# CONTROVERSIAL ISSUES IN THE MANAGEMENT OF HEAD AND NECK CANCER: A SWISS MULTIDISCIPLINARY AND MULTI-INSTITUTIONAL PATTERNS OF CARE STUDY

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# CONTROVERSIAL ISSUES IN THE MANAGEMENT OF HEAD AND NECK CANCER: A SWISS MULTIDISCIPLINARY AND MULTI-INSTITUTIONAL PATTERNS OF CARE STUDY

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The heterogeneity in the practice of diagnosis and treatment of head and neck squamous cell carcinoma (HNSCC) is known and expected to be inversely correlated with the level of evidence on a given topic. Literature on various aspects of management of HNSCC were previously published, but were usually restricted within narrow foci. Due to the lack of a similar comprehensive work published so far, the Head and Neck Cancer Working Group of Swiss Group for Clinical Cancer Research (SAKK) decided to perform a survey covering the whole spectrum of controversial topics concerning the diagnosis and the treatment of HNSCC among its member institutions.

This survey was designed to discuss current diagnostic and treatment strategies for HNSCC of all localizations, and to find out probable differences and level of consensus between the participating academic institutions by means of a questionnaire-based pattern of care study. The items in the survey was generated with a scored voting

system by inclusion of all involved centers, and divided into four sections, each of them not exceeding twenty questions: head and neck surgery, radiation oncology, medical oncology and biomarkers.

Surely, the topics and questions were intentionally chosen from controversial areas. Nonetheless, the lack of major consensus in most queried areas provide an insight to head and neck oncologist in terms of the scope of heterogeneity in their practice. Although none of the participated centers being plainly wrong, it is still disturbing to see, that a patient may be treated with quite discrepant diagnostic and treatment concepts even in a relatively small country adhering to up to date evidence based medicine. We believe that this work will serve the head and neck oncologists to be aware of their discrepancies and to stimulate discussion toward standardization of practice and prioritize topics of future clinical research.

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# A Review of Controversial Issues in the Management of Head and Neck Cancer: A Swiss Multidisciplinary and Multi-Institutional Patterns of Care Study—Part 1 (Head and Neck Surgery)

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**Background:** The Head and Neck Cancer Working Group of Swiss Group for Clinical Cancer Research (SAKK) has investigated the level of consensus (LOC) and discrepancy in everyday practice of diagnosis and treatment in head and neck cancer.

**Materials and Methods:** An online survey was iteratively generated with 10 Swiss university and teaching hospitals. LOC below 50% was defined as no agreement, while higher LOC were arbitrarily categorized as low (51–74%), moderate (75–84%), and high (≥85%).

**Results:** Any LOC was achieved in 62% of topics ($n = 60$). High, moderate and low LOC were found in 18, 20, and 23%, respectively. Regarding Head and Neck Surgery, Radiation Oncology, Medical Oncology, and biomarkers, LOC was achieved in 50, 57, 83, and 43%, respectively.

**Conclusions:** Consensus on clinical topics is rather low for surgeons and radiation oncologists. The questions discussed might highlight discrepancies, stimulate standardization of practice, and prioritize topics for future clinical research.

**Keywords: consensus, head and neck cancer, patterns of care, practice patterns, survey**

## INTRODUCTION

The cause of heterogeneity in the practice of diagnosis and treatment of head and neck squamous cell carcinoma (HNSCC) can be associated with multiple factors: differences in health care policies, financial and logistic factors, variations in tradition and medical culture between geographical areas, institutions, or even among physicians working in the same hospital. This heterogeneity in patterns of care is expected to be inversely correlated with the level of evidence on a given topic.

Literature on various aspects of management of HNSCC were previously published. Such reports usually focused on an anatomical site of the head and neck area (1, 2), a specific treatment approach in a clinical discipline (3–6), diagnostic modalities and strategies for diagnosis (7) and follow-up (8). Most of these survey-based studies were performed among institutions sharing the same geography or language.

The Head and Neck Cancer Working Group of Swiss Group for Clinical Cancer Research (SAKK) is a multidisciplinary collective of head and neck cancer specialists from many Swiss institutions meeting in regular intervals and collaborating in various projects. Due to the lack of a similar comprehensive work published so far, the group decided to perform a survey covering a broad spectrum of controversial topics concerning the diagnosis and the treatment of HNSCC among its member institutions.

This survey was designed to discuss current diagnostic and treatment strategies for HNSCC of all localizations undergoing within the Head and Neck Cancer Working Group of SAKK (multidisciplinary and multi-institutional) and to find out probable differences between the participating members/institutions in a pattern of care study.

## MATERIALS AND METHODS

In order to investigate the consensus and heterogeneity in the various aspects of diagnosis and treatment of HNSCC, an online survey via Surveymonkey® (San Mateo, CA) was generated and used by taking the following steps.

1) A steering committee of two head and neck surgeons, one medical oncologist and three radiation oncologists (P-M. P. serving as a consultant for methodology and technical issues) was founded to generate a questionnaire draft, evaluate the answers and writing the final manuscript.
2) Centers in which every patient diagnosed with a HNSCC is presented and discussed on a multidisciplinary tumor board on a regular basis, were defined and contacted through the member list of SAKK by email or phone and a local coordinator for each center was assigned. A rather balanced distribution of the specialists defined as local coordinators from the disciplines of head and neck surgery, medical oncology, and radiation oncology was encouraged. The responsibility of the local coordinator (e.g., the medical oncologist in a center) was to address the part of the questionnaire related to their specialty (medical oncology) and organize the information flow with her/his institutional colleagues from the remaining two major disciplines (head and neck surgery and radiation oncology). As a trade-off between being completely inclusive and realistically conducting the survey, specialists of the above-mentioned three disciplines were asked also to address the questions about imaging, pathology, and maxillo-facial surgery on behalf of the corresponding specialists of these disciplines.
3) The preliminary draft of the questionnaire was generated by the steering committee and sent to each local coordinator. Four categories were generated: head and neck surgery, radiation oncology, medical oncology, and biomarkers. Each center was asked to assign a numerical point for each question, proportionally reflecting its level of importance in the concerning category. Centers were also asked for feedback for any unclear questions, to suggest modifications and new questions.
4) After receiving feedbacks about the draft version, the questionnaire was finalized for improved wording as suggested and based on two criteria: (1) if a new question was suggested from more than one center in same or similar context, it was added to the final version, and (2) each category was limited with a maximal number of 20 questions, and questions with lower cumulative points were eliminated.
5) The final version (**Supplementary Material**) was transformed into an online survey and each center was asked to fill out the questionnaire. Each center is represented by a local coordinator as listed in the co-authors and their affiliations.
6) Answers were evaluated and discussed by the steering committee. Similar topics were grouped together.
7) For each question, an agreement per center is counted as 10 and a disagreement as 0, giving a minimal score of 0 and a maximal score of 100. Missing answers are indicated in the corresponding denominators. Level of consensus (LOC) was calculated by summing all center's answers and categorized as lack of LOC (0–50%), low LOC (51–74%), moderate (75–84%), and high (≥85%).

## RESULTS AND DISCUSSION

Ten centers participated in the survey. The survey was completed on 13 September 2017. Possible practice changes which may have occurred after this date were not reflected in this manuscript. Union for International Cancer Control (UICC) 7th edition (9) was used for discussions related to staging.

Some LOC was achieved in 62% of all topics of interest, while no LOC was found in 38% of questions. High, moderate and low LOC were 18, 20, and 23%, respectively. LOC in each section is summarized in **Table 1**.

Following section provides the results for the items concerning head and neck surgery discipline, each followed by a short discussion if deemed relevant.

### Head and Neck Surgery

#### Diagnostic Measures

➢ *Routine use of diagnostic panendoscopy: high LOC (100%).*

During the diagnosis and baseline workup, all (10/10) centers routinely performed an endoscopy of the upper aerodigestive tract under general anesthesia to detect synchronous secondary

**TABLE 1 |** Level of consensus in each section.

| Section | Overall (>50%) | Low (51–74%) | Moderate (75–84%) | High (85–100%) |
|---|---|---|---|---|
| Head and neck surgery | 50% | 21% | 0% | 29% |
| Radiation oncology | 57% | 14% | 33% | 10% |
| Medical oncology | 83% | 39% | 22% | 22% |
| Biomarkers | 43% | 14% | 14% | 14% |

malignancies. In one center, panendoscopy was not part of the routine workup for patients without history of tobacco or alcohol abuse.

The incidence of synchronous HNSCC around 5–6% (10, 11) is considered high enough to require a diagnostic panendoscopy. Usually, the second primary is of small size and thus curable. Hence, the diagnosis of synchronous lesions usually alters the therapeutic approach. Since $^{18}$F-fluorodeoxyglucose positron emission tomography combined with computerized tomography ($^{18}$FDG-PET/CT) is often performed during the evaluation or treatment planning, some have suggested that a $^{18}$FDG-PET/CT scan could replace endoscopy (12). However, $^{18}$FDG-PET/CT will not detect small superficial lesions which are main focus of endoscopy (13, 14) and Swiss centers are unanimous in using panendoscopy during the initial evaluation. However, this practice can be questioned in non-smoker patients who are diagnosed with a Human Papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) due to the decreased rates of secondary malignancies (15–17).

➢ *Routine diagnostic use of $^{18}$FDG-PET/CT to address loco-regional extension: low LOC (60%).*
➢ *Routine diagnostic use of $^{18}$FDG-PET/CT to address distant metastases or second primary tumors is preferred: high LOC (100%).*

The use of $^{18}$FDG-PET/CT for the purpose of determining the extent of the loco-regional disease is being used in 6/10 centers. In all centers $^{18}$FDG-PET/CT was undergone to detect/rule out distant metastases or locate the primary tumor in the staging of a clinical carcinoma of unknown primary (CUP).

There is no high-level evidence for or against the value of the $^{18}$FDG-PET/CT for an accurate estimation of the extent of the disease, especially for the primary site. Since the gold standard is the assessment of the surgical specimen, a correlation between parameters such as dimensions, volume, depth, or involvement of critical structures obtained radiologically and pathologically is sought (18). Because of the distortions and shrinkage of surgical specimen, few studies have been undertaken especially for $^{18}$FDG-PET/CT. The available data for $^{18}$FDG-PET/CT is restricted to laryngo-hypopharyngeal primaries and is based on a total of 19 patients (19, 20): tumor volume estimation seems accurate but the superficial extension was inaccurate. While surgeons possibly have the direct estimation of the superficial spread to complement the radiologic findings, the widespread use of $^{18}$FDG-PET/CT on target volume delineation for radiation could be questioned.

In some series, the sensitivity of $^{18}$FDG-PET/CT is shown to be superior to CT and MRI for the identification of occult neck lymph node metastases (21). However, the sensibility of all techniques remains low in this setting, around 60% (22). $^{18}$FDG-PET/CT seems to accurately estimate volumes of metastatic neck lymph nodes (23), but adds marginal value to the information obtained from standard imaging modalities, such as CT or MRI in clinically N+ patients (24).

The role of $^{18}$FDG-PET/CT for the diagnosis of distant metastases seems more straightforward, but because of the low incidence of distant metastases from HNSCC at initial presentation, it should be restricted to advanced N stages. Furthermore, $^{18}$FDG-PET/CT is useful to diagnose synchronous cancers such as lung or abdominal primaries, although the superiority over chest CT has not been demonstrated (25).

For unknown primaries, the added diagnostic value of $^{18}$FDG-PET/CT in the pre-HPV era was about 20% (26), while small recent studies and imaging modalities might increase the yield to 50% (27).

## Management of the Neck

➢ *Use of sentinel lymph node biopsy (SLNB) in cN0 oral cavity tumors: no consensus.*

In cN0 oral cavity primaries, SLNB is performed only in 4/10 centers. The reasons not to perform the technique were not queried.

The only randomized prospective study in cN0 oral cavity management concluded that neck exploration during the initial treatment resulted in better overall and disease-free survival than observation followed by therapeutic neck dissection for nodal recurrences. This study validated elective neck dissection, not sentinel neck biopsy (28).

Proponents of SLNB in cN0 neck stress that many patients (70%) will have a non-metastatic neck and therefore will be overtreated by a surgery associated with a substantial morbidity. If this line of arguments is followed, omitting SLNB in oral cavity primaries could be seen as suboptimal surgical oncology management.

The arguments against a SLNB approach when comparing it to the traditional elective neck dissection include: (1) oncologic inferiority, (2) unavailability or unreliability of frozen sections in SLNB, (3) need of a second procedure in case of SLNB positivity, (4) technical challenges and learning curve of the procedure, (5) lack of conviction in the difference in morbidity between the two approaches. The arguments for a SLNB include (1) less invasive approach, (2) second stage completion neck dissection only necessary in the minority of patients (25–30%), (3) selective detection of the lymph nodes of highest risk to harbor metastatic disease, (4) the pathologic workup of sentinel lymph nodes allows for the detection of small metastatic disease such as isolated tumor cells and micrometastases rather than macrometastases only leading to a more accurate staging of the neck.

Because of the pathology processing, most pathologists are reluctant to recommend frozen sections in a sentinel lymph node approach. Since frozen section of a sentinel lymph node usually consists in the examination of a single section, several studies have found this technique is suboptimal or unreliable (29). The unavailability of frozen sections or their lack of reliability makes most centers use SLNB during one procedure, with a subsequent neck dissection performed during a second operation. If the initial panendoscopy is performed as a separate procedure, this could make three general anesthesia for the treatment of a T1 carcinoma.

An elective neck dissection approach with frozen sections of lymph nodes appearing suspicious during the procedure allows for definitive neck management by completing the dissection in the same surgical setting (therapeutic neck dissection) when frozen section yields occult nodal metastasis.

The advocates of SLNB consider that 20–50 cases are necessary during the learning phase of the technique, while most head and neck surgeons dealing with cancer are quite proficient in elective neck dissection. Other problems include the necessity of a nuclear medicine exam, the necessity of the surgeon to be available for the intraoral injection, the pain associated with the awake intraoral injection, and difficulties of scheduling an operating theater with a specific delay after the injection.

Beyond difficulties accepting new techniques, if the morbidity associated with elective supra-omohyoid selective neck dissection was considerable, oncologic head and neck surgeons would have had adopted SLNB readily. However, around half of the centers probably consider that convincing data of such superiority is lacking (30, 31). Probably the main advantage of SLNB is the more thorough pathologic examination of the lymph nodes most at risk, but the exact oncologic significance of micro-metastasis in HNSCC remains to be determined.

Whether, an N0 neck is treated by elective neck dissection or SLNB, follow-up is essential, especially for necks not requiring adjuvant therapy. Radiologic surveillance could be accomplished by various modalities (CT, MRI, and US) with US-FNAC being the most accurate and cost-effective (32, 33). This neck follow-up policy is valid in other situations where the primary is treated surgically and the neck not treated, for example an early laryngeal primary.

➢ *Standard use of any up-front neck dissection strategy for advanced neck stages: no consensus.*

In the chemoradiotherapy (CRT) setting, 4/8 centers pursue a systematic elective neck dissection strategy. Three of those 4 perform an up-front neck dissection in case of a cN2/3 disease, whereas a planned neck dissection 8–12 weeks after CRT is preferred in the fourth center.

CRT has become the preferred strategy for pharyngeal (34) and laryngeal (35) primaries in some centers. Advanced stage disease is often associated with bulky (N3) or multiple (N2b/c, N3) neck lymph node metastasis and the optimal strategy to treat these metastatic neck diseases remains controversial. Possible strategies include: (1) up-front neck dissection before CRT; (2) planned neck dissection after CRT; or (3) radiologic surveillance. Several Swiss centers have pursued the up-front neck dissection since the 1990's (36, 37) and have not found convincing arguments to change their strategy (38). Until recently, the debate has been centered on whether a planned neck dissection after CRT is necessary and whether a post-treatment $^{18}$FDG-PET/CT scan can be used to select patients needing surgery. This has been settled in a randomized controlled trial showing that a post-treatment $^{18}$FDG-PET/CT scan would safely identify patients not requiring neck dissection after CRT (39). The question of up-front neck dissection vs. post-CRT treatment is the subject of an ongoing prospective multicenter study in Switzerland (NCT02918955).

➢ *Systematic division and reporting of lymph node levels after a neck dissection: no consensus.*

When performing a neck dissection, 4/8 centers systematically mark the lymph node stations before sending the material to pathology.

Whether neck dissection is therapeutic (cN+) or elective (cN0), one of its main purposes is to determine which patients are candidates for adjuvant therapy (40). Since neck irradiation is no longer performed by lateral opposed fields but by intensity modulated radiotherapy optimized via inverse planning, precise knowledge of the metastatic groups is crucial to the radiation oncologist. The American Head & Neck Society recommends that neck contents should be divided into levels and sublevels by the surgeon in the operating room immediately after the specimen is removed, each level being placed into a separate container and labeled appropriately (41, 42). One possible exception to these guidelines is obtaining negative margins on bulky and obviously metastatic nodes, which might require keeping two or three adjacent levels together. Even a pathologist specialized in HNSCC has trouble deciding on the limits of individual groups without the orienting presence of the hyoid bone and of the cricoid cartilage, especially on a neck dissection specimen fixed in formalin.

➢ *Impact of depth of tongue infiltration on the decision to perform a neck dissection: no consensus.*

For the carcinoma of the lateral side of the tongue, the depth of invasion does not influence the decision to perform a neck dissection in two centers. In five centers, 2–8 mm depth of invasion (mean and median 4 mm) would change the treatment strategy. Three centers did not provide any answer.

Convincing data on the relationship between tumor thickness and prognosis in oral cavity squamous cell carcinoma date back to the 1980's (43). Recently and after this questionnaire was completed, depth of invasion was incorporated in the T staging system for oral cavity carcinoma and validated in recent studies (44, 45). The treatment strategy, especially for neck management, should be more aggressive with depth of invasion >4 mm (44, 46).

## Management of Bone and Peri-Neural Invasion

➢ *Adequate resection margin of mandible in case of bone invasion: no consensus.*

In case the CT and/or MRI suggest a 2 cm long cortical defect on the body of the mandible with a 5 mm depth of invasion without any enhancement of the mandibular nerve, resection margins of 1, 2, and 3 centimeters would be used in 3, 2, and 1 centers, respectively. Four centers did not provide any answer.

Three decades ago, Slootweg and Muller (47) described two patterns of mandibular invasion: an "erosive pattern" carrying a good prognosis and associated with direct bone infiltration by the carcinoma, on a broad front, without infiltration of the periodontal ligament and of the inferior alveolar nerve. The "infiltrative pattern" carries a worse prognosis and histologically exhibits an aggressive invasion of mandibular cancellous marrow, periodontal ligament, as well as a frequent perineural invasion of the inferior alveolar nerve. Subsequent series (48, 49) have confirmed two- to three-fold higher recurrence rates and

approximately halved survival in the infiltrative pattern of invasion. Furthermore, because cortical bone invasion does not carry a poor prognosis, it has been suggested that to stage it as T3 (50).

The literature rarely speaks of "erosive" and "infiltrative" pattern but often refers to cortical vs. marrow infiltration. Preoperative performance for mandibular marrow invasion of MRI carries a high sensitivity (95–100%) but a lower specificity (60–70%) (51, 52).

According to the Dutch Guidelines Database (53), in the erosive pattern a bony margin of 1 cm is sufficient, while the infiltrative pattern requires bony margins of 1.5 cm and invasion within the canal of the mandibular nerve 2 cm. While these recommendations are cited in the literature, their exact scientific foundation is unclear.

➢ *The indication to perform a mandibulectomy in case of mandibular nerve invasion: no consensus.*

In case of an oral cavity tumor where the MRI suggests an enhancement of the mandibular nerve and the CT shows no erosion of the mandible, 2/8 centers would perform a mandibulectomy, whereas the rest would not or decide based on the intraoperative assessment.

Involvement of the inferior alveolar nerve is associated with a worse prognosis and requires more extensive resection (54). The question thus addresses the possibility of assessing perineural spread in mandibles with an intact bony cortex. Techniques derived from MR neurography using special sequences, such as 3D double-echo steady-state with water excitation have been shown to have high sensitivity (95–100%) for detection perineural spread (55, 56). While the radiological results have been pathologically validated for HNSCC in general, no publication has specifically targeted the inferior alveolar nerve.

## Optimal Resection Margins

➢ *Adequate resection margin should be 5 mm in T1-2 oral cavity tumors: high LOC (89%).*

In a T1-2 oral cavity tumor, the adequate resection margin was defined as 5 mm in 8 centers. For one center, it was defined as 10 mm. One center did not provide an answer.

A "sufficient" pathological margin implies a low risk for tumor recurrence and possibly makes adjuvant treatment redundant. However, this issue for oral squamous cell carcinoma is still a subject to debate. Combined analysis (57) of the EORTC 22931 (58) and the RTOG 9501 (59) trials concluded that the adverse prognostic factors requiring adjuvant CRT following surgical resection included extracapsular extension (ECE) of metastatic lymph nodes and positive margins. Somewhat provocative results were published from the Toronto group evaluating oral cavity pN0 patients with margins smaller than 5 mm, treated only surgically: negative margins of 1–5 mm were not associated with inferior local control; while tumor thickness, perineural invasion, and pattern of invasion were predictive of local recurrence (60). The data are in agreement with other studies, establishing pathological scores for resected oral squamous cell carcinoma (61). A review of the literature on the subject seems to confirm that most studies consider 5 mm as a negative margin (60), following the Guideline of the UK Royal College of Pathologists: >5 mm clear, 1–5 mm close, and <1 mm positive margin (62). This discussion pertains to margins assessed by the pathologist and given about 50% shrinkage of the specimen (63), resection should start about 10 mm from the tumor edge.

## Treatment of Laryngo-Hypopharyngeal Primaries

➢ *The status of vocal cord mobility is a key criterion for primary treatment decision: low LOC (63%).*

In glottic larynx cancer, vocal cord mobility affects the treatment decision in 5/8 centers.

The presence of vocal cord mobility indicates that there is probably an infiltration of the vocal muscle or in rare cases of the crico-arytenoid joint. This is a well-recognized adverse prognostic factor and has been incorporated in the TNM classification for glottic cancer since 1988: an otherwise T1 carcinoma would become a T2 in case of hypomobility, and T3 for complete immobility (64).

The main implication of vocal cord mobility impairment is that the tumor is much bulkier (65) and has extended laterally. Because of this, endoscopic surgery will be more extensive (66) and thus result in more important functional voice and swallowing impairment. Furthermore, especially for T3 cases, the resection might not be possible endoscopically and open partial laryngectomy might become the procedure of choice (67). Even if radiation is the chosen treatment modality, impaired vocal cord mobility carries the main adverse prognostic factor in T2 glottic cancers (68) and is associated with suboptimal cure rates (69).

Why vocal cord mobility does not bring a consensus higher than 63% is difficult to understand. Since vocal cord mobility clearly influences the surgical approach, only possibility is that in some centers, all low stage (T1–T2) carcinoma are treated with radiation therapy and surgeons do not see the mobility as a decisive factor.

➢ *Radiologic imaging is reliable to assess laryngeal cartilage invasion: high LOC (86%).*

Radiologic imaging modalities are considered to be reliable to assess cartilage invasion of larynx cancer in 6/7 centers.

Cartilage invasion has a major impact in the optimal management of laryngeal cancer (see the following question). Cartilage invasion cannot be assessed clinically and therefore, a reliable diagnostic test is essential. The main options are CT and MRI.

It should be kept in mind that the gold standard of evaluating performance of radiological exams is definitive pathology and thus studies evaluating CT and MRI only include patients that underwent surgery which is often total laryngectomy. Thus, compared to the general population of patients with laryngeal cancer, cartilage invasion is probably over-represented, and this bias probably leads to an overestimated positive predictive value (PPV) and to an underestimated negative predictive value (NPV) for the diagnostic modality under investigation.

A recent meta-analysis of CT shows a prevalence of cartilage invasion between 19 and 27%, a PPV ranging between 44 and 80%, and relatively high NPVs ranging between 85 and 100% (70). In other words, false positive CT scans are frequent, while false negative CT scans infrequent and according to the authors, false

negative cases stem from minor cartilage invasion, which might not be a contra-indication to conservative treatments, being CRT or partial laryngectomies. Similar results were found in classical studies on the subject (71). However, the performance of CT for extralaryngeal spread is insufficient with NPVs of only 71% (72), making CT not reliable for selecting patients for organ preservation strategies.

MRI can improve the NPVs of CT above 95% in experienced hands (18) and because of its excellent soft tissue evaluation, is the preferred evaluation method for extralaryngeal spread (73). The PPVs are however not better than CT.

➢ *To prioritize larynx preservation strategies in cT4a laryngeal primaries or not: no consensus.*

The first choice of treatment in cT4a laryngeal primaries is always to pursue a larynx preservation strategy in one center. Four centers prefer CRT only if the cartilage is not destructed. Other five centers always prefer total laryngectomy followed by adjuvant treatment.

T4a laryngeal carcinoma by definition invades the cartilaginous framework of the larynx and remains best treated by a multimodality regimen, starting with total laryngectomy (74). This has been reemphasized in the recently updated guidelines from the American Society of Clinical Oncology: for "extensive T3 or large T4a lesions and/or poor pretreatment laryngeal function, better survival rates and quality of life may be achieved with total laryngectomy rather than with organ-preservation approaches and may be the preferred treatment strategy" (74).

The debate originated after the VA trial (75) demonstrating that some T4a larynx tumors could be preserved by a CRT protocol. However, in this study, 56% of T4a patients underwent total laryngectomy, especially in glottic primaries with cartilage invasion. Because of that, this population was specifically excluded from the RTOG 91–11 trial (76). This trial was based on the 5th UICC classification of 1992, and the change in the T3–T4 larynx T-staging introduced in the 6th UICC edition added to the confusion. Small inner cortex erosion was classified as T4a in the 5th edition and as T3 in the 6th edition. It is probably safe to say that present day T4 patients were not included in the RTOG 91–11 trial.

As discussed in detail in the guideline of the American Society of Clinical Oncology (74), several high-quality retrospectives studies (77–82) support the better survival of T4a laryngeal cancer patients treated with total laryngectomy, rather than CRT protocols.

➢ *The preferred treatment of cT1/2 hypopharyngeal cancer is non-surgical: low LOC (60%).*

A cT1/2 hypopharyngeal primary is never treated surgically in 6/10 centers.

Hypopharyngeal primaries are associated with low survival (5-year overall survival about 30%) that has barely improved over the years (83). Radiotherapy or CRT are often considered as the standard treatment for hypopharyngeal primaries (84, 85), whereas surgical series with voice preservation are not new (86). No randomized trial has addressed early hypopharyngeal carcinoma. For early T1–T2 primaries, small series with surgical resection, often endoscopic and without adjuvant irradiation, provide encouraging results (**Table 2**).

**TABLE 2 |** Results of early stage hypopharynx cancer patients in selected surgical series.

| References | Stage I (*n*) | Stage I-5yLRC | Stage II (*n*) | Stage II-5yLRC |
|---|---|---|---|---|
| Laccourreye (87) | | | 34 | 95% |
| Eckel (88) | 10 | 75% | 22 | 75% |
| Steiner (89) | 10 | 95% | 23 | 95% |
| Kutter (90) | 24 | 90% | 28 | 90% |
| Martin (91) | 7 | 73% | 19 | 59% |
| *K*aratzanis (92) | 45 | 90% | 74 | 83% |

*5yLRC: 5-years loco-regional control; n: number.*

## CONCLUSION

The findings of our survey indicate a low LOC among head and neck oncologists working in academic and multidisciplinary setting in 10 Swiss institutions. Regarding the results and the discussion concerning the specialties other than head and neck surgery, the reader is advised to read the corresponding parts of this article. The highest LOC was achieved among medical oncologists, whereas the lowest was observed among head and neck surgeons. On the other hand, this level of disagreement may also depend on the topics chosen for the survey, and not necessarily the heterogeneity within the disciplines. It is also interesting to witness a low LOC regarding topics, where a high level of evidence actually does exist, and vice versa. This article is expected to serve the head and neck oncologists to be aware of their discrepancies and to stimulate discussion toward standardization of practice and prioritize topics of future clinical research.

## DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the manuscript/**Supplementary Files**.

## AUTHOR CONTRIBUTIONS

GH, MB, OE, PD, and PP: conception and design. OE and PP: collection of data. Generation of the initial and final versions of the questions, drafting of the manuscript, and approval of the final version by all co-authors.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2019.01125/full#supplementary-material

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# A Review of Controversial Issues in the Management of Head and Neck Cancer: A Swiss Multidisciplinary and Multi-Institutional Patterns of Care Study—Part 2 (Radiation Oncology)

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**Background:** The Head and Neck Cancer Working Group of Swiss Group for Clinical Cancer Research (SAKK) has investigated the level of consensus (LOC) and discrepancy in everyday practice of diagnosis and treatment in head and neck cancer.

**Materials and Methods:** An online survey was iteratively generated with 10 Swiss university and teaching hospitals. LOC below 50% was defined as no agreement, while higher LOC were arbitrarily categorized as low (51–74%), moderate (75–84%), and high (≥85%).

**Results:** Any LOC was achieved in 62% of topics ($n = 60$). High, moderate, and low LOC were found in 18, 20, and 23%, respectively. Regarding Head and Neck Surgery, Radiation Oncology, Medical Oncology, and biomarkers, LOC was achieved in 50, 57, 83, and 43%, respectively.

**Conclusions:** Consensus on clinical topics is rather low for surgeons and radiation oncologists. The questions discussed might highlight discrepancies, stimulate standardization of practice, and prioritize topics for future clinical research.

**Keywords: consensus, head and neck cancer, patterns of care, practice patterns, survey**

# INTRODUCTION

This is the second part of the article "A Review of Controversial Issues in the Management of Head and Neck Cancer: A Swiss Multidisciplinary and Multi-Institutional Patterns of Care Study," providing the results for the items concerning radiation oncology discipline, each followed by a short discussion if deemed relevant.

The details of the methodology is presented in the first part of this series.

# RESULTS AND DISCUSSION

## Radiation Oncology

### Definition and Compartmentalization of Target Volumes

➢ *Omitting the elective treatment of the contralateral neck is safe in well-lateralized primaries of the tonsil: moderate LOC (80%).*

For a cT2 carcinoma of the tonsil, the uninvolved contralateral neck is omitted if the tumor is well lateralized and with <10 mm of the superficial mucosa of soft palate and/or base of tongue in 8/10 centers. The remaining two centers always perform bilateral treatment.

Although no prospective randomized trial was performed to exclusively answer this question, there is mounting evidence to support the safety of ipsilateral treatment of well-lateralized OPSCC. As endorsed by the American College of Radiologists, treatment can be limited to the ipsilateral side in tonsil primaries with a N0-1 nodal stage when the primary exhibits <1 cm invasion into the soft palate or base of tongue (1). Other retrospective series also showed excellent results with N2b or unilateral N3 cases (2–4) and in other oropharyngeal (2, 5) as well as oral cavity subsites (6). However, no prospective randomized trial results for this question are available. In the recently updated international consensus guidelines, this issue is still regarded as controversial, and caution is advised especially for nodal stages above N2a (7).

➢ *Compartmentalization of the tumor bed and the levels of the nodal basin for post-operative radiotherapy in terms of dose and volume: no consensus.*

In 3/10 centers, the post-operative primary tumor bed is not included in the target volumes, if the indication for adjuvant radiotherapy arises only due to nodal factors after neck dissection. The remaining 7 centers do not separate the tumor bed and the dissected nodal levels.

Similarly, regarding the elective/low risk volumes in the post-operative setting, in 5/10 centers the whole post-operative neck is considered as an inseparable target compartment. In the other half of the centers, the levels are thought of separable compartments, and, in eligible cases based on the nodal distribution pattern reported by the pathology, radiotherapy to a portion/level of the post-operative neck is omitted.

The selection of radiotherapy target volumes is strongly influenced by tradition. More than a decade ago, the landmark EORTC 22931 and RTOG 9501 trials defined the major and minor risk factors for the indications of post-operative CRT and radiotherapy, respectively. However, the question of the necessity of such an "all or nothing" approach concerning different parts of the target volume(s) remains unanswered. Surely, one of the arguments for irradiating the primary tumor bed in case of multiple nodes with or without ECE has been the general loco-regional recurrence risk and difficulties to irradiate the primary tumor recurrences after previous nodal irradiation, especially in the past due to technical limitations. Nevertheless, from a purely medical and not a technical perspective, it is not clear, why the post-operative primary tumor bed should be irradiated due to multiple nodal positivity and/or ECE, whereas the same patient and tumor bed would not receive any radiation if the neck would have been pN0-1. Similarly, there is no data indicating perineural extension as a risk factor for nodal recurrence.

Concerning the post-operative nodal target volume, half of the radiation oncologists still treat the entire surgical bed covering both the primary tumor bed and the operated neck (at least the involved side). On the other hand concerning the post-operative primary tumor target volume, most oncologists still treat the entire surgical bed at least within a low risk volume irrespective of risk factors specifically related to the primary tumor or the neck (8). Nevertheless, the recently demonstrated long-term results of a prospective phase II study supports the safety of this compartmentalization approach (9). On the contrary, data indicating the risk of compartmentalization approaches also exist (10). However, such retrospective studies reporting unusually high recurrence rates should be critically interpreted in the lack of description of surgical techniques and radiotherapy approach especially in terms of online and offline image guidance protocols within the frame of the limited volume approach.

➢ *Adaptation of the dose or target volumes (except for the replacement of anatomical barriers) after induction chemotherapy is not preferred: moderate LOC (80%).*

After an induction chemotherapy, 8/10 centers would not adapt the dose or target volume (except for anatomical changes) regardless of a partial or complete response. In one center clinical target volume (CTV) would be adapted based on tumor shrinkage. In another center, both dose and volume would be de-escalated based on response.

For radiotherapy planning after induction chemotherapy radiotherapy, Salama et al. (11) recommended the irradiation of pre-induction volumes with full dose even in case of a clinical complete response while taking the volumetric changes in anatomical structures and barriers into consideration. Despite of that, there is a substantial heterogeneity in target volume definition concepts among different institutions (12, 13). Although not part of the main scientific question and primary endpoint, the target volumes and prescribed doses after a clinical response to induction chemotherapy were adapted in some contemporary prospective clinical trials (13, 14). In a recently published phase III randomized trial the non-adapted and adapted volume approaches after induction chemotherapy for nasopharyngeal cancer were compared (15). The investigators did not report any inferior oncologic outcome with the adapted strategy. However, volume reduction did not result in a substantial reduction of toxicity or improvement in quality of life except for a few among the many investigated domains.

It is also worth to note, that this study was underpowered to detect a non-inferiority in oncologic outcome in this regard. Moreover, there are quantitative analyses indicating that it is unsafe to adapt the high-risk volume based on the shrinkage of the macroscopically visible tumor in radiological imaging after a non-definitive treatment (16).

➢ *Definition of treatment volumes for the treatment of CUP: no consensus.*

No consensus was reached concerning the treatment volumes in CUP situation. Treatment volumes of a CUP always contain bilateral neck and potential mucosal sites (4/10); only the involved side(s) of the neck (3/10); and involved side(s) plus corresponding mucosal sites only in case of human papillomavirus (HPV) or Epstein-Barr Virus (EBV) positivity (2/10). One center always treats the mucosal sites but only with the involved side(s) of the neck.

The literature about the optimal management of CUP is conflicting. There is no convincing data supporting the elective irradiation of the contralateral uninvolved neck in the modern series (17–19), whereas the reports indicating the superiority of bilateral irradiation are outdated in terms of radiotherapy and imaging modalities (20). Some facts are worth considering for the selection of the optimal strategy (21–25): (1) The risk of nodal recurrence and distant metastases is at least twice higher than the subsequent appearance of a mucosal primary tumor ($\leq$10%). (2) The emergence rates of mucosal primary tumors after unilateral neck irradiation are similar to the risk of occurrence of metachronous second primary tumors in patients cured of a known head and neck SCC primary. (3) Survival rates are not related to the appearance of the primary tumor (21, 22, 26). Last but not least, doubling the target volume by means of bilateral irradiation substantially contributes to the toxicity burden, which would outweigh any marginal oncological benefit, which rather seems non-existent (18, 19).

➢ *Use of an isotropic margin and respecting the anatomical barriers is the preferred method to generate high-risk CTVs around the gross tumor volume (GTV): low LOC (60%).*

When contouring the high risk CTV around the primary tumor, 3/10 centers use the predefined anatomical subsites defined by Eisbruch et al. (27). One center treats these sites with 60 Gy by using an intermediate risk volume. The rest of the centers only use an anatomical isotropic margin and crop this volume from the anatomical barriers as suggested by Caudell et al. (28), who also reported a non-inferior outcome with the geometric extension approach compared to treatments with predefined anatomical subsites.

The survey was completed before the recent publication of the international consensus guidelines for the delineation of the primary tumor CTV by Grégoire et al. (29), in which the isotropic geometric expansion concept was also endorsed. These guidelines recommend the use of 5 and 10 mm around the GTV for high-risk and prophylactic CTVs, respectively. Nevertheless, these volumes shall be manually cropped by taking the anatomical barriers into account. The exceptions to this rule were defined for early stage glottic and locally-advanced stage hypopharyngeal primaries. For the former, prophylactic volumes were deemed unnecessary, whereas for the latter, a 15 mm margin in the cranio-caudal direction was suggested.

➢ *A restricted use of intermediate-risk dose only in the levels with ECE is preferred: high LOC (90%).*

In case of pathologically-confirmed ECE, only the involved levels are treated with an intermediate dose of 60–66 Gy in 9/10 centers. The rest of the neck is treated with an elective/low-risk dose. In one center, all involved levels are treated with 64 Gy irrespective of ECE, and the uninvolved levels are treated with a lower dose, since systematical anatomical marking of the lymph node levels on the surgical specimen is not performed sufficiently.

Traditionally, some head and neck cancer oncologists were concerned about the intraoperative spillage of the tumor cells, in case of ECE and/or positive resection margins. However, even in the twin landmark RTOG (9501) (30) and EORTC (22931) (31) trials, only the high risk areas were boosted up to 60–66 Gy. In the current international consensus guidelines for the delineation of nodal target volumes, a compartmentalized approach is recommended. It is worth to note, that the evidence level supporting the inclusion of non-involved postoperative levels into the prophylactic volumes even in the N+ neck is low, and this approach is rather based on tradition (8, 27). Nevertheless, it seems, that it is not always possible for the radiation oncologists of these 9 centers to compartmentalize the intermediate-risk volume, since only 4 centers systematically mark the lymph node levels on the surgical specimen before sending them to the pathology.

➢ *Use of tailored planning target volumes (PTV) for different anatomical subsites: no consensus.*

In some anatomical subsites (e.g., larynx, tongue, soft palate), 4/10 centers use additional geometric margins concept to compensate for possible organ movement. In one of these centers, an anisotropic margin for larynx and soft palate primaries are used. For the remaining 6 centers, such an internal target volume concept is not used based on subsite. On the other hand, the policy of these centers is to re-plan and adapt the margins according to movement based on daily imaging, if considered necessary.

The conventional fields in the 2D radiotherapy era encompassed the target volumes with enough margins to compensate for movement. As an example, the larynx is known to move up to 20–25 mm craniocaudally (32, 33). Despite of that, the traditional 2D fields did not require further enlargement due to the technical features of 2D-conventional radiotherapy (32). However, the sharp dose fall-off profile of intensity-modulated radiotherapy (IMRT) to spare sensitive tissues allows less tolerance for target volume delineation errors and marginal misses. Studies performed with volumetric imaging and dynamic MRI demonstrated the necessity of extra margins of 5 mm to every, and 6–7 mm to cranial direction for the primaries of soft palate, larynx, and hypopharynx (34, 35). Recently published data by Bruijnen et al. (36)

demonstrate considerably shorter ranges of intrafractional tumor motion <3 mm (95th percentile—excluding swallowing) with a decreasing order from laryngeal to oropharyngeal and nasopharyngeal primaries, respectively. However, in addition to intrafractional, the interfractional positional differences of soft palate, uvula, larynx, and tongue; moreover, the elastic changes in the relationship of different subvolumes of PTV [e.g., primary tumor and involved lymph node(s)] are more difficult to quantify and to tackle with. Unacceptable variations seen with daily imaging should lead to adaptive re-planning as quickly as possible. As a less systematically reported issue, swallowing frequency, and positional changes in the pharyngo-laryngeal anatomy during the treatment may be associated with changing treatment anxiety, consistency of saliva, and increasing mucositis throughout the course of treatment.

➢ *Definition of high- and low-risk volumes for laryngeal primaries: no consensus.*

Laryngeal primaries are treated by including the whole larynx in the high-risk volume in 2/10 centers. Five centers prefer to treat the primary tumor with a predefined margin. In the rest of the centers, the larynx (in one center the involved hemilarynx) is considered as a compartment which shall be treated with an elective dose. The primary tumor is treated to a high dose with a predefined margin.

The 3D volume definition for laryngeal primaries was just a translation of traditional 2D fields to the 3D era. This resulted in the continuation of treating the whole larynx within the high-risk volume receiving the highest dose, even for early stage tumors without infiltration to cartilaginous structures, contralateral extension, etc. This concept is still being used in some centers. At the other end of the spectrum, hemilarynx (37, 38), even single vocal cord irradiation (39) techniques were developed for early stage laryngeal primaries, yielding excellent results. For locally advanced laryngeal primaries, the inclusion of the whole larynx into the prophylactic target volumes is not recommended anymore by current consensus guidelines (29).

## Dose and Fractionation Concepts

➢ *The use of simultaneous integrated boost (SIB) is the preferred boost technique: moderate LOC (80%).*

Centers were asked to provide information about the boost techniques and dose/fractionation regimens for target volumes (**Table 1**). Simultaneous integrated boost (SIB) and sequential boost (SEQ) techniques are used in 8 and 2 centers, respectively.

IMRT with inverse planning allows SIB to multiple target volumes during the course of radiotherapy by means of a dose painting approach. The beams used to deliver the planned dose to the high-risk volume are exploited for the dose application to the encircling low-risk volume(s). In contrast to the traditional sequential shrinking field/volume approach, SIB enables the generation of single-phase plans with the possibility of a more flexible plan optimization process. This allows an advantage over SEQ in terms of better control of dose around the high risk PTV and reducing the unwanted high dose areas within. Although there are countless retrospective and prospective studies, in which patients were treated with SIB, no prospective randomized trial compared both technical modalities until recently. Lertbutsayanukul et al. (40) conducted a phase III randomized trial with the primary endpoint of acute and late toxicities during and after SIB vs. SEQ for the treatment of nasopharyngeal cancer. This study with a superiority design did not show any statistically or clinically significant difference in toxicity or oncologic endpoints. In theory, similar studies including other four major HNSCC subsites are needed. However, the toxicity results reported by Lertbutsaanukul et al. can be extrapolated to other subsites, considering the fact, that the treatment of nasopharyngeal cancer involves the largest and most complex target volume and organs at risk in the head and neck area.

➢ *Hypofractionation for the treatment of early stage glottic larynx cancer: no consensus.*

For early stage glottic larynx cancer, 4/10 centers perform hypofractionated radiotherapy ($\geq$2.25 Gy per fraction).

There is mounting evidence supporting the shortened treatment time in the treatment of stage I-II glottic larynx cancer for increased tumor control (41). Reports on large series from cancer registries (42, 43), prospective clinical databases (44), meta-analyses (41), and prospective randomized trials (45–47) demonstrated favorable results with altered fractionation either by means of hypofractionation and/or acceleration. The possible effect of hypofractionation is probably based on its treatment-accelerating effect, rather than the exploitation of the β value (44, 45, 48, 49). As reported so far, long-term toxicity is not a major point of concern with accelerated or moderately-hypofractionated irradiation (46, 47, 50), which is in line with the biological rationale regarding the time factor (49). It can be safely applied and may be preferred due to its benefits in terms of costs, logistics, and patient comfort. Hypothetically, the therapeutic window may also be widened with the use of contemporary treatment techniques (39). In this regard, impressive clinical results of a prospective study using SBRT (58.08 Gy in 16 fractions) with the primary endpoint of voice quality deserves attention (39): 2 years local control and overall survival of 100 and 90%, respectively, without any grade 3 or above toxicity. When compared with a historical control group, which was treated to the whole larynx (66 Gy in 33 fractions), single vocal cord irradiation yielded less grade $\geq$2 acute toxicity (17 vs. 66%, $p < 0.01$) and lower voice handicap index scores in almost all follow-up visits performed in regular short intervals until 18th month ($p < 0.01$). In contrast, a recently published phase I trial with extremely hypofractionated radiotherapy using robotic SBRT yielded inferior local control and not necessarily less toxicity compared to the literature (51). This was possibly because of the irregular laryngeal motions occurring during a protracted dose delivery and the lack of the current robotic SBRT unit's capability to handle them.

➢ *Altered fractionation is preferred in case of radiotherapy without concomitant systemic agents: moderate LOC (70%).*

Altered fractionation is used in 7/10 centers. In the corresponding question, altered fractionation was defined as any treatment not fitting to the following arbitrary description in the questionnaire: single fraction/day throughout the whole treatment course with a fraction size between 1.8 and 2.2 Gy for the high-risk volume. The distribution among the

**TABLE 1 |** Dose-fractionation schedules for definitive (chemo)radiotherapy.

| Center | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| High risk dose (Gy)/fractions | 69.96/33 | 72/36 | 70/35 | 66/30 | 69.63/33 | 70/35 | 69.3/33 | 70–76/35-38* | 69.63/33# | 70/33 |
| Intermediate risk dose (Gy)/fractions | 59.4/33 | 66/33 | 66/33 | 60/30 | 66/33 | 60/35 | 56.1/33 | 64/32 | 60/33 | 59.4/33 |
| Low risk dose (Gy)/fractions | 52.8/33 | 54/30 | 50/25 | 54/30 | 56/33 | 54/35 | 52.8/33 | 50–54/25-27* | 54/33 | 52.8/33 |
| Boost technique | SIB | SIB | SEQ | SIB | SIB | SIB | SIB | SEQ | SIB | SIB |

*SEQ, sequential boost; SIB, simultaneous integrated boost.*
**Higher dose in case of no concomitant systemic therapy.*
*# 70 Gy in 35 fractions for "large" tumors.*

altered fractionation regimens were as following: acceleration (six fractions per week or concomitant boost) in 6 centers, hyperfractionation in 3 centers (two centers use both strategies). Three centers combine systemic agents with hyperfractionation and/or acceleration.

Compared to normofractionated radiotherapy, the survival and loco-regional control benefit of altered fractionation is proven, particularly in the form of hyperfractionation in the definitive radiotherapy setting without concomitant systemic treatment (52). However, this added benefit of altered fractionation wanes out with increasing age (53), most probably due to competing risks for death, such as comorbidities. Therefore, the role of altered fractionation may be questioned in the selected elderly and/or fragile patients who are deemed not to tolerate systemic treatment.

There are numerous combinations of systemic agents and altered fractionation schedules for the treatment of HNSCC (54). In summary, there seems to be no benefit of combining accelerated fractionation and concomitant chemotherapy. For example, the GORTEC 99-02 trial randomized 840 patients into three arms with the primary endpoint as loco-regional control. In one of the two arms with chemotherapy (carboplatin and 5-fluorouracil), patients received 70 Gy in 35 fractions over 7 weeks, and in the other arm 70 Gy in 40 fractions over 6 weeks (40 Gy in 20 fractions over 4 weeks followed by 30 Gy in 20 fractions over 2 weeks). At 7 years, the difference in outcome was statistically not significant among the arms. Acute mucositis and feeding tube requirement were higher with accelerated radiotherapy by means of concomitant boost and chemotherapy than normofractionated radiotherapy and chemotherapy. Late toxicities were comparable (55, 56). The RTOG 0129 randomized 743 patients into two arms, both with concomitant cisplatin: normofractionated radiotherapy (70 Gy in 35 fractions over 7 weeks with three cycles of cisplatin) versus accelerated radiotherapy by means of concomitant boost (36 Gy in 18 fractions over 3.5 weeks followed by 36 Gy in 24 fractions over 1.5 weeks with two cycles of cisplatin). At 8 years, no significant difference in overall survival (primary endpoint), any oncological endpoints, or acute and late toxicities was observed (57). The question left unanswered is whether there would be an added benefit of combining hyperfractionated radiotherapy and concomitant chemotherapy compared to conventionally fractionated radiotherapy and chemotherapy. The statistical models indicate a potential advantage in this regard (58), which needs to be confirmed by prospective randomized trials. Unfortunately, it is quite unlikely to witness any large-scale trials conducted to answer this question due to the lack of financial attractiveness for the industry. The EORTC 22962 trial would have been the ideal phase III study with four arms, comparing normofractionated radiotherapy (70 Gy in 35 fractions) with hyperfractionated radiotherapy (80.5 Gy in 70 fractions) in 7 weeks with or without cisplatin. Unfortunately, the trial terminated prematurely due to slow accrual after recruiting only 57 patients. The above-mentioned RTOG 0129 was designed with the MD Anderson combined boost schedule. It is unknown what would have happened if the hyperfractionated arm of the RTOG 9003 (59) was chosen instead of the accelerated regimen.

➢ *There is no standard in terms of dose prescription and plan normalization: no consensus.*

During the radiotherapy planning process, 5/9 centers use the median dose to PTV for dose prescription. Of those, only 2 centers normalize the plan according to a minimum dose coverage criterion (e.g., $D_{95\%} = 95\%$ of the prescribed dose).

The authors of the ICRU 83 report (60) only suggested to prescribe on the median absorbed dose to the target volume ($D_{50\%}$), but without a strict restriction of the use other dose-volume prescription values. In practice, there is a large variety in internal clinic protocols and clinical trial protocols. As an example, in the modern EORTC trials for HNSCC (e.g., NCT02984410, NCT01880359), it is requested to prescribe the dose on $D_{50\%}$, and obtain a dose coverage of at least 95% of the prescribed dose to the 95% of the PTV, whereas normalization to $D_{95\%}$ instead of $D_{50\%}$ is demanded in the RTOG protocols (e.g., NCT01302834, NCT01953952, NCT00265941). It is likely, that no consensus will exist in the near future. Nevertheless, it is important to be aware of these differences to correctly implement the dose, fractionation, and incorporate new techniques used in clinical trials into routine practice.

## Evaluation of the Treatment Response

➢ *Refer to **Table 2** for LOC for each post-treatment response evaluation modality for the neck.*

The participating centers were asked to provide their post-(chemo)radiotherapy response evaluation schedules, which are summarized in **Table 2**. Morphologic and metabolic imaging modalities are the most frequently (8/10 for each) used tools for the assessment of treatment response, whereas there is a prominent heterogeneity regarding the regular use of physical examination, ultrasound (± fine-needle aspiration) and the time interval to perform these imaging examinations. There is no

**TABLE 2 |** Post-(chemo)radiotherapy response evaluation schemes for stage III-IV/B disease.

| Center (LOC) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Physical examination (no) | X | X | X | | | X | | | | |
| Morphologic imaging (moderate) | X | X | X | X | X | X | | X | | X |
| Metabolic imaging (moderate) | X | X | X | X | X | X | X | X | | |
| Regular ultrasound ± FNA (moderate) | | | | X | X | X | X | X | X | X |
| Time interval for the post-treatment imaging in weeks (high LOC around 12, but no LOC for a strict time frame) | 8–12 | 6–8 | 12–16 | 10–12 | 4–12 | 8–12 | 12 | 12 | 6–12 | 10–12 |

*FNA, fine-needle aspiration; LOC, level of consensus.*

**TABLE 3 |** Dose-fractionation schedules for palliative radiotherapy.

| Center | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Preferred regimen (dose in Gy/fraction) | None | 50/20 | QS | None | QS | QS* or 37.5/15# | 40/16 or 45/18 | 42/13* or 12/2# | QS* or 25/5# | None |
| Number of fractions/week | NA | 5 | 4 | NA | 4 | 4* or 5# | 5 | 5* or 2# | 4* or 5# | NA |

*NA, not available; QS, Quad-Shot, i.e., 3 cycles of (4 × 3.5–3.75 Gy BID in 2 days) each 4 weeks apart.*
**,# The values with these signs under each column correspond to the preferred regimen and the number of fractions under the same column.*

center, in which no regular post-treatment response evaluation imaging is performed.

Although there is no international consensus about the post-(chemo)radiotherapy response evaluation tools and the optimal time interval, the highest level of evidence was generated by the PET/NECK Trial (61), which demonstrated the futility of the planned neck dissection approach after CRT. Despite of being a relatively expensive imaging modality on its own, $^{18}$FDG-PET/CT is indeed cost-effective (62) compared to planned neck dissection and yields similar outcome in terms of survival and quality of life (61).

For response evaluation, $^{18}$FDG-PET/CT is reported to have a higher accuracy in the detection of recurrent lesions when compared to CT and MRI (63). Its negative predictive value is very high, but the positive predictive value is suboptimal. In other words, $^{18}$FDG-PET/CT is an ideal modality to rule out residual disease after (chemo)radiotherapy. Recent studies demonstrated further increased accuracy with delayed image acquisition around 16 weeks after treatment with NPVs reaching 100% (64–66). On the other hand, the access to $^{18}$FDG-PET/CT in low-cost setting is not always warranted, and morphologic imaging alone with MRI or CT should be relied on. Another well-known issue is the delayed response in involved lymph nodes of HPV+ oropharyngeal tumors (67), which sometimes exceeds 24 weeks after the end of treatment. Such patients are under increased risk of undergoing unnecessary biopsies and salvage neck dissections. Nevertheless, that does not mean, that the suspicious findings which indicate an incomplete remission (regardless of HPV status) can be left to routine clinical observation without performing a timely pathology examination.

The rationale of a regular ultrasound ± fine-needle aspiration policy (regardless of clinical response) is not clear, especially if the above-mentioned imaging modalities are already planned.

## Palliative Radiotherapy and Salvage Re-Irradiation

➢ *No particular preference exists for palliative radiotherapy regimens: no consensus.*

Among centers, there was a heterogeneity in palliative radiotherapy regimens. Three centers did not provide any preferred regimen. The most frequently mentioned regimen was the Australian Quad-Shot (4/10). Details are provided in **Table 3**.

There are various radiotherapy regimens for the palliative treatment of head and neck cancer (68). In the lack of evidence to back a particular dose-fractionation regimen, the following aspects of palliative radiotherapy concept should be considered. Shorter treatment time and hospital visits play an important role for patient comfort. Hypofractionation and split-course regimens are safe in palliative setting (69). However, previously applied doses and normal tissue reserves should be always taken into consideration when choosing the optimal dose and fractionation. The use of IMRT is recommended to further minimize treatment toxicity.

➢ *Hypofractionated stereotactic body radiotherapy (SBRT) is considered in re-irradiation setting with curative intent: low LOC (60%).*
➢ *SBRT is considered for palliative irradiation: low LOC (60%).*

SBRT is performed in (or via referral to another center) 6/10 centers with an indication for re-irradiation with a curative intent. In 6/10 centers (partially overlapping with the former) it is used for palliative treatments. In one center, it is also used to apply the boost dose following the elective course of radiotherapy. In 2/10 centers it is never used.

Various applications of SBRT in head and neck cancer are reported (its use in glottic larynx cancer is mentioned previously):

1) Prospective clinical trials investigated the role of SBRT in re-irradiation of unresectable recurrences. The dose fractionation schedules were extremely hypofractionated (70–72). Although no head-to-head comparisons exist, the survival rates seem to be not inferior to normofractionated (73, 74) or hyperfractionted (75, 76) schedules, and the toxicity profiles look comparable with slightly being superior (77). The last phase II trial ($n = 50$) demonstrated 6% acute and 6% late grade 3 toxicity rates with 40–44 Gy in five fractions over 2 weeks (72). The same group also published the largest retrospective series so far ($n = 291$) (78). The results of this study indicate, that the SBRT is safe and effective. Nevertheless, due to higher risk for late toxicity, the laryngeal and hypopharyngeal primaries should be carefully selected (72, 78).

   IMRT appears to be a feasible alternative as well (77). Recently, the Multi-Institution ReIrradiation (MIRI) Collaborative defined three classes of re-irradiated patients treated with IMRT by means of recursive partitioning analysis (RPA). RPA class I (>2 years after initial radiotherapy with resected tumors; 2 years overall survival: 62%) outperformed the class II (>2 years with unresected tumors or <2 years and without tracheostomy or feeding tube dependence; 2 years overall survival: 40%) and class III (remaining patients; 2 years overall survival: 17%) (79). Despite a potential selection bias due to the retrospective nature of the data, MIRI also demonstrated the redundancy of elective nodal irradiation and hyperfractionation regarding loco-regional control and overall survival. The same work indicated the need to administer ≥66 Gy equal dose in 2 Gy fractions to unresected tumors (80). This dose-tumor control relationship with conventional fractionation is also supported by the findings of a recent systematic review by the AAPM Working Group about hypofractionated SBRT, which shows superior tumor control with similar biologically 2 Gy/fraction equivalent doses of >35 Gy in 5 fractions, and suggests to administer 40–50 Gy in 5 fractions if possible (81).

   In another multi-institutional study, re-irradiation cohorts of IMRT and SBRT were compared using the same MIRI RPA classes II and III (no class I due to lack of operated patients). SBRT was associated with slightly less toxicity than IMRT (Grade ≥4 5.1% vs. 0.5%, $p < 0.01$). Both techniques showed similar overall survival in RPA class III, but significantly better survival with IMRT in class II. Comparable overall survival and loco-regional control were reported on RPA class II small tumors (≤25 $cm^3$) with SBRT (>35 Gy in ≤5 fractions) and IMRT (77). After adjustment for potential confounders, SBRT and IMRT yielded similar overall survival and loco-regional control in the whole cohort. Either way, the patients seem to benefit from advanced technology by means of SBRT or IMRT compared to conventional techniques. Therefore, conservative reluctance to re-irradiation should be re-questioned. Validated tools for better patient selection criteria and prospective randomized studies to define the optimal strategies in re-irradiation setting are needed.

2) The Erasmus MC group published their results of T1–2 OPSCC cases treated with either pulsed-dose brachytherapy ($n = 148$; 22 Gy in 8 fractions over 24 h) or SBRT ($n = 102$; 16.5 Gy in 3 fractions over 1 week) boost following 46 Gy in 23 fractions with concomitant cisplatin (82). Toxicity and quality-of-life scores were comparable with both modalities. The authors favored the use of the non-invasive SBRT strategy, mainly based on the fact that it is less labor intensive, while brachytherapy is associated with perioperative and anesthesia-associated complications and requires specially trained personnel with hand dexterity.

## CONCLUSION

The findings of our survey indicate a low LOC among head and neck oncologists working in academic and multidisciplinary setting in 10 Swiss institutions. Regarding the results and the discussion concerning the specialties other than radiation oncology, the reader is advised to read the corresponding parts of this article. The highest LOC was achieved among medical oncologists, whereas the lowest was observed among head and neck surgeons. On the other hand, this level of disagreement may also depend on the topics chosen for the survey, and not necessarily the heterogeneity within the disciplines. It is also interesting to witness a low LOC regarding topics, where a high level of evidence actually does exist, and vice versa, such as definition of post-induction chemotherapy or post-operative treatment volumes, diagnostic modalities and time interval used to evaluate treatment response, use of boost techniques and dose/fractionation in early stage glottic laryngeal cancer. This article is expected to serve the head and neck oncologists to be aware of their discrepancies even among academic institutions and to stimulate discussion toward standardization of practice and prioritize topics of future clinical research. We support the concept of and the adherence to standardized guidelines, which should address controversial but relevant topics as well. Importantly, the level of evidence or the lack of thereof should always accompany the guideline recommendations. Last but not least, we would like to emphasize that this article series is not a literature review in the classical sense.

## DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the manuscript/supplementary files.

## AUTHOR CONTRIBUTIONS

GH, MB, OE, PD, and PP: conception and design. OE and PP: collection of data. All co-authors: generation of the initial and final versions of the questions, drafting of the manuscript and approval of the final version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# A Review of Controversial Issues in the Management of Head and Neck Cancer: A Swiss Multidisciplinary and Multi-Institutional Patterns of Care Study—Part 3 (Medical Oncology)

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**Background:** The Head and Neck Cancer Working Group of Swiss Group for Clinical Cancer Research (SAKK) has investigated the level of consensus (LOC) and discrepancy in everyday practice of diagnosis and treatment in head and neck cancer.

**Materials and Methods:** An online survey was iteratively generated with 10 Swiss university and teaching hospitals. LOC below 50% was defined as no agreement, while higher LOC were arbitrarily categorized as low (51–74%), moderate (75–84%), and high (≥85%).

**Results:** Any LOC was achieved in 62% of topics ($n = 60$). High, moderate, and low LOC were found in 18, 20, and 23%, respectively. Regarding Head and Neck Surgery, Radiation Oncology, Medical Oncology, and biomarkers, LOC was achieved in 50, 57, 83, and 43%, respectively.

**Conclusions:** Consensus on clinical topics is rather low for surgeons and radiation oncologists. The questions discussed might highlight discrepancies, stimulate standardization of practice, and prioritize topics for future clinical research.

**Keywords: consensus, head and neck cancer, patterns of care, practice patterns, survey**

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## INTRODUCTION

This is the third part of the article "A Review of Controversial Issues in the Management of Head and Neck Cancer: A Swiss Multidisciplinary and Multi-Institutional Patterns of Care Study," providing the results for the items concerning medical oncology discipline, each followed by a short discussion if deemed relevant. The details of the methodology is presented in the first part of this series.

## RESULTS AND DISCUSSION

### Medical Oncology

This section contains some overlapping topics with the previous sections regarding concurrent CRT and induction chemotherapy. The focus remains on the medical oncologists' point of view.

#### Concurrent Chemoradiotherapy

➢ *Cetuximab is preferred in combination with definitive radiotherapy in loco-regionally advanced HNSCC for cisplatin-ineligible patients: moderate LOC (80%).*

An important question remains which approach is preferred in cases where cisplatin cannot be applied due to contraindications or patient related factors precluding its application (age, performance status, hearing loss etc.). For this situation, cetuximab (1) as alternative choice is favored in 8/10 centers. One center prefers carboplatin, whereas in another center a combination regimen with 5-fluorouracil (5-FU) and mitomycin C (2, 3) vs. Cetuximab is discussed on patient basis.

> Different systemic modalities for concurrent treatment were investigated during the last decades. Cisplatin given every 3 weeks remains the standard of care (4, 5). A minimal dose of $\geq$200 mg/m$^2$ cisplatin has to be administered to achieve optimal outcome (6). Nevertheless, only 61% of patients tolerate the standard dose of 100 mg/m$^2$ times three (7). Therefore, different alternatives are investigated. Among them, the well-tolerated platinum alternative carboplatin, alone, or in combination with 5-FU was the combination used by the GORTEC group (8). Cetuximab, based on high level evidence (1), was the preferred choice within our survey, despite the lack of randomized comparison to cisplatin at the time of the survey. Recently, two phase III randomized trials showed that cetuximab is associated with inferior overall survival compared to cisplatin even in the low and intermediate risk HPV-associated OPSCC (9, 10). For mitomycin C in combination with 5-FU, one randomized trial showed superiority of CRT in terms of locoregional control and survival to a dose escalated hyperfractionated accelerated radiation therapy schedule without systemic therapy (11, 12). For mitomycin C, as monotherapy or in combination, no randomized phase III data is available, in comparison to standard of care cisplatin or cetuximab.

➢ *No agreement in the radiosensitizer indication in post-operative setting for cisplatin-ineligible patients: no consensus.*

The same question in the adjuvant CRT setting yielded a different pattern: cetuximab was the preferred choice in 4, carboplatin in 5 centers, In the remaining center, the radiation oncologist would prefer 5-fluorouracil with mitomycin c, whereas the medical oncologist would opt for cetuximab, or carboplatin instead.

> In the adjuvant setting, no high-level evidence is available for cetuximab. Despite this fact, almost half the centers adopt the data from non-operated locally advanced disease (1) and prescribe cetuximab. Carboplatin is the preferred agent as monotherapy. For mitomycin C as monotherapy or in combination with dicumarol, an improvement was shown but not regarding overall survival (13). For the combination of 5-FU an extrapolation from the existing data from non-operated locally advanced disease is assumed.

➢ *The cisplatin regimen in terms of dose and cycle frequency concomitant with radiotherapy is quite heterogeneous: no consensus.*

Platinum-based regimens are administered weekly in 4/10, every 3 weeks in 5 centers, and every 3 weeks but distributed over 5 days every 3 weeks in 1 center.

> Shortly after our survey was completed, data presented at the annual congress of clinical oncology ASCO 2017 was presented and later on published, showing superiority of the 3-weeks application of cisplatin vs. a weekly application (14). Probably, from the four centers applying cisplatin weekly, some would consider changing their opinion.

➢ *All centers prefer to continue the treatment with another systemic agent in patients who cannot complete the planned number of cycles of cisplatin: high LOC (100%).*

If a patient was not able to continue with cisplatin after $\geq$1 cycle, systemic treatment is switched to another regimen in 10/10 centers. In one center, treatment is switched to 5-FU and mitomycin c or carboplatin alone. All other centers prefer cetuximab or carboplatin.

> We are not aware of any solid data confirming the benefit of any switch strategy, and with which combination, if there is any value at all. Of note, one of the participating centers recently published a hypothesis-generating retrospective study indicating a higher incidence in second primary cancers, when cetuximab was administered after the discontinuation of platinum-based chemotherapy, compared to pure cetuximab, or platinum-based therapy (15).

➢ *Age is not considered as a strict factor regarding the decision whether to administer concomitant chemotherapy: high LOC (100%).*

There was total consensus (10/10) about administering chemotherapy concomitant with radiotherapy to selected, medically fit patients even older than 70 years.

> Even if there is no randomized prospective data confirming the efficacy of a concomitant strategy in this patient group, all centers apply the same regimen as in their younger counterparts. Some analyses show similar outcomes for these patients despite the higher age (16). Biological age seems to be of importance more than chronological age.

➢ *ECE is a well-established high-risk factor for post-operative concomitant CRT indication: high LOC (100%).*

➢ *In most centers, positive resection margin is considered a high-risk factor for post-operative concomitant CRT indication: high LOC (90%).*

Risk factors warranting adjuvant concomitant chemotherapy to radiotherapy vary between centers and are elucidated in **Table 1**.

## Induction Chemotherapy

➢ *The use of induction chemotherapy is not part of the routine: low LOC (60%).*

The use of induction chemotherapy with the intention of increasing oncological outcome is used in 4/10 centers. The other centers either never administer induction chemotherapy, or only do so in rare cases in presence of bulky disease, in which performing an up-front curative CRT with full-dose is not realistically applicable or feasible. An exact specification of the induction regimen was not pointed out [classic TPF regimen (docetaxel, cisplatin, 5-fluorouracil) (17, 18), adapted TPF, other combination chemotherapy].

Induction chemotherapy is a controversial topic in HNSCC. Nevertheless, during the last decade one regimen, applied "classically" or "adapted" showed level I evidence for having better survival compared to radiotherapy alone in selected patients (17, 18). With the standard of care approach of concurrent radiotherapy and cisplatin, trials comparing these two approaches were eagerly awaited. From five randomized phase III trials, only two compared standard concurrent treatment vs. induction with TPF followed by the same treatment (19, 20). All the other trials were underpowered or did not reach their recruitment goal. Moreover, inadequate systemic agents were applied concurrently to radiotherapy. The trial by Hitt et al. showed a trend toward an improvement of overall survival, but was formally negative (19). A trial with an "adapted" TPF regimen also called "Italian" TPF was able to show a marked and impressive overall survival benefit of more than 20 months (20). The trial is controversial for its design, but the main question, whether an induction approach irrespective of the following concurrent treatment (cisplatin and 5-FU or cetuximab), defined after a second randomization, improved outcome was clearly answered. Concerns about a lower rate of completion of radiotherapy and a higher mortality rate were raised, but could in part be refuted by recent trials. Despite these arguments, induction chemotherapy reduces distant metastases rates more prominently than concurrent CRT alone (21). In the particular case of locally advanced laryngeal cancer, value of induction chemotherapy is higher, due to available data and long-term outcome of pivotal trials, showing better outcome with higher larynx-preservation rate (22–24).

Whether to administer induction chemotherapy in nasopharynx cancer or not is an ongoing discussion. The most recently published study by Sun et al. (25) is a well-designed and conducted study, whose results indicate a favorable progression-free survival with the addition of TPF administered before CRT. However, it is important to note the eligibility criteria and the patient collective of this study. Only cN+ patients younger than 60 years old were allowed. Moreover, the distribution of WHO histological subtypes are neither reported nor mentioned in the published article. Considering the dramatic geographic differences of the histology, a direct implementation of the results of a study from China to European and American patients, especially those with non-EBV tumors, is questionable. Nevertheless, for those who find the study results convincing enough to change their practice, the investigators of the same study created a helpful nomogram based on the trial database to predict the extent of potential gain via induction chemotherapy for a given patient (26).

➢ *The use of induction/neoadjuvant chemotherapy for optimal decision-making in locally advanced laryngeal cancer is preferred: low LOC (70%).*

However, 7/10 centers favor the use of induction/neoadjuvant (the term "neoadjuvant" is rather used, if a surgery is planned afterwards) chemotherapy for decision making purposes concerning larynx preservation (22, 27).

## Nasopharyngeal, Nasal, and Paranasal Sinus Tumors

➢ *Administration of chemotherapy before the primary treatment of sino-nasal tumors is preferred due to various reasons: low LOC (60%).*

For the treatment of clinically aggressive, highly proliferating nasal cavity and paranasal sinus tumors, induction/neoadjuvant chemotherapy is considered in 6/10 centers, especially in case of bulky tumors, and/or presence of symptoms to avoid disease progression until start of radiotherapy (5/6), further to achieve clear surgical margins (1/6).

Due to the relatively low incidence and variety of histological subtypes of nasal cavity and paranasal sinus tumors, there is no convincing level of evidence for or against the use of chemotherapy before, during, or after the primary treatment.

**TABLE 1 |** Depending on the following risk factors the centers administer concurrent chemotherapy together with adjuvant radiotherapy.

| Center | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Number of pos. lymph nodes | | X | X | | X | | X | | X | |
| Extracapsular spread | X | X | X | X | X | X | X | X | X | X |
| Vascular embolism | | X | | | | | | | | |
| Perineural disease | | X | | | X | | | | | |
| Positive resection margins | X | X | | X | X | X | X | X | X | X |
| Stage III-IVB disease | | X | | | | | | | | |

Nevertheless, it is interesting to see a low but presence LOC among participating centers.

➢ *Concomitant CRT is preferred for the treatment of sino-nasal tumors: moderate LOC (70%).*

For the treatment of loco-regionally advanced nasal and paranasal sinus tumors, concurrent chemotherapy is regularly administered in 7/10 centers. In 2 centers, it is administered only in selected cases based on tumor board discussion. One center never performs radiotherapy with concomitant chemotherapy.

There is moderate consensus, that locally advanced disease needs multimodality treatment. This according to almost all guidelines available (NCCN, ESMO, etc.). One center seems to diverge from this approach, probably due to toxicity concerns.

➢ *Concerning the indication of adjuvant chemotherapy for nasopharynx cancer, no standard approach was observed: no consensus.*

Among participating centers, adjuvant chemotherapy for nasopharynx cancer is omitted in three out of ten centers; performed in all cases in three centers; in selected cases at four centers. However, when asked, the definition of "selected cases" was not further specified in three centers. In one center selection was based on treatment response and EBV titer if applicable.

Treatment of nasopharyngeal cancer is a field of controversy. Stages > I need multimodality treatment, where CRT is established as the standard of care (28, 29). Further adjuvant chemotherapy, traditionally proposed for years is based on a pivotal Intergroup 0099 study (30), which had its caveats, raising concerns about the quality of the radiotherapy in the trial and highlighting the importance of patient selection. Despite the co-existence of negative trials showing the futility of adjuvant chemotherapy after radiotherapy alone (31, 32) or CRT (33, 34), an added benefit of adjuvant treatment was confirmed by meta-analyses, one published in 2015 of 19 trials with a total of 4,806 patients, showing the most favorable overall survival (HR 0.65; 95% CI, 0.56–0.76) compared to CRT without adjuvant chemotherapy (HR, 0.80; 95% CI, 0.70–0.93) (35). The other meta-analysis including 20 trials and 5,144 patients, showed that the addition of adjuvant chemotherapy to CRT was associated with better PFS compared to CRT only (HR 0.81; 95% CI, 0.66–0.98) (36). On the other hand, the most recently published phase III trial showed no benefit of adjuvant chemotherapy when added to CRT, even though the study only included high-risk patients with detectable post-CRT plasma EBV DNA (37). Moreover, a majority of patients do not tolerate full adjuvant treatment. Therefore, induction treatment was studied within phase III trials and showed differing results. Nevertheless, two phase 3 trials (25, 38) and a meta-analysis (36) were positive for the primary endpoint overall survival.

### *Supportive Measures and Oligometastatic Disease*

➢ *Prophylactic use of colony stimulating factors is not preferred during CRT: moderate LOC (80%).*

In 2/10 centers, prophylactic use of colony-stimulating factors during CRT was reported.

Cautious application of colony-stimulating factors is probably due to reports finding adverse outcome during chemo-radiation (39) and pre-clinical data suggesting tumor proliferation (40) with such agents. Additionally, the efforts of reducing treatment-related mucositis were futile (41, 42). Although not belonging to the same category of agents, it is also worth to note that the use of erythropoiesis-stimulating agents to overcome anemia and hypoxia was shown to cause an unexpected negative outcome (43).

➢ *Induction/neoadjuvant chemotherapy for subsequent decision-making is preferred in oligometastatic HNSCC: low LOC (60%).*

For the treatment of oligometastatic (defined as up to 3 metastases) cases at the initial diagnosis, 6/10 centers consider administering induction/neoadjuvant chemotherapy, and decide thereafter based on response the final treatment concept (curative vs. palliative). Three centers never pursue this strategy. One center directly treats the locoregional and distant disease with curative intent.

Compared to other tumor entities (e.g., breast, colorectal, prostate, non-small lung cancer, malignant melanoma), the concept of oligometastatic disease and its treatment in HNSCC were not extensively investigated. Retrospective series demonstrate 5-years survival rates of 20% and higher after local ablation by means of surgery or SBRT of oligometastatic disease (44, 45). However, a high level of evidence is still lacking. Moreover, the optimal strategy for the synchronous presentation of the oligometastases at the time of initial diagnosis poses a more specific question, which still remains unanswered. The heterogeneity in the patterns of treatment among our 10 centers seems to reflect this ambiguity.

### *Systemic Treatments for Recurrent/Metastatic Disease*

➢ *In first line, EXTREME is the preferred systemic treatment regimen for recurrent/metastatic disease (R/M): low LOC (60%).*

➢ *The use of 2nd line anti-PD1 checkpoint inhibitors are preferred in anti-EGFR pre-treated and not pre-treated R/M: moderate LOC (70–80%, respectively).*

➢ *Anti-EGFR pre-treated patients would be encouraged to participate in clinical trials for ≥2nd line treatment: low LOC (60%).*

➢ *Anti-EGFR-naïve patients are considered for anti-EGFR treatment as ≥2nd line: low LOC (60%).*

The EXTREME regimen containing a platinum compound with 5-fluorouracil and cetuximab is considered for patients with R/M and an ECOG performance status 0–2 in 6/10 centers. The remaining four centers do not necessarily consider systemic treatment according to the pivotal EXTREME trial especially for patients with higher ECOG performance status (46). Second-line systemic treatment choice was mostly based on whether or not previous treatment contained cetuximab (**Table 2**). There

**TABLE 2 |** Preferred second-line systemic treatments depending on previous anti-EGFR application.

| Center | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| **ANTI-EGFR PRE-TREATED** | | | | | | | | | | |
| Methotrexate | | | X | | | | X | | X | |
| Cetuximab | | | | | | | X | | | |
| Taxane | | | C | | | M | | | M | |
| Anti-PD1 antibody* | X | | X | X | X | | X | | X | X |
| Clinical trial | | X | X | | X | | X | X | X | |
| Best supportive care | | | | | X | | X | | X | |
| **ANTI-EGFR-NAÏVE** | | | | | | | | | | |
| Methotrexate | | | X | | | | | | X | |
| Anti-EGFR antibody | | X | X | | X | | X | X | X | |
| Taxane | | | C | | | | | | M | |
| Anti-PD1 antibody* | X | | X | X | X | X | X | | X | X |
| Clinical trial | | | X | X | X | | | | X | |
| Best supportive care | | | | | X | | | | | |

**We reassessed second-line treatment choice after approval of novel anti-PD-1 checkpoint inhibitors. These agents were given under the category "compassionate use." C, combination; M, monotherapy.*

was a moderate LOC (70–80%) among the centers about the application of nivolumab in this setting (47). Nevertheless, the general heterogeneity in the R/M setting among participating centers is not to be overlooked.

## CONCLUSION

The findings of our survey indicate a low LOC among head and neck oncologists working in academic and multidisciplinary setting in 10 Swiss institutions. Regarding the results and the discussion concerning the specialties other than medical oncology, the reader is advised to read the corresponding parts of this article. The highest LOC was achieved among medical oncologists, whereas the lowest was observed among head and neck surgeons. On the other hand, this level of disagreement may also depend on the topics chosen for the survey, and not necessarily the heterogeneity within the disciplines. It is also interesting to witness a low LOC regarding topics, where a high level of evidence actually does exist, and vice versa. This article is expected to serve the head and neck oncologists to be aware of their discrepancies and to stimulate discussion toward standardization of practice and prioritize topics of future clinical research.

## DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the manuscript/supplementary files.

## AUTHOR CONTRIBUTIONS

GH, MB, OE, PD, and PP: conception and design. OE and PP: collection of data. All co-authors: generation of the initial and final versions of the questions, drafting of the manuscript, and approval of the final version.

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# A Review of Controversial Issues in the Management of Head and Neck Cancer: A Swiss Multidisciplinary and Multi-Institutional Patterns of Care Study—Part 4 (Biomarkers)

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**Background:** The Head and Neck Cancer Working Group of Swiss Group for Clinical Cancer Research (SAKK) has investigated the level of consensus (LOC) and discrepancy in everyday practice of diagnosis and treatment in head and neck cancer.

**Materials and Methods:** An online survey was iteratively generated with 10 Swiss university and teaching hospitals. LOC below 50% was defined as no agreement, while higher LOC were arbitrarily categorized as low (51–74%), moderate (75–84%), and high (≥85%).

**Results:** Any LOC was achieved in 62% of topics ($n = 60$). High, moderate, and low LOC were found in 18, 20, and 23%, respectively. Regarding Head and Neck Surgery, Radiation Oncology, Medical Oncology, and biomarkers, LOC was achieved in 50, 57, 83, and 43%, respectively.

**Conclusions:** Consensus on clinical topics is rather low for surgeons and radiation oncologists. The questions discussed might highlight discrepancies, stimulate standardization of practice, and prioritize topics for future clinical research.

**Keywords: consensus, head and neck cancer, patterns of care, practice patterns, survey**

## INTRODUCTION

This is the fourth part of the article "A Review of Controversial Issues in the Management of Head and Neck Cancer: A Swiss Multidisciplinary and Multi-Institutional Patterns of Care Study," providing the results for the items concerning biomarkers, each followed by a short discussion if deemed relevant. The details of the methodology is presented in the first part of this series.

## RESULTS AND DISCUSSION OF BIOMARKERS WITH CURRENT POTENTIAL USE

➢ *Imaging findings indicating hypoxia and/or central necrosis are not standard factors influencing the treatment decision: no consensus.*

In 5/10 centers, imaging findings indicating hypoxia or central necrosis affects the decision for the primary treatment modality.

According to the literature (1), tumor hypoxia can be associated with aggressive tumor phenotype affecting the natural course of disease in these patients (2) due to assumed radiotherapy resistance. Based on laboratory experience, a up to three times higher photon radiation dose is needed to cause the same cytotoxic effect in hypoxic cells compared to normal tumor cells (3). Whether such dose escalation could be performed, while keeping low toxicity rates in normal tissue is questionable (4). The advantage of dose escalation to hypoxic sub-volumes with conventional photon radiation has been analyzed in clinical practice to overcome this bad prognostic factor (5–8). However, the clinical identification, measurement, and localization of hypoxia in tumors remain debatable. The studies range from non-invasive clinical assumptions to direct measurements with oxygen electrodes, and indirect methods such as serum biomarkers or immunohistochemistry (IHC) of hypoxia-related markers. There has been found a significant heterogeneity in regional oxygenation as well as in biological response to hypoxia confounding these tissue-sampling methods. In current clinical practice, boost dose is guided by CT scans and is based primarily on size criteria (1). However, the correlation between tumor hypoxia and common clinical parameters such as size, morphology, and histology is scarce (9). PET scans could deliver more functional information based on tumor metabolism (10).

In tumors with presence of diffuse hypoxia a systemic approach using a hypoxic cell cytotoxin or anti-growth factor drugs might be beneficial to overcome the limitations of hypoxia (11). Alternatively, in a more focal hypoxia a local/regional approach, such as IMRT-based radiation dose escalation to the hypoxic sub-volume might be more successful (12, 13). In different studies, the complementary role of radiation and systemic hypoxia-specific pro-drugs to overcome the hypoxia-induced resistance has been established (14, 15). Furthermore, there is a higher risk for persistence of hypoxic tumors after primary CRT and the timing of salvage surgery such as planned neck dissection should be adapted.

Anyhow, regarding the limited evidence for the role of imaging findings indicating hypoxia, it is quite remarkable that half of the centers in Switzerland integrate them in treatment decisions.

➢ *De-differentiation grade is not a standard factor influencing the treatment decision: no consensus.*

De-differentiation grade of tumors also influences treatment decision in 5/10 centers. This question did not differ between squamous cell cancer and other malignancies of the head and neck.

In salivary gland carcinoma, the histologic grade is a significant predictor of treatment response and an established factor for therapeutic decisions, but due to the rarity and wide variety of different tumor types the definition of predictive grading schemes is challenging (16).

In HNSCC, histologic grade is not part of the current staging criteria, probably because its prognostic impact remains controversial. Weijers et al. (17) found no significant correlation between grade and prognosis in early stage oral cancer. In contrast, other studies (18–20) found a significant impact of tumor differentiation and staging on recurrence and overall survival. Furthermore, a recent study (21) in early stage oral cancer has demonstrated a strong association between histologic grade and survival. High histologic grade was associated with poorer survival and carried an independent prognostic value in addition to tumor size, node status, and presence of distant metastasis (TNM) stage (21). Even though grade is not part of the UICC staging system, some centers do consider high grade as an indication for adjuvant treatment (22, 23).

➢ *Determining the HPV status is a standard practice in oropharyngeal squamous cell carcinoma (OPSCC): high LOC (100%).*

➢ *There is no standard method established for the definition of HPV status: no consensus.*

All (10/10) centers regularly determine the HPV status in OPSCC. The definition of an HPV attributable tumor is IHC overexpression of p16 as a single marker (5 centers), HPV high-risk type DNA positivity by polymerase chain reaction (PCR) (2 centers); HPV high risk type DNA positivity by ISH (1 center) and p16, followed by PCR if needed according to College of American Pathologists guidelines (1 center).

The survey was performed prior to the release of the 8th edition of the UICC TNM classification system, implementing p16 IHC as a crucial biomarker for staging of OPSCC. Nevertheless, all centers had already started to routinely determine the HPV-status in OPSCC. Interestingly, the definition of a positive HPV-status widely differs between the centers, reflecting the lack of a worldwide-accepted consensus for the accurate definition of an HPV-driven cancer. In the new UICC staging system (8th edition), p16 is accepted for practical and cost-related reasons considering the guideline to be international (24), but the definition of a high-risk HPV-attributed cancer is still a matter of debate (25).

Currently, detection of $p16^{INK4A}$ (inhibitor of cyclin-dependent kinase 4) overexpression in tumor tissue by IHC is used as a surrogate marker for HPV-driven HNSCC (26). However, $p16^{INK4A}$ IHC as a single diagnostic marker has shown insufficient sensitivity (27–30) and specificity (27, 29–31).

Due to its high sensitivity, high-risk HPV-DNA detection by quantitative PCR has been commonly employed to detect

HPV-driven tumors, but was found to lack sufficient specificity, which could lead to false positive results (32). Indeed, HPV-DNA detection in tumor specimens is not proving a causal viral association of carcinogenesis but could also be the result of a past non-transforming HPV-infection or contamination (33). Detection of the transcripts of viral oncogenes E6 and E7 in tumor through mRNA techniques is widely accepted as gold standard for determining the oncogenic role of HPV in tumor. However, extraction techniques and analyses of RNA from the routinely available formalin-fixed paraffin-embedded tissue specimens remain challenging and costly, limiting their widespread use (27). In this context, Smeets et al. (31) validated an algorithm based on the combination of $p16^{INK4A}$ IHC followed by HPV-DNA analysis to detect an oncogenically active HPV infection in formalin-fixed paraffin-embedded tissue specimens: the accuracy, sensitivity, and specificity were 98, 96, and 98%, respectively when compared to RNA detection (34), that is why it would probably be the most suitable definition for tumoral HPV-association in clinical routine.

➢ *Most centers determine the HPV status in a carcinoma of unknown primary (CUP): low LOC (60%).*

In 6/10 centers, HPV status is routinely determined in lymph node metastases without evidence of a primary tumor.

Cervical lymph node metastases from clinically undetectable primary squamous cell carcinoma present a diagnostic and therapeutic challenge. There is no clear consensus for the optimal treatment in CUP. Recommendations range from surgery of the neck alone to primary radiotherapy of the mucosa at risk and both neck sides (35–39). In the era of treatment de-intensification, the potential benefit of radiotherapy of putative primary tumor sites has to be weighed against its detrimental effect on quality of life and additional toxicity. The role of high-risk HPV infection in the development of HNSCC has gained evidence (40, 41), in particular for CUP. Several studies showed a high correlation between HPV-positive lymph node metastases and the detection of the primary tumor in the oropharynx. Many HPV-associated tumors present with prominent nodal disease and small, difficult or even undetectable (clinically and radiologically) primaries hidden in palatine and lingual tonsillar crypts (42). Therefore, a rising incidence of HPV-positive lymph node metastases manifesting as CUP has been reported (43–46). Unfortunately the sensitivity of $^{18}$FDG-PET/CT is adversely affected by false positives from hypermetabolic oropharyngeal lymphoid tissue (42). Even in patients with CUP HPV-positivity in lymph node metastases is a positive prognostic factor and influencing treatment decisions (47). This was accounted for in the updated 8th edition of the UICC classification by integrating HPV-positivity of the primary tumor or the lymph node metastases in CUP staging. Since the survey was performed prior to the release of the 8th edition of the UICC TNM classification system it is interesting to see, that at that time the importance of HPV infection in CUP was not evident in 40% of the centers in Switzerland.

After an intensive literature search in Pubmed and Medline we have only found one comparable survey about patterns of care for CUP. It has been performed recently in Germany, only included radiation oncologists and has revealed that 82% of the departments routinely determined HPV status in CUP (48). This rate is significantly higher than in Switzerland. According to the authors it is explained by the requirements to stage a CUP according to the 8th TNM-classification edition and known as an increasingly important prognostic factor.

➢ *Determination of the HPV status in non-oropharyngeal HNSCC is not accepted as a standard practice: no consensus.*

HPV status is also determined in non-oropharyngeal primaries in 4/10 centers.

This question is related to whether the presence of HPV in non-oropharyngeal HNSCC represent viral-mediated carcinogenesis, or merely a "bystander" infection and whether HPV-positivity in such cases influences the treatment strategy and clinical outcome (49). Large data on HPV DNA detection by PCR and p16 expression in HNSCC biopsies suggests that the probability of a cancer of the oral cavity, larynx, and hypopharynx being attributable to HPV is at least 5-fold lower than that for OPSCC (49, 50). High-risk HPV DNA was also detected in a significant proportion of sinonasal, nasopharyngeal, and salivary gland cancers, but the clinical significance of these findings in these malignancies has not been clearly defined. Limited data on HPV E6/E7 mRNA suggests that HPV-attributable HNSCC is rare in the oral cavity (3%), larynx (7%) and lacking in the hypopharynx (0%). Concerning the prognostic impact of HPV-positivity in non-oropharyngeal subsites, no data currently supports that HPV is significantly associated with improved outcome in oral or laryngeal cancer (49), while data are lacking for other subsites (49). In the absence of appropriately powered, well-designed studies, HPV-detection in non-oropharyngeal sites does not seem to impact staging or treatment.

➢ *Most centers do not base their treatment decision on HPV status: moderate LOC (80%).*

HPV status does not influence the treatment decision in 8/10 centers. Two centers stated that they may consider changing the treatment intensity.

Although HPV-positivity in OPSCC is an established positive prognostic marker, treatment decisions should so far not be influenced by it. There is a lot of ongoing discussion about treatment de-escalation in this low-risk tumor but centers should wait for the shortcoming results of prospective clinical trials to decide on less intensive treatment regimen.

## SUMMARY

In summary, there is no consensus regarding the applicability of imaging findings indicating hypoxia as well as histological differentiation grade. In all centers, the determination of the HPV-status is a standard practice in oropharyngeal squamous cell carcinoma rather than in cancer of unknown primary. Since the survey was performed prior to the release of the 8th edition of the UICC TNM classification system it is interesting to see, that at that time the importance of HPV infection especially in CUP was not evident in almost half of the centers in Switzerland.

Furthermore, there is a lack of standard method established for the definition of HPV-status ranging from p16 IHC as a single marker, HPV-DNA by PCR or ISH as single

markers or the combination of both reflecting the lack of a worldwide-accepted consensus for the accurate definition of an HPV-driven cancer. In the majority of centers, there is no therapeutic consequence of HPV-testing in both OPSCC and CUP due to lack of practice guidelines based on prospective clinical trials.

## CONCLUSION

The findings of our survey indicate a low LOC among head and neck oncologists working in academic and multidisciplinary setting in 10 Swiss institutions. The highest LOC was achieved among medical oncologists, whereas the lowest was observed among head and neck surgeons. On the other hand, this level of disagreement may also depend on the topics chosen for the survey, and not necessarily the heterogeneity within the disciplines. It is also interesting to witness a low LOC regarding topics, where a high level of evidence actually does exist, and vice versa. This article is expected to serve the head and neck oncologists to be aware of their discrepancies and to stimulate discussion toward standardization of practice and prioritize topics of future clinical research.

## DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the manuscript/supplementary files.

## AUTHOR CONTRIBUTIONS

GH, MB, OE, PD, and PP: conception and design. OE and PP: collection of data. Generation of the initial and final versions of the questions, drafting of the manuscript, and approval of the final version by all co-authors.

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