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Review Article

AIRO GORTEC consensus on postoperative radiotherapy (PORT) in low-intermediate risk early stages oral squamous cell cancers (OSCC)



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ABSTRACT

Evidence on the efficacy of postoperative radiotherapy (PORT) in low-intermediate risk squamous cell carcinoma of the oral cavity (OSCC) remains inconclusive.

Members of a task force from two national radio-oncology Associations (AIRO and GORTEC) defined 14 clinically relevant questions to identify "gray areas" pertinent to the indication for PORT in this clinical setting.

Consequently, a literature review was performed on the topic. The resulting statements were then rated by an Expert Panel (EP) using a modified Delphi method. Only radiation oncologists were part of the discussion and voting on the scenarios.

There was agreement on the 14 statements at the first round of voting. The task force then decided to propose clinical cases for the two more controversial statements that had received a lower agreement to better capture the Experts' attitudes. The clinical cases highlighted a more significant decisional heterogeneity. However, the good level of consensus reached among the two Associations gives relevant support in informing clinical choices while acknowledging general indications cannot fit all clinical situations and do not replace multidisciplinary discussion.

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Treatment for OSCC primarily comprises surgical resection, with neck dissection and PORT reserved for patients at risk of disease progression and recurrence.

PORT or postoperative radio-chemotherapy (RTCT) are generally recommended based on the presence of minor risk factors (miRF) (lympho-vascular invasion; perineural infiltration; pres-

ence of two or more nodal metastases) or major risk factors (MRF) (positive margin; extranodal extension), respectively [1].

In specific clinical settings, particularly those with a lower risk of recurrence, there is no high-quality evidence on the PORT impact on clinical outcomes or the prognostic value of miRF. These factors refer mainly to the tumor (e.g., tumor biological features and close surgical margins), patient (e.g., age and comorbidities) or treatment (e.g., re-excision in case of positive surgical margins)-related characteristics [2].

Consensus methods can be useful in guiding in situations with insufficient evidence.

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For this purpose, the Head and Neck Study Group of the Italian Association of Radiation Oncology (HNSG-AIRO) and the Groupe d'Oncologie Radiothérapie Tête Et Cou (GORTEC) assessed experts' consensus among radiation oncologists. The aim was to examine clinical scenarios of low-intermediate risk of LRR and some so-called "grey areas" on the indication of PORT currently neglected by scientific evidence. The statements proposed for the clinical scenarios analyzed are the result of an Italian and French consensus involving experts from their Oncological Radiotherapy Associations.

The interpretation of available data and the subsequent voting of the proposed statements were based on published clinical-pathological risk factors and personal experience, if applicable. Only radiation oncologists were involved in the consensus and voting process on the analyzed scenarios, as selection of target volumes was at stake.

Materials and methods

For the present analysis, we considered OSCC staged as pT1-T2 pN0-N1 (without ENE) or pT3pN0 (TNM 8th ed.).

As the definition of stages has changed from the 7th to the 8th Edition of the American Joint Committee on Cancer (AJCC)-Tumor Node Metastasis (TNM) staging system, we formulated the questions using depth of infiltration (DOI) and tumor size to allow for broader inclusion of the studies in the literature [3 4].

Nine radiation oncologists experts in head and neck cancer from both associations made up the project team (PT) and met twice via web meetings. The PT defined 14 clinically relevant questions considered "gray zones" in clinical practice according to their experience and knowledge of literature data. The list of the questions is reported in Table 1. Members of the PT performed a narrative review of the literature focused on each selected topic (Appendix 1 reports the search strategy for all the questions) and proposed a list of statements formatted as a questionnaire.

The assumptions common to all the statements were.

1. cervical lymph node dissection is "adequate" when a minimum of 18 lymph nodes of levels I-III have been removed;
2. patients with primary tumors close to or involving the midline receive bilateral neck dissection;
3. PORT is a postoperative radiation treatment delivered within 6–8 weeks from the surgical procedures;
4. if not explicitly declared, margins are free (≥ 5 mm);
5. Perineural invasion (PNI) and lymphovascular invasion (LVI) are to be considered negative unless otherwise specified.

Another fourteen experienced radiation oncologists from AIRO and GORTEC (Expert Panel-EP) elaborated and voted on each statement. To reach consensus, we applied the Modified Delphi technique using a scale of four steps (1) "high consensus", 2) "low consensus", 3) "no consensus", 4) "unable to express an opinion" [5].

Seventy-five percent (summative of agreeing and strongly agreeing) was the threshold set for the agreement.

Appendix 2. shows the details of how we applied the Delphi methodology.

Results

After the first voting round, we obtained the agreement (sum of high-low agreement ≥ 75 %) on all questions, thus we could have skipped the second round.

However, after analyzing the first-round comments, the PT decided to accept the suggestion to change the rewording of two

statements to improve their clarity and avoid misinterpretations. So, these statements were submitted to the second round of voting.

In addition, the PT decided to propose clinical cases related to the statements that had received a lower agreement to better capture the Experts' attitudes.

Appendix 3. gathers the narrative reviews for each question.

The list of statements and their modifications and the agreement reached in each voting round are shown in Table 1.

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?

Rationale

There seems to be a trend of increasing incidence of oral tongue cancer in young patients while the rate of SCCs in the other oral cavity subsites is declining [6]. In particular, the incidence in patients not exposed to traditional risk factors for head and neck tumors seems to be increasing. Thus, some authors hypothesize that OSCC (particularly the tumors of the tongue), which arise at a young age, could be a different biological entity with a different prognosis.

Statement

It is not possible to establish whether young patients (<40–45 years) not- or light smokers (<10 pack-years) with early-stage OSCCs tumors and the same other prognostic factors as their older counterparts are at increased risk of death or relapse.

Management for this subcategory of early-stage OTSCC should not be different based on the patient's age and smoking status alone.

However, young non- or light-smoking patients should receive personalized follow-up plans because of the possible earlier and higher rates of recurrence suggested in some series.

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?

Rationale

The prognostic significance of DOI has been introduced in the TNM 8th edition to supplement the tumor diameter measure for defining the T stage in OSCC. It is unknown whether a larger size could independently modify the prognosis and help the decision to administer PORT in the early stages of OSCC. In a study by Lee et al. [7], among other factors, increasing tumor size (i.e., AJCC 7th Ed. pT classification; $P < .001$) was independently associated with an increased risk of death.

Statement

It is not possible to establish whether the size (<3 cm versus ≥ 3 cm ≤ 4 cm) in OSCC with a DOI > 5 mm ≤ 10 mm, is an independent prognostic factor for local recurrence (LC), locoregional control (LRC) and overall survival (OS). Other adverse prognostic indicators may better inform prognosis and the need for adjuvant RT.

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

Rationale

In most guidelines, there is a lack of clear indications on contralateral neck irradiation in early-stage pN0 patients.

NCCN guidelines [8] provide no indications on elective contralateral radiotherapy.

Table 1

List of the questions addressed by PT and list of statements and their modifications and the agreement reached by EP in each voting round.

#	statement	Consensus first round	Consensus second round
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?	It is not possible to establish whether young patients (<40–45 years) not- or light smokers (<10 pack-years) with early-stage OSCCs tumors and the same other prognostic factors as their older counterparts are at increased risk of death or relapse. Management for this subcategory of early-stage OTSCC should not be different based on the patient's age and smoking status alone. However, young non- or light-smoking patients should receive personalized follow-up plans because of the possible earlier and higher rates of recurrence suggested in some series.	70 % high agreement 30 % low agreement
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?	It is not possible to establish whether the size (<3 cm versus ≥ 3 cm ≤ 4 cm) in OSCC with a DOI > 5 mm ≤ 10 mm, is an independent prognostic factor for local recurrence (LC), locoregional control (LRC) and overall survival (OS). Other adverse prognostic indicators may better inform prognosis and the need for adjuvant RT.	70 % high agreement 20 % low agreement 10 % unable to express opinion
3	In tumors ≤ 4 cm with DOI > 3 mm ≤ 10 mm, pN0, when PORT is considered, is contralateral neck radiotherapy indicated?	The rate of contralateral neck metastases in early-stage pN0 OSCC is low. Thus, PORT to the contralateral neck is not recommended in this subset of patients. It is reasonable to consider PORT to contralateral elective neck in patients with tumors approaching midline (≤1 cm), particularly those localized in the oral tongue and floor of the mouth.	100 % high agreement
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?	There is no evidence that one miRF is sufficient to offer PORT in early-stage OSCC. Two or more miRFs are necessary to recommend PORT to this setting. PNI may be the unique miRF to require PORT, as it is related to local and locoregional recurrence, but further studies need to confirm this evidence.	70 % high agreement 30 % low agreement
5	In tumors ≤ 4 cm and DOI ≤ 10 mm pN0, is PNI an independent risk factor for local or locoregional recurrence?	PNI is related to a higher risk of local and locoregional recurrence in early oral cancer. In particular, it seems to be related to a significant risk of nodal involvement. Therefore, as an isolated risk factor, it could impact the likelihood of experiencing a locoregional recurrence. Further studies are needed to confirm the benefit of PORT on survival outcomes in patients with early-stage tumors and PNI as the only risk factor.	90 % high agreement 10 % low agreement
6	Should we offer PORT for intra-operatively converted R1 to R0 margins without other risk factors?	When the tumor bed margin is negative, but the resection specimen margin is positive, we should offer PORT to improve local control, relying on the status of resection specimen margins.	40 % high agreement 50 % low agreement 10 % no agreement In this specific clinical case: 69 years old male, heavy smoker, pT1 (1,7 cm DOI 5 mm) pN0 OSCC of the left floor of the mouth, G3, no PNI, no LVSI, positive deep tumor margin on the intraoperative frozen section (on the tumor specimen), tumor bed margin revision negative at definitive histology. PORT on tumor bed and homolateral neck = 25 % PORT only on tumor bed = 33,33 %

(continued on next page)

Table 1 (continued)

#	statement	Consensus first round	Consensus second round	
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?	In tumors ≤ 4 cm and DOI ≤ 10 mm pN0, in case of close margins (<5 mm) without other risk factors, a watchful-waiting approach is to prefer over PORT because of the risk of added toxicity and no potential impact on local control and DSS. However, close margins should be considered a miRF that, in addition to other features of aggressive behavior, requests PORT.	50 % high agreement 50 % low agreement	No PORT = 41,67 % In this specific clinical case: 35 years old female patient, no smoker, pT2 (3 cm, DOI 8 mm) pN0 lateral oral tongue, close margin (3 mm), G2, LVSI focal, no PNI PORT on tumor bed and homolateral neck = 41,67 % PORT on tumor bed and bilateral neck = 8,33 % PORT only on tumor bed = 41.67 % No PORT = 8,33 %
8	Can we omit PORT in the neck in patients with tumors ≤ 4 cm and DOI ≤ 10 mm pN1 without other adverse characteristics?	For patients with early-stage tumors with clear resection margins, no other adverse features, and adequate neck dissection, the presence of a single positive lymph node (pN1) may warrant an indication to PORT given the intermediate-risk profile, however, this is a controversial matter [9]. In case adjuvant radiotherapy is prescribed, considering the substantial lack of literature on the extent of clinical target volume in such cases, no data supports the notion that PORT should be restricted to the primary tumor bed only and omitted for the dissected neck. In the absence of prospective evidence, PORT should be performed following standard principles of dose prescription and volume selection. However, individualized counseling to discuss the risk-benefit ratio of a standard PORT is warranted.	80 % high agreement 10 % low agreement 10 % no agreement	
9	Is PORT indicated in tumors ≤ 4 cm with DOI > 5 mm ≤ 10 mm cN0 in the absence of any other adverse features on the primary site?	It is impossible to establish if PORT is a valid alternative to SND after the surgical removal of the primary tumor site. It could be proposed to patients with primary oral tumors ≤ 4 cm with DOI > 5 mm ≤ 10 mm (pT2 according AJCC 8th Ed.) without any adverse features and not undergone SND (cN0) for medical/surgical contraindication or patient's refusal. Also, in these patients, RT should be delivered only to nodal neck stations.	The question submitted to the first voting round was: is PORT indicated in tumors > 2 cm < 4 cm with DOI > 5 mm ≤ 10 mm cN0 in absence of any other adverse features on the primary site? 50 % high agreement 50 % low agreement	after adding "for medical/surgical contraindication or patient's refusal" in the statement, we performed a second voting round 75 % high agreement 25 % low agreement
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)?	In patients with small (≤4 cm) OSCCs with DOI > 10 mm (pT3 according to AJCC TNM 8th) and absence of any other risk factors, PORT should not be routinely indicated only on the sole basis of DOI. However, individualized counseling to discuss the risk-benefit ratio of a standard PORT is warranted.	10 % high agreement 70 % low agreement 20 % no agreement	the high rate of "low agreement" clearly reflects the lack of literature on the topic, we decided not to perform a second round of voting
11	Does delayed neck dissection (pN0) after positive sentinel node dissection promotes tumor dissemination and indicate PORT?	Indication for PORT after immediate or delayed secondary ND following positive sentinel node biopsy (SNB) cannot be handled differently and should follow the current recommendations for PORT in OSCC.	90 % high agreement 10 % low agreement	
12	Are patients with tumors ≤ 4 cm 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?	There are insufficient data to suggest PORT in patients subjected to discontinuous surgery for tumors ≤ 4 cm DOI ≤ 10 mm pN1 without other risk factors. If continuous surgery has been performed, the information on the T-N tract could serve as an additional prognostic factor in defining adjuvant treatments. It may be recommended to contour the T-N tract when there is an indication to perform RT in patients treated with a discontinuous surgical approach.	60 % high agreement 40 % low agreement	

Table 1 (continued)

#	statement	Consensus first round	Consensus second round
13	In case of tumors with flap reconstruction, when PORT is indicated, should the entire flap volume be included in the target volume?	Relapses within the reconstructive flaps are rare and occur mainly in locally advanced tumors. The risk area is the junction/interface between the flap and the tumor bed. However, current practice is to include the entire flap and not only the flap-tissue junction. Because data on oncologic results for reducing RT dose to the flap body is missing, the whole flap should be included in the clinical target volume (CTV), also in the early stages. Adequate information should be available (surgical description, clips that outline the tumor bed, postoperative CT with contrast medium) to better delineate CTV. In any case, the flap should be contoured to reduce hot spots, especially at the vascular pedicle.	90 % high agreement 10 % low agreement
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)?	Given the paucity of available data, it is not possible to assess the oncological safety of the omission of the irradiation of the primary tumor bed when the indication to radiotherapy is driven by adverse factors in the neck. However, given the promising results observed by this approach in oropharyngeal cancer, this volume de-escalation strategy may be tested within investigational studies in OSCC.	90 % high agreement 10 % low agreement

ASCO guidelines recommend contralateral irradiation (or surgery) in patients with more advanced primary tumors (T3 and T4) or tumors approaching midline, also suggesting to consider tumor thickness in the context of other pathological adverse factors [9]. Besides recommends elective neck dissection for OSCCs that require clinically negative neck management and elective radiotherapy to a non-dissected neck as an alternative when surgery is not feasible.

United Kingdom National Multidisciplinary guidelines indicate contralateral prophylactic neck treatment when the estimated occult risk spread exceeds 15–20 %, as occurs with tumors invading or crossing the midline [10]. Besides, contralateral irradiation may be preferable when both neck sides deserve treatment.

DAHANCA guidelines [11] define midline tumors as those of the tongue, the floor of the mouth, hard palate, and any tumors with involvement of these structures that have the propensity of bilateral nodal involvement. In pT1-2 cases with PORT indication, the irradiation of the primary tumor site alone is suggested.

In early-stage OSCC, the rate of neck failure (either ipsilateral or contralateral) is nearly less than 10 % in the absence of pathological lymph nodal metastases [2 12 13]. While many [10] advocate elective nodal irradiation (ENI) to treat microscopic disease in the contralateral neck when a contralateral END has been omitted, this approach is not generally endorsed for managing the undissected clinically negative ipsilateral neck.

In the light of these unclear indications, criteria to estimate the risk of contralateral occult metastases and a clear definition of “tumor approaches midline” would be beneficial to guide treatment.

Statement

The rate of contralateral neck metastases in early-stage pN0 OSCC is low. Thus, PORT to the contralateral neck is not recommended in this subset of patients.

It is reasonable to consider PORT to contralateral elective neck in patients with tumors approaching midline (≤ 1 cm), particularly those localized in the oral tongue and floor of the mouth.

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?

Rationale

The presence of pathological MRFs guides the decision to offer PORT and chemotherapy in early-stage OSCC.

While these adverse features are well established in the literature, the weight of miRF (i.e., DOI, PNI, LVI, and close margins) is still unclear and controversial [14].

In particular, if patients with multiple miRF tend to have a poorer outcome and benefit from PORT [15 16], the impact of the single histologic risk factor on treatment outcome lacks definitive evidence [17].

Statement

There is no evidence that one miRF is sufficient to offer PORT in early-stage OSCC. Two or more miRFs are necessary to recommend PORT to this setting. PNI may be the unique miRF to require PORT, as it is related to local and locoregional recurrence, but further studies need to confirm this evidence.

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

Rationale

PNI represents a poor prognostic factor in oral cancer, correlating with aggressive tumor behavior and local recurrence [18].

It is common in locally advanced oral cancer or associated with other risk factors, so analyzing its weight on locoregional control in early-stage OSCC is challenging.

Current evidence in the literature is controversial on whether PNI as a sole risk factor could be associated with higher local or locoregional recurrence, particularly in early oral cancer.

Statement

PNI is related to a higher risk of local and locoregional recurrence in early oral cancer. In particular, it seems to be related to a significant risk of nodal involvement. Therefore, as an isolated risk factor, it could impact the likelihood of experiencing a locoregional recurrence.

Further studies are needed to confirm the benefit of PORT on survival outcomes in patients with early-stage tumors and PNI as the only risk factor.

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

Rationale

Early-stage OSCCs should ideally be treated with surgery as a single therapeutic modality. Locoregional recurrence rates after margin-free surgical resections range between 16 and 20 % [1920]. Ensuring resection within large (1 cm) free surgical margins ab initio is sometimes challenging due to the complex oral anatomy and the need to preserve vital anatomical structures, oral function, and quality of life. Failure to eradicate the disease at the primary site increases the likelihood of disease recurrence and poorer overall survival [21].

There is a lack of consensus on what to consider tumor involvement at the resection margin since some authors include mucosal dysplasia or carcinoma-in-situ at the margin in the definition of involved margin. In contrast, others exclude them [21]. In a literature review from the pathologists' perspective, the authors conclude that only invasive carcinoma at the margin should be considered a positive margin [22].

Among other prognostic factors, the impact of intraoperative margin status on prognosis and the need for adjuvant therapies is not well defined.

Moreover, there is no consensus regarding the best intraoperative method for assessing margins (IOARM).

The evidence that specimen-driven IOARM is superior to defect-driven IOARM is growing [23242526], and recently the American Joint Committee on Cancer (AJCC) has recommended specimen-driven IOARM as the standard of care since 2017 [27].

The implication of microscopic tumor cut-through (i.e., positive tumor margin on the intraoperative frozen section) surgically revised to a negative final margin on permanent sections is currently unclear. Intraoperative determination of margins in OSCC seems still to be suboptimal. Intraoperatively negative margins may be later diagnosed as positive at definitive histology in 2–10 % of cases, thus suggesting a weak sensitivity value of intraoperative frozen section analysis [26].

In a recent meta-analysis [28], margin revision of initially positive margins to “negative” based on frozen section guidance does not equal an initial negative margin and does not significantly improve local control. Patients with tumors R1 converted intraoperatively to R0 had worse locoregional relapse-free survival compared to the R0 “ab initio” group (hazard ratio [HR] = 2.897, $P < .001$). These results could be because some patients did not receive PORT although they could have benefited from it.

Statement

When the tumor bed margin is negative, but the resection specimen margin is positive, we should offer PORT to improve local control, relying on the status of resection specimen margins.

As this statement received a low agreement, we performed a second voting round to explore the experts' reasons.

Sixty-two point-five percent of those who responded with “low agreement” in the first round said that the reason was poor or not homogeneous results of literature data, 25 % personal experience, 12,5% that the question was unclear.

Since the statement was particularly controversial, we have submitted the following clinical case to the EP: 69 years old male, heavy smoker, pT1 (1,7 cm DOI 5 mm) pN0 OSCC of the left floor of the mouth, G3, no PNI, no LVSI, positive deep tumor margin on the intraoperative frozen section (on the tumor specimen) with tumor bed margin revision negative at definitive histology. Twenty-five percent of the voters proposed PORT on tumor bed and homolateral neck, 33.33 % PORT only on tumor bed, and 41.67 would not have performed PORT.

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?

Rationale

In recent years, there has been a trend toward de-escalation of surgery for early-stage OSCC (stage I/II AJCC 7th Ed). Some studies have attempted to quantify what size resection margin constitutes a safe margin. That has clinical implications as a “close” margin (considered as ≤ 5 mm) may be an indication for PORT or re-excision or both.

If a margin is close, evidence favoring adjuvant treatment or a “watchful waiting” policy is lacking.

Statement

In tumors ≤ 4 cm and DOI ≤ 10 mm pN0, in case of close margins (<5 mm) without other risk factors, a watchful-waiting approach is to prefer over PORT because of the risk of added toxicity and no potential impact on local control and DSS.

However, close margins should be considered a miRF that, in addition to other features of aggressive behavior, requests PORT.

Comment on the second round: this question also received a low agreement. Therefore, we performed a second round to highlight the reasons. The majority (86 %) of those who responded with “low agreement” in the first round said that the cause was poor or not homogeneous results of literature data. Fourteen percent of the responders considered the question unclear.

We then asked the EP to consider the clinical scenario depicted below and choose one option: 35-year-old female patient, no smoker, pT2 (3 cm, DOI 8 mm) pN0 lateral oral tongue, close margin (3 mm), G2, LVSI focal, no PNI. They proposed PORT on tumor bed and homolateral neck in 41.67 %, PORT on tumor bed and bilateral neck in 8,33 %, PORT only on tumor bed in 41.67 %, and no PORT in 8,33 %.

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

Rationale

According to the NCCN guidelines, in patients with early-stage OSCC, the presence of a single involved lymph node (<3 cm in its maximum diameter) in the surgical specimen without any additional adverse features may by itself justify the consideration for post-operative radiotherapy (PORT). Two relevant caveats should be kept in mind when addressing the ensuing implications for clinical practice for such an intermediate-risk case. First, there's an evi-

dent lack of high-quality evidence to corroborate the adjuvant management, not only in defining the inherent anticancer value of PORT but also in terms of radiation dose prescription and, maybe most importantly, of target volumes. Provided that an adequate number of lymph nodes is dissected (>18 according to ASCO clinical practice guideline) [9], the radiation oncologist may be confronted with the question of whether PORT to the neck could secure additional loco-regional control. However, the finding of a pN1 disease would still be associated with a stage III classification, independently from the primary tumor characteristics. Second, patient-related factors such as age, performance status, comorbidities, post-operative recovery, and willingness to undergo PORT may represent the critical factor to opt between PORT (to both the primary tumor bed and the dissected neck or without the latter) or no further treatment.

Statement

For patients with early-stage tumors with clear resection margins, no other adverse features, and adequate neck dissection, the presence of a single positive lymph node (pN1) may warrant an indication to PORT given the intermediate-risk profile, however, this is a controversial matter [9]. In case adjuvant radiotherapy is prescribed, considering the substantial lack of literature on the extent of clinical target volume in such cases, no data supports the notion that PORT should be restricted to the primary tumor bed only and omitted for the dissected neck. In the absence of prospective evidence, PORT should be performed following standard principles of dose prescription and volume selection. However, individualized counseling to discuss the risk–benefit ratio of a standard PORT is warranted.

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

Rationale

Cervical lymph node metastases are associated with diminished overall survival in patients with OSCC [29]. A large number of patients with OSCC have a positive neck at diagnosis, and 10–40 % of patients with a clinically negative neck (cN0) at presentation will develop nodal metastases [30–31].

The risk of occult nodal involvement in cT1–2 OSCC is 20–30 % [32].

Surgical dissection is the primary choice for neck management in patients affected by OSCC [33].

In a minority of patients, due to anesthesiological reasons mainly, the neck is not surgically staged.

The role of RT alone as a replacement of selective neck dissection (SND) in cN0 patients has been poorly investigated by the current literature, most data coming from studies investigating the role of definitive RT as an alternative to surgery in locally advanced OSCC. Thus, if elective neck radiotherapy (ENRT) is indicated in pts with OSCC tumors ≤ 4 cm with DOI > 5 mm ≤ 10 mm cN0 without any associated adverse features who did not undergo neck dissection is a debatable question.

Statement

It is impossible to establish if PORT is a valid alternative to SND after the surgical removal of the primary tumor site. It could be proposed to patients with primary oral tumors ≤ 4 cm with DOI > 5 mm ≤ 10 mm (pT2 according AJCC 8th Ed.) without any adverse features and not undergone SND (cN0) for medical/surgical contraindication or patient's refusal. Also, in these patients, RT should be delivered only to nodal neck stations.

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)?

Rationale for the question

The 8th edition of the AJCC TNM staging system inserted DOI as a new prognosticator for OSCC [27]. Therefore, small cancers (< 4 cm) classified as pT1–pT2 in the previous staging system (AJCC 7th Ed) are upstaged to pT3 in the case of DOI > 10 mm. Whether patients classified as pT3 only for DOI and without any other risk factors (close/positive surgical margins, and/or PNI, and /or LVI, and/or high-grade histology) require postoperative radiotherapy (PORT) after radical surgery is a matter of debate.

Statement

In patients with small (≤ 4 cm) OSCCs with DOI > 10 mm (pT3 according to AJCC TNM 8th) and absence of any other risk factors, PORT should not be routinely indicated only on the sole basis of DOI. However, individualized counseling to discuss the risk–benefit ratio of a standard PORT is warranted.

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

Rationale

Approximately 20 %–30 % of the patients with early-stage head and neck cancer have occult cervical metastases (micrometastases) undetectable by current imaging techniques. Therefore, they should receive prophylactic treatment of the neck, including early T1 and T2 OSCC [10].

Sentinel node biopsy (SNB) is one of the evolutions of minimorbid surgery.

Two randomized Phase III [34–35] provided level I evidence for SNB: isolated nodal relapse rates were in the order of 10 % at 2 or 3 years (consistent across N0 HNSCC in the literature), with most events in the first two years. Estimated 2y and 5y survival was also similar between arms, avoiding 70 % unnecessary neck dissection (ND) in T1 T2 N0.

However, both trials showed that SNB with intraoperative pathology analysis has relatively poor sensitivity and negative predictive value. The sensitivity of intraoperative pathology analyses is low, 63.9 %. More extensive analyses with immunohistochemical (IHC) and molecular assay of sentinel neck nodes are time-consuming and would excessively increase the length of surgery. Final pathology analysis with IHC more likely shows isolated tumor cells or tumors < 200 micron (ITC +) after surgery. ITC + and pN0(sn) had similar outcomes and therefore do not require neck dissection. However, patients with tumors > 200 micron should undergo delayed ND, although some have suggested that SNB alone is an adequate treatment for pN1 neck disease without adverse histological features [10]. There may be limitations with floor-of-mouth primaries and SNB procedure [36]. To manage shine-through issues (i.e., the proximity of level I and II nodes to the primary tumor leads to shine-through radioactivity, thus masking signal from the relevant sentinel), some have suggested resection of the primary tumor before SNB [36].

Whether delay between SNB and ND influence outcomes is unclear.

Statement

Indication for PORT after immediate or delayed secondary ND following positive sentinel node biopsy (SNB) cannot be handled differently and should follow the current recommendations for PORT in OSCC.

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?

Rationale

The en-bloc approach with in-continuity neck dissection in the advanced stages guarantees better oncological outcomes [37]. It is suggested in the guidelines when there is a direct extension of the primary tumor into the neck [8]. In oral tongue cancer, involvement of the T-N tract is a prognostic factor requiring PORT [38]. In the early stages OSCC, the surgery trend is towards minimally invasive procedures and SNB. Thus, the information of the potential involvement of the T-N tract can be lost. Data on the incidence of microscopic disease in the T-N tract are scarce. Twelve percent of patients with pathologically negative lymph nodes still can have tumor cells within the T-N tract. Moreover, 18 % of patients with T1-T2 N + cancers can have a microscopic involvement of the T-N tract [38]. Thus, if the T-N tract has not been removed, there could be a risk of microscopic involvement requiring PORT.

Statement

There are insufficient data to suggest PORT in patients subjected to discontinuous surgery for tumors ≤ 4 DOI ≤ 10 mm pN1 without other risk factors. If continuous surgery has been performed, the information on the T-N tract could serve as an additional prognostic factor in defining adjuvant treatments. It may be recommended to contour the T-N tract when there is an indication to perform RT in patients treated with a discontinuous surgical approach.

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

Rationale

In the presence of reconstruction flaps, PORT is challenging due to possible unknown dissemination routes. Excluding flaps from the target volume could leave untreated areas of unknown risk; on the contrary, including them could expose both the flap and OARs to higher doses with consequent toxicity. The area at risk is mainly represented by the junction between the flap and native tissues. An area of lesser risk of relapse might be the surface flap with no contact with lateral or deep native tissues, as can be the case in reconstructed tongues.

Statement

Relapses within the reconstructive flaps are rare and occur mainly in locally advanced tumors. The risk area is the junction/interface between the flap and the tumor bed. However, current practice is to include the entire flap and not only the flap-tissue junction. Because data on oncologic results for reducing RT dose to the flap body is missing, the whole flap should be included in the clinical target volume (CTV), also in the early stages. Adequate information should be available (surgical description, clips that outline the tumor bed, postoperative CT with contrast medium) to better delineate CTV. In any case, the flap should be contoured to reduce hot spots, especially at the vascular pedicle.

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)?

Rationale

Postoperative radiotherapy treatment volumes usually include the entire surgical bed, the reconstructed area, the dissected ipsi-

lateral neck, and possibly the contralateral neck. The use of postoperative radiotherapy in OSCC is associated with non-negligible rates of acute and late toxicities, including dysphagia, mucositis, xerostomia, dermatitis, fibrosis, osteoradionecrosis, voice changes, ototoxicity, and hypothyroidism [39]. That is particularly evident whenever large radiotherapy treatment volumes are used. Given that the current volume selection and definition approach is based on historical practice rather than guided by randomized evidence, researchers are presently investigating the possibility of radiotherapy volume de-escalation in oral cavity cancers. An option in terms of volume de-escalation is the radiotherapy omission of the primary tumor surgical bed in case the indication to radiotherapy is driven by adverse features pertinent to the nodal involvement of the neck [40].

Statement

Given the paucity of available data, it is not possible to assess the oncological safety of the omission of the irradiation of the primary tumor bed when the indication to radiotherapy is driven by adverse factors in the neck. However, given the promising results observed by this approach in oropharyngeal cancer, this volume de-escalation strategy may be tested within investigational studies in OSCC.

Discussion

Most of the statements received a high degree of agreement at the first vote showing good concordance between the Experts of the Italian and French Associations.

This result reflects a similar clinical practice among experts despite the lack of solid literature evidence.

Nevertheless, two statements (number 6 and 7) were more debated.

Statement # 6 suggesting that we should offer PORT to improve local control by relying on resection specimen margins' status was quite controversial. Not only was the agreement low in the first round of voting, but when we tried better to investigate the experts' attitude toward a clinical case, the agreement was even lower. Different considerations could have prompted a more conservative approach in the proposed clinical case. Despite the intraoperative positive margin and the G3 differentiation, the patient's smoking habit conveys a risk of second cancer and, therefore, the potential need for future surgical or radiotherapy treatments. Furthermore, the tumor has a DOI of 5 mm and no other risk characteristics. However, the positive intraoperative margin was deep, therefore more difficult to follow up; in fact, the majority of Experts still suggested PORT in this case.

Moreover, in literature, the risk of false-negative margins when positive margins are intraoperatively converted to negative is reported up to 10.9 % if a fresh frozen section on the tumor bed is used. This risk can be perceived as not high enough to compensate for the adjunct toxicity of PORT.

Besides, 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 because some patients receive adjuvant therapy for other reasons than an inadequate resection (e.g., extra-capsular spread and perineural involvement).

Statement # 7, too, achieved a low agreement in the first voting round. Most Experts found the watchful waiting policy not safe in the clinical case proposed. Probably, the patient's young age, the fact that she was a non-smoker, the tumor size and DOI made her perceived at a higher risk of local recurrence, therefore deserving of PORT treatment even if the supporting data are minimal.

Other possible explanations of the apparent contradiction between the vote of the statement and the vote for the clinical case

are: the different definitions of “close margin” in published series (some include between 0 and 5 mm, others less than 2 mm, others consider margins ≤ 1 mm or more as positive)[41–44]; shrinkage of the surgical specimen that may compromise the measurement after resection; different intraoperative surgical margins management (in many studies frozen sections were obtained intraoperatively from the tumor bed and not from the surgical specimen).

Another issue is that this question does not account for the vast heterogeneity in biological behavior seen in OSCC 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.

The high “low agreement” rate for statement #10 reflects the lack of literature on the topic, and we decided not to perform the second round of voting.

An expert consensus-based indication challenged in a clinical case is a common occurrence in the clinical practice of all multidisciplinary groups. Personal experience, patient’s age and comorbidities, the impact of the potential treatment-related toxicities on quality of life, or the feasibility of surgical salvage in case of local relapse are all considerations that fall within the balance of the choices that should be discussed with the patient in case of borderline indication to PORT.

Heterogeneity of clinical situations along with the introduction of novel prognosticators, could increase the number of cases in which indication to adjuvant radiotherapy is not supported by a strong literature evidence. The need for an expert opinion discussion on such “gray zone” could improve the homogeneity of treatment approaches providing valuable tools for daily clinical practice.

Similarly to our work, Experts who commented on a clinical case of a young patient with a pT2N1 OSCC of the oral tongue presented in the Red Journal, suggested radiotherapy not only on the ipsilateral neck but also on the contralateral neck [43]. In contrast, ASTRO guidelines suggest that radiotherapy on the neck may be omitted, although acknowledging the controversy of the matter [9].

The present work has many limitations besides the lack of literature data.

First, the PT provided a narrative review to inform the consensus statements, which is not a standardized objective method for the selection of studies. Nevertheless, the paucity of information retrieved from published studies specifically addressing the considered topics did not allow to provide a more robust methodology. The second issue was the difficulty of transferring literature evidence from the 7th to the 8th TNM AJCC. [44]. To overcome the modification of the staging system classification, we formulated all questions using DOI and tumor size to allow for a broader inclusion of the studies in the literature. However, DOI was not always available in the reviewed studies.

Furthermore, examining the impact of each individual risk factor without taking into account the wide tumor biological heterogeneity might have produced an oversimplification of the presented clinical scenarios.

Due to the “practical” nature of the issues analyzed, we are convinced that the same questions are of interest to the communities of radiation oncologists in other countries worldwide. How much the consensus statements obtained in this work may apply to other countries cannot be established. Various factors can affect the applicability of our expert’s opinions: demographic profile and different risk factors of the population, access to treatments, health reimbursement policies, and access to follow-up.

We believe that international guidelines cannot be generated without high-level evidence, and hence consensus documents generated by experts can be relevant.

Finally, it may be questionable the choice to involve in this working group only experienced radiation oncologists in the absence of specialists of other disciplines (mainly surgeons, medical oncologists and radiologists). Still we wanted to verify the agreement between experts in the radiotherapy community from two different countries on the indication of PORT in “borderline” situations.

There could be different suggestions for overcoming the absence of evidence for these clinical scenarios. Genomic and molecular factors, several biomarkers, and other potential risk factors are under investigation. Still, given the difficulty of conducting studies in the early stages, efforts should probably be concentrated on multicentric data collections (e.g., retrospective or prospective international databases) to develop predictive models and nomograms that can guide the choice of indications and volumes of PORT in low-intermediate risk early-stage patients.

We hope that this work can be an inspiration to develop this type of project, internationally.

The present work aimed to investigate the homogeneity among experts in the field in indicating PORT for some borderline clinical situations. Although the results of this analysis cannot support clinical recommendations, we believe that suggestions provided by experts in the field could help the decision-making process in some particular clinical scenarios. This document, therefore, is intended to support and not replace the multidisciplinary discussion, which remains a fundamental step in all cases.

Conclusions

Evidence-Based Medicine has been insufficiently developed to support the use of PORT in patients with OSCC pT1-2pN0-1(AJCC 7th Ed) in the absence of major risk factors; a consensus opinion of experts is therefore valuable.

Experts of two National Radiation Oncology Associations reached a good agreement in evaluating different scenarios of low-intermediate risk OSCC requiring consideration for PORT.

Given the unclear therapeutic ratio, multidisciplinary discussion and individualized counseling to discuss the risk–benefit ratio of PORT are warranted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Copyright agreement transfer to journal.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2022.10.035>.

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