤ 4 and DOI ≤ 10 mm pN1 without other adverse characteristics?

Synthesis of evidence and discussion:
Compared with TNM/AJCC 7th edition, the introduction of DOI in the 8th version [91] was one of the most significant changes in head and neck cancer staging. In particular, the latest classification can better discriminate the prognosis of patients with OCSCC based on DOI assessment. Several studies describe the impact of DOI in early-stage cases (pT1, pT2 N0) in terms of loco-regional control, overall survival, and need of PORT [30] [92]. However, none of them allows addressing the issue as to whether adjuvant radiotherapy to the dissected neck can be omitted in "bulky" pT2 tumors in the presence of a single metastasized lymph node, nor what is the cost-benefit ratio of such approach. Still, it is worth reminding the interplay between the extent of DOI in early-stage tumors and the risk of regional dissemination. In a single-center retrospective analysis on 212 patients from the MD Anderson Cancer Center, Tam et al. [93] reported that a median DOI of 7.25 mm was the most predictive cutoff for occult nodal spread. Overall, minimal data are available to address our search question specifically. In general, two comprehensive reviews of the literature [63] [64] focused on PORT for early-stage OCSCC briefly address the topic of pN1 disease, pointing towards a positive role of radiation, without further providing details on radiation fields. In a large retrospective analysis on 644 patients treated with upfront surgery between 2006 and 2017, McMahon et al. [94] attempted to provide a postoperative risk-stratification based on the criteria introduced by the TNM/AJCC 8th edition. Of note, only 9% of the whole cohort had a pN1 disease. The authors identified an intermediate-risk group comprising patients with pN1 and those with pT3 solely based on a depth of invasion (DOI) of more than 10 mm. They conclude that PORT may benefit these patients, although the small numbers may prevent definitive conclusions.
A small retrospective study from Barry et al. [95] reported similar findings: a case-matched analysis on 90 patients with pT1-T2, pN0-N1 tumors showed that better locoregional control with PORT (84% vs. 60% without; p=0.039) was restricted to the pN1 (p=0.036) subgroup only. A cohort study of the National Cancer Database on 898 patients who received PORT for pN1 OCSCC patients further suggested that adjuvant radiotherapy was associated with a survival benefit (HR 0.82, 95% CI: 0.72-0.94). With the caveat of subgroup analysis from a retrospective study, the authors also reported that the size of the involved lymph node might play some role in the indication for PORT, showing no benefit for metastases smaller than 1 cm.

Question 9: is PORT indicated in tumors ≤ 4 cm with DOI > 5mm ≤ 10 mm cN0 in the absence of any other adverse features on the primary site?

Synthesis of evidence and discussion:

In the small prospective study by Robertson et al. [96] comparing exclusive RT with surgery followed by postoperative RT in advanced OSCC, a 2 years OS of 10% was reported in the RT arm compared with the 55% in the postoperative RT arm suggesting a better management of the neck with a primary surgical approach. However, authors reported that the primary site of recurrence was mainly in the originally cN+ rather than in the cN0 levels of the ENRT.-Interestingly, Brennan et al. [97] reported results of a small single-center non randomized prospective trial in early OSCC. The study was aimed at specifically comparing local surgery followed by PORT on the primary site (in presence of pathological adverse features) and ENRT with an exclusive END in absence of pathological adverse features on the primary tumor site. The study, that was stopped early due to more than 20% of locoregional failures, reported a 16% (3/18) of overall crude rate of recurrences in the electively irradiated neck. A larger prospective non randomized study by Boysen et al. [98] investigated the role of the ENRT on an heterogeneous (both for primary site and for T-stage) head and neck patients population. In general primary small tumor were preferentially treated with RT whereas larger tumors were treated with combined RT and surgery. Among the 254 enrolled pts, 115 were OSCC and a total of 10 regional recurrences (8.7%) was reported. Also, Vergeer et al. [99] retrospectively reported on 619 head and neck patients, less than half of whom were OSCC, who were postoperatively irradiated with ENRT for a total of 785 necks of whom 227 (29%) were pN0 and 558 (71%) were cN0. Overall regional control at 3 years was 94% in the cN0 neck with a 3 years regional control of 78% in the ipsilateral compared with 96% in the contralateral cN0 neck. In addition, regional control resulted significantly worse in presence of positive or close margins compared with free surgical margins on the primary tumor site (91 and 87% vs 97%) even if neck control in the ipsilateral cN0 neck did not depend on surgical margins. Finally, other retrospective experiences [100] [101] [102] mainly aimed at investigating the efficacy of definitive RT on locally advanced OSCC, reported low rates of overall regional failures in the elective nodal levels (approximately between 5 and 10%), mostly of them occurring in the high dose regions.
In a retrospective series of 420 oral cancers [103], a subgroup analysis of 97 patients with T1-T2 N0 tumors who received adjuvant treatment of the neck (END or PORT on undissected neck) from 2009 onwards (using modern RT techniques), showed there was no advantage for END compared to PORT on undissected neck regarding DSS and RFS.
The main limitations of the above reported data might to be the lack of a modern imaging technique in several studies that might have underestimated the presence of gross disease in the undissected neck as well as the lack of advanced RT treatment delivery techniques (in several studies a 2D-RT technique was used) that might have affected the oncologic outcome. Moreover, in the most reported series, pts underwent to irradiation of both primary tumor site (operated or not) and undissected neck making it difficult to discern if the elective neck RT should be combined or not with the irradiation of primary tumor bed. Noteworthy, several experiences reported that the presence of adverse features in the primary tumor site (such as positive surgical margins; perineural invasion; depth of invasion) represents a prognostic factors of nodal involvement [99] [60] [104].
However, despite the above reported limitations, a possible valid role of ENRT as an alternative to neck dissection cannot be excluded mostly in early OSCC.

Question 10: is PORT indicated in tumors ≤ 4 cm and DOI > 10 mm pN0 in absence of any other risk factors (close/positive surgical margins, and/or PNI / or LVI and/or G3)?

Synthesis of evidence and discussion:
A recent meta-analysis confirmed that DOI is associated with a higher risk of developing nodal recurrences and is detrimental to survival in early-stage OCSCCs [105]. Nevertheless, whether DOI represents an independent prognostic factor in such a cohort of small tumors and whether the

presence of only DOI should be considered sufficient to indicate PORT has not been established, yet.

For the aim of the analysis, we reported only papers analyzing the primary tumor thickness reclassified according to DOI.

Moreover, to answer whether PORT could improve clinical outcomes of patients staged as pT3 for DOI, we reported a preliminary analysis on the value of DOI as an independent prognosticator in small (< 4 cm) OCSCCs.

Ebrahimi et al. reported that, in a cohort of 1409 patients, DOI seemed to strongly correlate with other risk factors including primary tumor size, pN category, ECE, and close or positive surgical margins ($p < 0.001$ for all factors) [30]. Authors also performed an analysis on 769 low-risk (negative lymph-node and surgical margins) patients with small (T < 4 cm) tumors, showing no statistically significant difference in 5-year disease-specific mortality among patients with DOI < 5 mm and those with DOI > 10 mm (6% vs. 10%, respectively, $p = 0.169$), in the absence of other risk factors. Therefore, the authors suggested that a worsening prognosis related to increasing DOI could be primarily due to other-than-DOI prognostic factors.

McMahon et al. reported a retrospective analysis on 211 patients with pT1, pT2, or pT3 solely for DOI, negative lymph nodes, and negative surgical margins and who did not undergo adjuvant radiotherapy [94]. Multivariate analysis showed that the DOI category was an independent prognostic factor for both locoregional recurrence (LRR) (p=0.024; HR 1.79; 95% CI 1.08 to 2.95) and disease-specific survival (DSS) (p=0.051; HR 1.71; 95% CI 1.00 to 2.95). In the subgroup of 55 patients comprising those with pN1(AJCC 8th Ed) disease as well as those with pN0 tumors and a DOI of more than 10 mm, a diameter of less than 4 cm, and uninvolved (R0) surgical margins, no variable showed residual independent prognostic significance for LRR or DSS.

Alterio et al., in an analysis on 92 small OCSCCs (pT1-pT2 according to ACJJ 7th Ed), showed that the increasing value of DOI was strongly associated with PNI (with a median DOI of 4.25 mm for those with no PNI and of 12mm for those with PNI, $p < 0.0001$,Wilcoxon rank test) [53]. When DOI was considered as a categorical variable (<5 mm, 5–10 mm, and >10 mm), a statistically significant association was maintained with the PNI ($p < 0.0001$, Chi-square test). Moreover, a significant correlation between DOI and high histological grade (G3) was also identified ($p = 0.0005$). In the multivariate analysis, DOI was not found to be and independent prognostic factor for any clinical outcomes. On the other hand, the absence of PNI was associated with a 75% less probability of relapse ($p = 0.02$ for relapse-free survival and $p = 0.04$ for local relapse-free survival).

In conclusion, whether DOI represents an independent prognosticators in small OCSCCs has not been established, yet.

Regarding the impact of PORT in pT3 tumors only for DOI > 10 mm, Ebrahimi et al. showed that in the absence of risk factors (nodal involvement and positive surgical margins), the 5-year disease-specific mortality in patients with DOI > 10 mm was only 2%, regardless of the execution of PORT [30]. Therefore, the authors concluded that DOI alone should not indicate PORT in the absence of other pathologic risk factors.

Similarly, Submarian et al. did not find any differences in terms of OS and DSF between 17 patients with DOI > 10mm, tumor dimension > 4cm treated with PORT, and a comparative cohort of 55 patients with DOI > 10mm, with tumor dimension >4 cm who did not receive PORT [106]. According to these findings, the authors concluded that the routine administration of PORT in patients upstaged to pT3 for DOI may not be warranted in the absence of other adverse features

On the other hand, Cramer et al. analyzed the impact of PORT in 823 patients upstaged to pT3N0M0 AJCC 8th for DOI, excluding patients with LVI and positive margins [107]. Results showed that PORT was associated with an improved OS (adjusted hazard ratio [aHR] 0.47, 95% confidence interval [CI] 0.30-0.73).

Similarly, Lee et al. analyzed a subset of 247 patients who were formerly AJCC 7 pT1-2N0 and had a DOI >10 mm [108]. In the multivariate analysis, receipt of PORT resulted in a reduced hazard of death compared to not receiving PORT (HR, 0.56; 95%CI, 0.33-0.95; P.03).
Alterio et al. [53] found that in a cohort of 94 patients upstaged to pT3N0 for DOI (23 and 71 patients submitted or not to adjuvant radiotherapy, respectively), PORT resulted in being significantly associated with disease-free survival as well as with a trend toward a better diseases specific free survival. Nevertheless, PORT failed to impact oncological outcomes in the case of DOI > 10 mm. In that analysis, no patient with DOI < 10 mm received PORT. Due to the widespread presence of pathological risk factors among that cohort of patients, it was not possible to perform any subgroup analysis to investigate further the role of PORT in the case of specific risk factor combinations. Authors concluded that the increasing DOI alone was not sufficient to impact the prognosis. Therefore, the sole DOI should not be sufficient to dictate PORT indications in early-stage patients upstaged.
Overall, no definitive conclusions can be drawn on the role of PORT in the case of small OCSCCs and the absence of other biological adverse features (PNI, LVI, close/positive margins, positive lymph nodes).
The major limitation of this analysis is represented by the absence of prospective trials facing the topic. Indeed, all reported studies were retrospective series of patients treated according to the institutional clinical practice. Moreover, the emerging biological adverse features (such as tumor budding, lymphocytic infiltration, and the worst pattern of invasion) have not yet been analyzed in this contest.

Question 11: does delayed neck dissection (pN0) after positive sentinel node dissection promotes tumor dissemination and indicate PORT?

Synthesis of evidence and discussion:

Although not well defined in the literature, the delay between SNB and ND in the setting on non-bulky nodal disease and early OSCC is usually a week or two, which per se is not expected to lead to a higher risk of primary or nodal tumor relapse.
Whether postoperative inflammation and immunosuppression may favor tumor growth from occult nodal disease or iatrogenic seeding or tumor reseeding from the nodes is unclear and no data suggests that SNB+ND promotes dissemination more than ND alone.
In the French trial [109], 21 patients / 132 were pSN+, 111 were pSN0. Of the latter, 12 were subsequently diagnosed as pSN+ after definitive pathology and had secondary ND. They had similar oncologic and functional outcomes compared to patients of the SNB group who underwent immediate surgery following intraoperative diagnosis of pSN+, although the limited numbers prevent powerful conclusions.
Both groups equally received PORT: 24.5% in the ND vs. 22.5 in the SNB groups. Reasons for PORT were not reported. Oncologic outcomes were similar in the SNB and ND groups, with 13/132 (9.3%) of SNB patients having an isolated nodal relapse compared to 10.1% in the ND group, consistent with the 10% rate of isolated nodal recurrences in the literature.
SNB may be more relevant than elective ND to detect contralateral neck drainage that would have been missed by conventional ipsilateral ND [110]. In lateralized tumors, SND found bilateral nodal metastasis in 10% of cases that an elective ND strategy would not have identified.
However, the echelon of nodal involvement might be found in all levels [111] with a decreasing probability from level I to IV. Additionally, some positive non-sentinel node (NSN) rates were reported in series when both SNB and ND were performed as a preliminary assessment of the SNB technique. However, rates of non-sentinel node positivity were very low in the order of 1-2% in patients with early OSCC and negative SN [112] [113].

Intriguingly, skip metastases, although described as a typical problem in OSCC, are not classically reported in SNB [111].
Current data suggest that PORT should be indicated depending on classical histopathologic criteria, i.e., number of nodes, ECS+, primary characteristics [114]. PORT for adverse histologic features following SNB confers control rates comparable with more extensive procedures [115].

Question 12: are patients with tumors ≤ 4 DOI ≤ 10 mm pN1 treated with neck dissection with a discontinuous approach at higher risk of relapse than those who underwent en-bloc neck dissection? Does it represent a "per se" indication to PORT?

Synthesis of evidence and discussion:

A meta-analysis showed that in-continuity neck dissection had a statistically significantly lower rate of locoregional recurrence than discontinuous neck dissection in patients with T2 and T3 SCC of the tongue and floor of the mouth (fixed-effects model: relative risk, 0.281; 95% confidence interval, 0.183 to 0.433; P < .001) [116].
For buccal mucosal cancers, Xie et al. found that 5-year DSS rates for the discontinuous neck dissection and in-continuity neck dissection groups were 38 and 62% (P = .023), respectively. The 5-year RC rate for the in-continuity neck dissection group (81%) was significantly better (P = .004) than for the discontinuous neck dissection group (54%). At Cox regression analysis, in-continuity ND meaningfully contributed to a higher RC rate and subsequently better DSS [117].
Chen et al. analyzed patients with only one positive lymph node (pN1) and found that the addition of adjuvant therapy was not associated with higher OS (72.1% vs 66.3%, .253), LRFS (65.9% vs 62.8%, P.671), RRFS (64.7% vs 64.3%,P.859), or DMFS (72.1% vs 65.4%, P.175) [118].
Tagliabue et al. showed that, for early-stage, clinical outcomes of patients with T-N tract not removed were not different from those with negative T-N tract [119].
Ansarin et al. showed that in-bloc resection did not achieve significantly better outcomes than discontinuous resection in patients with DOI < 10 mm [120]. They assigned patients to one of three groups: group 1 (in-continuity resection), group 2 (discontinuous resection), and group 3 (delayed discontinuous resection). They found no differences in disease-free survival (p=0.10) and cancer-specific survival (p=0.78) among the three group.
Few literature data are addressing this issue. Overall, the provided information is scarce and difficult to interpret because of the different classification of T1-T2 according to the new TNM staging system. Moreover, data on PORT (whether performed or not) have not always been reported.
Despite T-N tract could be affected by microscopic tumor seeding even in a certain percentage of node-negative or small (<4cm) oral cavity cancers, there are no sufficient data to support indication to PORT in pT1pT2 N1 tumors treated with a discontinuous approach in the absence of other pathologic risk factors.

Question 13: in case of tumors with flap reconstruction, when PORT is indicated, should the entire flap volume be included in the target volume?

Synthesis of evidence and discussion:

Only two guidelines address the question [121], [122], both indicating the inclusion of the whole flap but in different volumes at risk (one in CTV3 and one in CTV1). In an ongoing phase II trial in OSCC, with the purpose of spare swallowing function, the entire flap is always included in CTV at 60 Gy, and de-escalation is obtained omitting neck pN0 [123].

The evidence supporting the inclusion of the entire flap in the tissue at risk is low, especially for low-risk patients (early-stage with minor risk factors), also because in these patients, reconstructive surgery with flaps is needed less frequently.
Few retrospective series showed that the flap rarely is the site of recurrence [124],[125],[126],[127].
Gérard et al.[124] retrospectively delineated the flap in a series of 100 patients. Patients with flap had more locally advanced tumors. The flap was included by 80.9% in any clinical target volume and received a mean dose of 64.9 Gy, meaning it was intended as an area at risk. More extended clinical target volume and higher toxicity correlated with the presence of flaps. Recurrence within the flaps was rare (3.7%).
Cho et al. [125] analyzed a series of 114 pts, 33% stage IV (AJCC VII), 95 OSCC, all submitted to reconstructive surgery with flaps. No failure was in the flap body, while 96.3% of the relapses were in the anastomosis marginal site.
Chakraborty et al. [126] analyzed 75 patients, 41 (55%) patients had oral tongue cancers, and 52 (69%) of the patients had Stage IVA cancers. They included the whole flap in different CTV depending on its location related to the nodal volumes and observed no in-flap recurrences.
Geretschläger et al. [127] analyzed 53 locally advanced or high risk OSCC. They observed multifocal recurrence in patients with extensive surgery requiring flap reconstruction, and 5 of these had a multifocal failure involving the flap. They propose to include the entire flap in the case of ECE.
On the one hand, the risk of colonization of microscopic disease of the flap is unknown; on the other hand, the risk of more significant toxicity when the whole flap is irradiated is certain.
Variations in the volume and function of the flap induced by radiotherapy are also known [128], [129], [130], [131], [132].
Recently a consensus conducted by GORTEC, validated by HNCIG [133], did not reach an agreement on in-flap tumor spread patterns and could not determine whether a flap should be considered as part of the clinical target volume. They conclude that flap-tissue junction is at higher risk of tumor spread than other flap areas. They also recommend limiting the maximum and mean doses to the flap to reduce the risks of radiation-induced atrophy, fibrosis, and osteoradionecrosis.
To facilitate the reduction of the mean dose to the flap, including only flap-tissue junction in the high-risk dose, surgeons should accurately report the placement of flaps and place clips to delineate better tumor bed [133].
Bittermann et al. [134] propose a method to reduce the radiation dose to vascular free flap reconstructions marking resection borders with titanium ligature clips. In their experience, this allows for accurate delineation of the tumor resection margins and the possibility to deliver lower doses to the body of the flap, thus sparing dose also to OARs. Reduction of the mean dose to the flap could not be feasible in early-stage patients due to the more frequent use of smaller free flap reconstruction. In fact, in their article Bittermann et al. show the case of a patient with a pT1 tumor of the floor of the oral cavity with a free radial forearm flap in which the area of the flap to be spared (PRV-flap) is 0.2 cm^3 [134].
The flaps should always be delineated to recognize toxicity and relapse patterns better. An atlas has been proposed for this purpose [135].

Question 14: can tumor bed irradiation be omitted if PORT is indicated only for risk factors related to N (e.g., pN1 nodal metastasis 3 cm with less than 10 lymph nodes dissected)?

Synthesis of evidence and discussion:

A recent non-randomized prospective phase II trial omitted postoperative radiotherapy to the pN0 neck in 72 head and neck cancer patients (oral cavity tumors: 20%), demonstrating excellent results with no isolated failures and 97% control in the unirradiated pN0 neck. Taken together, the current

retrospective and prospective data suggest that omitting postoperative in patients with a pN0 neck likely has a recurrence rate of less than 15–20% [136].

Another option in volume de-escalation is the radiotherapy omission of the tumor bed in case the indication to radiotherapy is driven by adverse features pertinent to the nodal involvement of the neck [137]. Few data about this approach are available for oral cavity tumors. Conversely, more data are available for oropharyngeal cancer. The recent adoption of trans-oral robotic surgery (TORS), coupled with selective neck dissection, allowed to minimize the need for RT, decrease radiation dose, or avoid radiation in the contralateral N0 neck. One justification for TORS is the potential for smaller radiation volumes by avoiding radiation to the tumor bed in selected cases of node-positive OPC when the primary tumor is widely resected with negative margins and no adverse pathologic features. As an example, in the AVOID trial, a phase II trial evaluating alternative volumes of oropharyngeal irradiation for de-intensification, the authors tested the omission of the resected primary tumor bed after TORS for HPV-related SCC of the oropharynx [138]. The study enrolled 60 patients with stage pT1-pT2 N1-3 HPV-associated oropharyngeal SCC, treated with TORS and selective neck dissection. They had favorable features at the primary site (negative surgical margins >2 mm, no perineural invasion, and no lymph-vascular invasion) but required adjuvant therapy based on lymph node involvement. Patients received postoperative RT to at-risk areas in the involved neck (60-66 Gy) and uninvolved neck (54 Gy). The resected tumor bed was considered as an active avoidance structure in the treatment planning. Concurrent chemotherapy was administered for patients with extranodal extension. A single patient recurred at the primary site for a 2-year local control of 98.3%. One patient (1.7%) developed a regional neck recurrence, and 2 patients (3.3%) developed distant metastases. Measured 2-year local recurrence-free survival was 97.9%. Overall survival was 100% at the time of analysis. The mean radiation dose to the primary site was 36.9 Gy (standard deviation, 10.3 Gy).

A retrospective cohort study found similar results [139]. It included p16-positive T1-T4 oropharyngeal SCC, operated on with TORS, receiving or not radiotherapy to the primary tumor bed. At a median observation time of 61 months, local relapse occurred in 3% of patients with T1-T2 tumors and 17% for those having T3-T4 lesions when radiation to the primary tumor bed was omitted. In patients with T1-T2 tumors, the Absolute Risk Reduction of local relapse with primary bed radiation was 3.26% and the Number Needed to Treat to prevent one local relapse was 31 (95% CI: 14.5, 271). The Absolute Risk Increase for gastrostomy-tube with primary bed radiation was 34.4% (95% CI: 24%, 45%); the Number Needed to Harm was 3 (95% CI: 2.2, 4.2), i.e., for every three patients with T1-T2 tumors receiving primary bed radiation, one had a gastrostomy-tube. These findings proved radiotherapy omission to the primary tumor bed to be oncologically safe for T1-T2, margin-negative resected, p16 positive oropharyngeal SCC, with a lower gastrostomy rate. For T3-T4 tumors, this approach led to an increase in local relapse.

Whether this approach can be applied also in early-stage OSCC with widely resected primary and indication for PORT in the neck need further studies.

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