Recommendations for postoperative radiotherapy in head & neck squamous cell carcinoma in the presence of flaps

Carsuzaa, Florent; Lapeyre, Michel; Gregoire, Vincent; Maingon, Philippe; Beddok, Arnaud; Marcy, Pierre-yves; Salleron, Julia; Coutte, Alexandre; Racadot, Severine; Pointreau, Yoann; Graff, Pierre; Beadle, Beth; Benezery, Karen; Biau, Julian; Calugaru, Valentin; Castelli, Joel; Chua, Melvin; Di Rito, Alessia; Dore, Melanie; Ghadjar, Pirus

DOI:
10.1016/j.radonc.2021.04.026

Radiotherapy and Oncology

Recommendations for postoperative radiotherapy in head & neck squamous cell carcinoma in the presence of flaps: a GORTEC internationally reviewed consensus

--Manuscript Draft--

Manuscript Number:	RADONC-D-21-00509
Article Type:	Full length article
Section/Category:	Head & Neck Cancers
Keywords:	head and neck; cancer; Radiotherapy; postoperative; reconstructive surgery; flap; consensus; recommendation
Corresponding Author:	juliette thariat, MD PhD centre Baclesse Caen, FRANCE
First Author:	Florent Carsuzaa, MD
Order of Authors:	Florent Carsuzaa, MD
	Michel Lapeyre, MD
	Vincent Gregoire, MD
	Philippe Maingon, MD
	Arnaud Beddok, MD
	Pierre-Yves Marcy, MD
	Julia Salleron, MSc
	Alexandre Coutte, MD
	Severine Racadot, MD
	Yoann Pointreau, MD
	Pierre Graff, MD
	Beth Beadle, MD
	Karen Benezery, MD
	Julian Biau, MD
	Valentin Calugaru, MD
	Joel Castelli, MD
	Melvin Chua, MD
	Alessia Di Rito, MD
	Melanie Dore, MD
	Pirus Ghadjar, MD
	Florence Huguet, MD PhD
	Pauline Jardel, MD
	Jorgen Johansen, MD
	Randall Kimple, MD
	Marco Krengli, MD
	Sarbani Laskar, MD
	Lachlan Mcdowell, MD
	Anthony Nichols, MD

	Silke Tribius, MD
	Izaskun Valduvieco, MD
	Chaosu Hu, MD
	Xavier Liem, MD
	Antoine Moya-Plana, MD
	Ida D'onofrio, MD
	Upendra Parvathanen, MD
	Vinita Takiar, MD
	Ester Orlandi, MD
	Amanda Psyrri, MD
	George Shenouda, MD
	David Sher, MD
	Conor Steuer, MD
	Xu Shan Sun, MD
	Yungan Tao, MD
	David Thomson, MD
	Mu-Hung Tsai, MD
	Noemie Vulquin, MD
	Philippe Gorphe, MD
	Hisham Mehanna, MD PhD
	Sue S. Yom, MD
	Jean Bourhis, MD PhD
	juliette thariat, MD PhD

Abstract:

Introduction

Head and neck reconstructive surgery using a flap is increasingly common. Best practices and outcomes for postoperative radiotherapy (poRT) with flaps have not been specified. We aimed to provide consensus recommendations to assist clinical decision-making highlighting areas of uncertainty in the presence of flaps.

Material and methods

Radiation, medical, and surgical oncologists were assembled from GORTEC and internationally. The consensus-building approach covered 59 topics across four domains: 1) identification of postoperative tissue changes on imaging for flap delineation, 2) understanding of tumor relapse risks and target volume definitions, 3) functional radiation-induced deterioration, 4) feasibility of flap avoidance.

Results

Across the 4 domains, international consensus (median score ≥7/9) was achieved only for functional deterioration (73.3%); other consensus rates were 55.6% for poRT avoidance of flap structures, 41.2% for flap definition and 11.1% for tumor spread patterns. Radiation-induced flap fibrosis or atrophy and their functional impact was well recognized while flap necrosis was not, suggesting dose-volume adaptation for the former. Flap avoidance was recommended to minimize bone flap osteoradionecrosis but not soft-tissue toxicity. The need for identification (CT planning, fiducials, accurate operative report) and targeting of the junction area at risk between native tissues and flap was well recognized. Experts variably considered flaps as prone to tumor dissemination or not. Discrepancies in rating of 11 items among international reviewing

	participants are shown. Conclusion International recommendations were generated for the management of flaps in head and neck radiotherapy. Considerable knowledge gaps hinder further consensus, in particular with respect to tumor spread patterns.

COVER LETTER

This manuscript entitled **: Recommendations for postoperative radiotherapy in head & neck squamous cell carcinoma in the presence of flaps: a GORTEC internationally reviewed consensus**

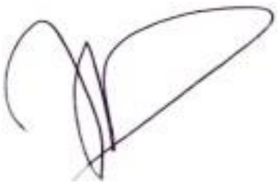
This timely article provides a consensus recommendations reviewed by international experts to assist clinical decision-making highlighting areas of uncertainty in the presence of flaps.

Best regards.

Prof. Juliette Thariat

Centre François-Baclesse, département de radiothérapie, 3, avenue Général-Harris, 14000 Caen, France ; Laboratoire de physique corpusculaire IN2P3/ENSICAEN - UMR6534, boulevard du Marechal-Juin, 14050 Caen, France.

Electronic address: jthariat@gmail.com



HIGHLIGHTS

1. Our GORTEC internationally-reviewed consensus showed that the flap-tissue junction should be considered at higher risk of tumor spread compared to other areas of the flap and that postoperative planning should be based on a contrast-enhanced CT;
2. Surgeons should report the placement of flaps more accurately and consider clip placement to guide radiotherapy planning;
3. The risks of radiation-induced atrophy, fibrosis, and osteoradionecrosis should be considered and the maximum and mean doses limited by radiotherapy optimization

Title page : **Recommendations for postoperative radiotherapy in head & neck squamous cell carcinoma in the presence of flaps: an international consensus from the GORTEC**

Running title **: Recommendations for postoperative radiotherapy in head & neck squamous cell carcinoma in the presence of flaps**

Florent Carsuzaa[1], Michel Lapeyre[2], Vincent Gregoire[3], Philippe Maingon[4], Arnaud Beddok[5], Pierre-Yves Marcy[6], Julia Salleron[7], Alexandre Coutte[8], Severine Racadot[3], Yoann Pointreau[9], Pierre Graff[10], Beth Beadle[11], Karen Benezery[12], Julian Biau[2], Valentin Calugaru[5], Joel Castelli[13], Melvin Chua[14], Alessia Di Rito[15], Melanie Dore[16], Pirus Ghadjar[17], Florence Huguet[18], Pauline Jardel[19], Jorgen Johansen[20], Randall Kimple[21], Marco Krengli[22], Sarbani Laskar[23], Lachlan Mcdowell[24], Anthony Nichols[25], Silke tribius[26], Izaskun Valduvieco[27], Chaosu Hu[28], Xavier Liem[29], Antoine Moya-Plana[30], Ida D'onofrio[31], Upendra Parvathanen[32] , Vinita Takiar[33], Ester Orlandi[34], Amanda Psyrri[35], George Shenouda[36], David Sher[37] , Conor Steuer[38], Xu Shan Sun[39], Yungan Tao[30], David Thomson[40], Mu-Hung Tsai[41] , Noemie Vulquin[42], Philippe Gorphe[30], Hisham Mehanna[43], Sue S. Yom[44], Jean Bourhis[45], Juliette Thariat[46]

1 Department of Head and Neck Surgery, CHU de Poitier, France.
2 Department of Radiation oncology, Centre Jean Perrin – Clermont-Ferrand, France.
3 Department of Radiation oncology, Centre Léon Bérard, Lyon, France.
4 Department of Radiation Oncology, Hôpital de la Pitié-Salpêtrière, Paris, France.
5 Department of Radiation Oncology, Institut Curie, Paris, France
6 Department of Radiology, Clinique du Cap d'Or, La Seyne-sur-mer, France.
7 Department of Biostatistics, Institut de cancérologie de Lorraine, France
8 Department of Radiation Oncology, Amiens Picardie University Medical Center, Amiens, France
9 Department of Radiation Oncology, Centre Jean Bernard, Le Mans, France.
10 Department or Radiation Oncology, Institut C. Regaud, Toulouse, France.
11 Department of Radiation Oncology, Stanford University Medical Center, CA, USA. Stanford University Medical Center
12 Department of Radiation Oncology, Centre Antoine Lacassagne, Nice, France.
13 Department of Radiation Oncology, Centre Eugène Marquis, Rennes, France.
14 Department of Medical oncology, National Cancer Centre Singapore, Malaysia.
15 Department of Radiation Oncology, OC Radioterapia Ospedale "Mons. A.R. Dimiccoli" di Barletta, Rome, Italy
16 Department of Radiation Oncology, Institut de cancérologie de l'Ouest, St Herblain, France.
17 Department of Radiation Oncology, Charité, Berlin, Germany.
18 Department of Radiation Oncology, Hospital de Tenon, Paris, France.
19 Department of Radiation Oncology, CHU de la Milétrie, Poitiers, France.
20 Department of Radiation Oncology, Odense University Hospital, Denmark.
21 Department of Medical Oncology, University of Wisconsin-Madison, WI, USA.
22 Department of Translational Medicine University of Piemonte Orientale, Novara, Italy
23 Department of Radiation Oncology, TATA, Mumbai, India.

24 Department of Radiation Oncology, Peter McCallum Cancer Center, Melbourne, Australia.
25 Department of Head and Neck surgery, London Health Sciences Center, Ontario, Canada.
26 Department of Radiation Oncology, Hermann-Holthusen-Institute for Radiation Oncology, Asklepios Hospital St. Georg, Hamburg, Germany.
27 Department of Radiation Oncology, Hospital clinic, Barcelona, Spain.
28 Department of Radiation Oncology, Fundan University, Shanghai, China.
29 Department of Radiation Oncology, Centre Oscar Lambret, Lille.
30 Department of Head and Neck Surgery, Gustave Roussy, Villejuif, France.
31 Department of Radiation Oncology, Hospital Naples, Italy.
32 Department of Radiation Oncology, University of Washington, DC, USA.
33 Department of Radiation Oncology, University of Cincinaty, Ohio, USA.
34 Department of Radiation Oncology, CNAO, Milan, Italy.
35 Department of Medical Oncology, Attikon University Hospital, Athens, Greece.
36 Department of Radiation Oncology, McGill University Health Centre, Montreal, Quebec.
37 Department of Radiation Oncology, UT Southwestern, Dallas, USA.
38 Department of Head and Neck Surgery, Winship Cancer Institute, Atlanta, USA.
39 Department of Radiation Oncology, Centre Hospitalier André Boulloche, Montbéliard, France.
40 Department of Radiation Oncology, The Christie NHS Foundation Trust, Manchester, UK.
41 Department of Radiation Oncology, National Cheng Kung University Hospital, Tïnan, Taïwan.
42 Department of Radiation Oncology, Centre Georges François Leclerc, Dijon, France.
43 Department of Radiation Oncology, Institute for Global Innovation, Birmingham, UK.
44 Department of Radiation Oncology, NRG Oncology Cancer Research Group, California, USA.
45 Department of Radiation Oncology, UNIL-CHUV, Lausanne, Suisse.
46 Department of Radiation Oncology, Centre François-Baclesse, Caen, France.

Disclosures : None
Funding : None
Conflict of Interest : None

Authors‘ contributions : each author has contributed significantly (FC, ML, VG, AB, PYM, AC, SR, JB, JT designed the questions, JS did the statistics, others quoted the proposals, either once (independent international review group) or twice (GORTEC quotation group), all reviewed the final ms) to the manuscript.

Address for reprints / to corresponding author: Juliette Thariat / email : jthariat@gmail.com

Centre François-Baclesse, département de radiothérapie, 3, avenue Général-Harris, 14000 Caen, France ; Laboratoire de physique corpusculaire IN2P3/ENSICAEN - UMR6534, boulevard du Marechal-Juin, 14050 Caen, France.

Corresponding author : Pr Juliette Thariat / email : jthariat@gmail.com

Responsible statistical analysis author : Julia Salleron / email : j.salleron@nancy.unicancer.fr

Title: Recommendations for postoperative radiotherapy in head & neck squamous cell carcinoma in the presence of flaps: an international consensus from the GORTEC

Authors: Affiliations + group belonging: GORTEC / HNCIG

Florent Carsuzaa[1], Michel Lapeyre[2], Vincent Gregoire[3], Philippe Maingon[4], Arnaud Beddok[5], Pierre-Yves Marcy[6], Julia Salleron[7], Alexandre Coutte[8], Severine Racadot[3], Yoann Pointreau[9], Pierre Graff[10], Beth Beadle[11], Karen Benezery[12], Julian Biau[2], Valentin Calugaru[5], Joel Castelli[13], Melvin Chua[14], Alessia Di Rito[15], Melanie Dore[16], Pirus Ghadjar[17], Florence Huguet[18], Pauline Jardel[19], Jorgen Johansen[20], Randall Kimple[21], Marco Krengli[22], Sarbani Laskar[23], Lachlan Mcdowell[24], Anthony Nichols[25], Silke tribius[26], Izaskun Valduvieco[27], Chaosu Hu[28], Xavier Liem[29], Antoine Moya-Plana[30], Ida D'onofrio[31], Upendra Parvathanen[32] , Vinita Takiar[33], Ester Orlandi[34], Amanda Psyrri[35], George Shenouda[36], David Sher[37] , Conor Steuer[38], Xu Shan Sun[39], Yungan Tao[30], David Thomson[40], Mu-Hung Tsai[41] , Noemie Vulquin[42], Philippe Gorphe[30], Hisham Mehanna[43], Sue S. Yom[44], Jean Bourhis[45], Juliette Thariat[46]

Affiliations

1 Department of Head and Neck Surgery, CHU de Poitier, France.
2 Department of Radiation oncology, Centre Jean Perrin – Clermont-Ferrand, France.
3 Department of Radiation oncology, Centre Léon Bérard, Lyon, France.
4 Department of Radiation Oncology, Hôpital de la Pitié-Salpêtrière, Paris, France.
5 Department of Radiation Oncology, Institut Curie, Paris, France
6 Department of Radiology, Clinique du Cap d'Or, La Seyne-sur-mer, France.
7 Department of Biostatistics, Institut de cancérologie de Lorraine, France
8 Department of Radiation Oncology, Amiens Picardie University Medical Center, Amiens, France
9 Department of Radiation Oncology, Centre Jean Bernard, Le Mans, France.
10 Department or Radiation Oncology, Institut C. Regaud, Toulouse, France.
11 Department of Radiation Oncology, Stanford University Medical Center, CA, USA. Stanford University Medical Center
12 Department of Radiation Oncology, Centre Antoine Lacassagne, Nice, France.
13 Department of Radiation Oncology, Centre Eugène Marquis, Rennes, France.
14 Department of Medical oncology, National Cancer Centre Singapore, Malaysia.
15 Department of Radiation Oncology, OC Radioterapia Ospedale "Mons. A.R. Dimiccoli" di Barletta, Rome, Italy
16 Department of Radiation Oncology, Institut de cancérologie de l'Ouest, St Herblain, France.
17 Department of Radiation Oncology, Charité, Berlin, Germany.
18 Department of Radiation Oncology, Hospital de Tenon, Paris, France.
19 Department of Radiation Oncology, CHU de la Milétrie, Poitiers, France.
20 Department of Radiation Oncology, Odense University Hospital, Denmark.
21 Department of Medical Oncology, University of Wisconsin-Madison, WI, USA.
22 Department of Translational Medicine University of Piemonte Orientale, Novara, Italy
23 Department of Radiation Oncology, TATA, Mumbai, India.
24 Department of Radiation Oncology, Peter McCallum Cancer Center, Melbourne, Australia.
25 Department of Head and Neck surgery, London Health Sciences Center, Ontario, Canada.
26 Department of Radiation Oncology, Hermann-Holthusen-Institute for Radiation Oncology, Asklepios Hospital St. Georg, Hamburg, Germany.

27 Department of Radiation Oncology, Hospital clinic, Barcelona, Spain.
28 Department of Radiation Oncology, Fundan University, Shanghai, China.
29 Department of Radiation Oncology, Centre Oscar Lambret, Lille.
30 Department of Head and Neck Surgery, Gustave Roussy, Villejuif, France.
31 Department of Radiation Oncology, Hospital Naples, Italy.
32 Department of Radiation Oncology, University of Washington, DC, USA.
33 Department of Radiation Oncology, University of Cincinaty, Ohio, USA.
34 Department of Radiation Oncology, CNAO, Milan, Italy.
35 Department of Medical Oncology, Attikon University Hospital, Athens, Greece.
36 Department of Radiation Oncology, McGill University Health Centre, Montreal, Quebec.
37 Department of Radiation Oncology, UT Southwestern, Dallas, USA.
38 Department of Head and Neck Surgery, Winship Cancer Institute, Atlanta, USA.
39 Department of Radiation Oncology, Centre Hospitalier André Boulloche, Montbéliard, France.
40 Department of Radiation Oncology, The Christie NHS Foundation Trust, Manchester, UK.
41 Department of Radiation Oncology, National Cheng Kung University Hospital, Tïnan, Taïwan.
42 Department of Radiation Oncology, Centre Georges François Leclerc, Dijon, France.
43 Department of Radiation Oncology, Institute for Global Innovation, Birmingham, UK.
44 Department of Radiation Oncology, NRG Oncology Cancer Research Group, California, USA.
45 Department of Radiation Oncology, UNIL-CHUV, Lausanne, Suisse.
46 Department of Radiation Oncology, Centre François-Baclesse, Caen, France.

Financial Support: none

Conflict of Interest: no conflicting relationship exists for any author.

Running head: Recommendations for postoperative radiotherapy in head & neck squamous cell carcinoma in the presence of flaps.

Acknowledgements: Camille Vidaud (Head and Neck Cancer International Group + Gortec) and Nazim Khalladi.

Authors ‘ contributions: each author has contributed significantly to the manuscript.

Address for reprints / to corresponding author: Juliette Thariat / Centre François-Baclesse, département de radiothérapie, 3, avenue Général-Harris, 14000 Caen, France ; Laboratoire de physique corpusculaire IN2P3/ENSICAEN - UMR6534, boulevard du Marechal-Juin, 14050 Caen, France. Email : jthariat@gmail.com

Corresponding author:

Prof. Juliette Thariat

Centre François-Baclesse, département de radiothérapie, 3, avenue Général-Harris, 14000 Caen, France ; Laboratoire de physique corpusculaire IN2P3/ENSICAEN - UMR6534, boulevard du Marechal-Juin, 14050 Caen, France. Electronic address: jthariat@gmail.com

Abstract

Introduction: Head and neck reconstructive surgery using a flap is increasingly common. Best practices and outcomes for postoperative radiotherapy (poRT) with flaps have not been specified. We aimed to provide consensus recommendations to assist clinical decision-making highlighting areas of uncertainty in the presence of flaps.

Material and methods: Radiation, medical, and surgical oncologists were assembled from GORTEC and internationally. The consensus-building approach covered 59 topics across four domains: 1) identification of postoperative tissue changes on imaging for flap delineation, 2) understanding of tumor relapse risks and target volume definitions, 3) functional radiation-induced deterioration, 4) feasibility of flap avoidance.

Results: Across the 4 domains, international consensus (median score ≥7/9) was achieved only for functional deterioration (73.3%); other consensus rates were 55.6% for poRT avoidance of flap structures, 41.2% for flap definition and 11.1% for tumor spread patterns. Radiation-induced flap fibrosis or atrophy and their functional impact was well recognized while flap necrosis was not, suggesting dose-volume adaptation for the former. Flap avoidance was recommended to minimize bone flap osteoradionecrosis but not soft-tissue toxicity. The need for identification (CT planning, fiducials, accurate operative report) and targeting of the junction area at risk between native tissues and flap was well recognized. Experts variably considered flaps as prone to tumor dissemination or not. Discrepancies in rating of 11 items among international reviewing participants are shown.

Conclusion: International recommendations were generated for the management of flaps in head and neck radiotherapy. Considerable knowledge gaps hinder further consensus, in particular with respect to tumor spread patterns.

Key words: head and neck, cancer, radiotherapy, postoperative, reconstructive surgery, flap, consensus / recommendation

Introduction

For large head and neck tumors, reconstructive surgery is frequently performed using an autologous flap, harvested from the patient donor site and transferred to the tumor bed to compensate for the loss of substance [1–4]. Increasingly versatile flaps have aimed to achieve high fidelity to the native tissues to improve functional outcomes and quality of life [5].

Target volumes have been extensively defined and evaluated for patients undergoing definitive primary radiotherapy [6]. However, postoperative target volumes have been described less extensively [7–11] and new developments in head and neck cancer surgery have yet to be evaluated in terms of their consequences on the performance of poRT [2,12,13]. The poRT clinical target volume (CTV of the primary resection site) is classically defined to include the tissues that contain macroscopic or microscopic tumor at risk for tumor recurrence. On the other hand, flaps are present in about half the patients (oral cavity and oropharynx in particular) undergoing poRT (poRT)[14], and flaps result in substantial tissue changes [11,15]. Additionally, several surgical reports have suggested that radiotherapy has deleterious effects on flaps with respect to functional outcomes (dysphagia/swallowing, speech, cosmesis, range of motion) [16–24]**.** Current radiation oncology literature lacks recommendations for the delineation and management of poRT target volumes when there is a flap in the tumor bed [24–29].

We assessed the current state of knowledge based on literature and expertise. Practice patterns among the Groupe d'Oncologie Radiotherapie des Tumeurs de la tete Et du Cou (GORTEC) were analyzed to develop an initial set of recommendations. Subsequently, these proposals were circulated to an international reviewing group from HNCIG for validation and endorsement. The goal was to develop an international consensus to aid clinical decision-making and to identify areas of controversy and uncertainty related to postoperative irradiation of flaps.

Material and methods

A stepwise consensus-building method was used [30,31](Figure 1). The GORTEC steering group, defined by the GORTEC and French Head and Neck InterGroup (HNFIG) coordinator (JT, FC) and composed of head and neck radiation oncologists (N=4), surgical oncologists (N=2) and one radiologist, defined relevant questions based on a systematic review of the literature (Figure 1). A search of MESH terms including "radiotherapy" and "flap" in title yielded 82 references from 1971 to 2021. After eliminating, based on a review of titles and abstracts, non-head, and neck references (N= 41 (>80% breast)), references addressing salvage flap surgery after prior radiotherapy (N= 25), and neoadjuvant radiotherapy and delayed reconstruction (N= 5), there remained 15 articles. These included three case reports in English or other language (N=1) (evidence-based grade C), five retrospective series of 13 to 100 patients [24,25,32–34] (grade C) and seven prospective series of 12 to 44 patients [33,35–40], addressing flap changes (N=2) or functional and quality of life outcomes (N=5)(grade B).

As a first step, the GORTEC steering group designed a 59-item online questionnaire (www.easy-crf.com/Delphi-Flap-RT). The questionnaire included numerous statements or proposals, covering four major domains, to be agreed or disagreed with. The four domains were: 1) identification of flaps on imaging for flap delineation, 2) understanding of the risk of tumor relapse and tumor spread patterns and definition of target volumes, 3) functional deterioration with respect to expectations of reconstructive surgery with a flap, and 4) feasibility of dose painting using intensity modulated radiotherapy (IMRT) considering a need to adapt poRT in the presence of flaps.

In the second step, a GORTEC rating group of 15 radiation oncologists from academic university and general hospitals, comprehensive cancer centers and private clinics, with ≥ 10-year experience in head and neck cancers, rated all of the statements in two successive rounds (Figure, Table 1). Each proposal was rated between 1 and 9 (1: disagree; 9: totally agree) in rounds 1 and 2 (Table 1). They were informed of their scores and others between rounds 1 and 2. Items not reaching strong or relative agreement (defined in Table 1, requiring a median score of ≥7/9) following round 1 were submitted to the same panelists to be rated again in light of the answers (quantitative feedback) and corresponding arguments (qualitative feedback) of the other panelists (collected during round 2). Proposals not yielding strong or relative agreement after round 2 were eliminated.

All items reaching strong or relative agreement following round 2 (Table 1) were then rated by 30 international reviewers. This group was composed of radiation oncologists (N=26), surgical oncologists (N=2) and medical oncologists (N=2), selected for their international reputation for expertise in head and neck cancer management and leadership

Items were accepted when rated between 5 to 9 by 90% of the reviewer committee and these constituted the final recommendations (Figure 1). Surgeons and medical oncologists reviewed all of the statements related to combined modality treatments; they were invited to review the statements from a multidisciplinary perspective and their responses were incorporated and analyzed separately.

Results

After the two successive rounds, strong agreement, relative agreement, or no consensus was achieved for 26, 9 and 24 items out of the initial 59 items, respectively (Table 2). Median scores and final consensus categorizations are provided in table 2. In all, after external review, overall consensus was only clearly achieved across of the four domains, with 11/15 items (73.3%) achieving consensus on the risk of radiation-induced functional deterioration of flaps. In the other domains, there was consensus achieved on specific items: 5/9 items (55.6%) on feasibility of poRT dose-painting for flap avoidance; 7/17 (41.2%) items on flap definition; and 2/18 items (11.1%) on risk of tumor relapse and patterns of tumor spread in the presence of a flap (Table 2). Among the items initially validated as achieving strong/relative consensus in the rating group, those not achieving consensus in the third-round reviewing group (n=10) were related to flap delineation (n=3) and tumor spread pattern (n=7).

Flap definition on imaging has hardly been addressed in the literature and is described with grade C evidence at best [2,14,15,25,41]. Still, at final review, flap definition was able to achieve strong agreement for 6 items (Table 2). The final recommendations were as follows: (1) surgeons should accurately describe the flap with respect to the native anatomy following tumor resection in standardized operating reports; (2) surgeons should also report whether clips were used in the tumor bed point to areas of dubious R0 or R1 resection or hemostasis; (3) clips should be placed in a standardized manner and regardless of the negligible artifacts that they produce, which do not interfere with delineation and dose calculation; (4) the planning CT should be contrast-enhanced for better flap visualization and to help pick up ignored residual tumor or early relapse.

Ten items were controversial: 7 after the second round and 3 after external review (Table 2). Experts disagreed on the degree of difficulty in identifying flap contours or components on a planning CT as well as identification of the junctional area [15]. More importantly, no consensus was reached within the committee as to how the flap should be delineated (Table 2). Uncertainties remained on whether to place clips at the flap-tissue junction [42], the usefulness of contrast enhancement to distinguish the vascular anastomosis, and acquisition of magnetic resonance imaging to visualize the flap versus referring to a surgeon for delineation.

Tumor risk assessment with respect to the installed flap has only been addressed in a few grade C publications [42–44]. Only 2 items that achieved strong agreement after the rating phase were validated by the reviewing group (Table 2) stating that: (1) clinicians should be aware that the flap-tissue junction is at higher risk of tumor recurrence compared to other areas of the flap and (2) the dose delivered to the junctional area should be the same as the dose delivered to the primary high-risk CTV, if the final resection margin is involved (R2), close (R1) or if there is ambiguity about complete clearance (Table 2). Nine items did not achieve consensus after the rating phase and were not circulated to the review group. The rating group disagreed on enlarged expansions around the preoperative GTV to compensate for delineation uncertainties. The rating group was uncertain about the likelihood of microscopic tumor spread from the junctional area toward the "mucosal or cutaneous" flap surface and the impact of histology or tumor primary site on risk of recurrence. No consensus was reached as to whether the "junctional area" should be considered to be 10 mm or more [41]. No consensus was reached as to whether the body of the flap should be included in the low-risk area to decrease morbidity, or if it should be included in the high-risk area to compensate for delineation uncertainties. For pedicled flaps, no consensus was reached as to whether the vascular pedicle should be included in the CTV. For free flaps, it was uncertain as to whether vascular anastomosis is a means of tumor dissemination.

Interestingly, 7 items related to tumor spread patterns into flaps and flap definition as a CTV or organ at risk, previously achieving strong/relative agreement after round 2, were not supported by the international review group (Figure 1, Table 2). The review group disagreed on the need for systematic coregistration of the preoperative imaging with the postoperative CT scan to define the postoperative CTV, and on the inclusion in the CTV of "direct" postoperative modifications (edema, hematoma, lymphocele) due to flap surgery. The review group did not agree on the likelihood of microscopic tumor spread patterns from the junctional area toward deep native tissues or whether tumor spread pattern was dependent on flap components (mucosa / skin, fat, muscle / fascia, bone) [15]. The review group also would not endorse consensus on a 6 mm size to define the junction area [44]. Similarly, no consensus was reached as to whether very large flaps and vascular anastomosis should be included in the CTV, nor was consensus reached as to which dose should be delivered to the junction area if the resection is R0.

A functional deleterious impact of radiotherapy on flaps has been repeatedly suggested in the surgical literature (grade B pr C) but has not been formally assessed using controlled studies [24,35]. Strong agreement was achieved for 9 items and relative agreement for 2 items (Table 2). The rating group did not reach consensus on differential effects of poRT on vascular anastomosis from free vs pedicled flap, the impact of flap atrophy on functional deterioration or the need for surgical overcompensation. These items were therefore not submitted to the review group. There was consensus after the rating phase that flap necrosis could not result from damage of vascular anastomosis or thrombosis, but rather would occur in the early postoperative period (caused by the vessel quality, morbidity, or technical procedure) regardless of poRT. However, the international recommendation was to consider that poRT altered soft-tissue flap versatility and its functional results (swallowing, phonation) as well as increased the risk of osteoradionecrosis in bone flaps. The final recommendation stated that flap fibrosis or (fat) atrophy occurred spontaneously but could increase with poRT and with dose.

Feasibility of complex IMRT modulation for flap avoidance was controversial. The rating group did not achieve consensus on the risk of osteoradionecrosis in the presence of metal in the poRT field, or on the need to avoid irradiating the titanium plate fixing the flap and whether such materials should be substituted. Thus, these items were not submitted to the review group and no final recommendation can be made about them. In the end, strong and relative agreement was achieved for 3 and 2 items, respectively, on international review (Table 2). The final, internationally validated recommendations were (1) to use steep gradients to achieve elimination of maximum dose (hot spots) to a delineated vascular pedicle if feasible but (2) that avoidance might not be achievable in thin flaps and (3) the flap mean dose or maximum dose be reduced if necessary, to limit the risks of fatty atrophy, muscle fibrosis or osteoradionecrosis.

One should note that there was substantial variability between the international reviewers for 11 items which had achieved strong/relative consensus in the rating committee but were rejected by the review group (Figure 2). There were also trends by country.

Discussion

In the past, experience with flaps and radiotherapy was usually limited to salvage surgery occurring in irradiated tissues. With increasing surgical expertise, immediate rather than delayed reconstruction has become standard. Flaps have been used in primary reconstructive head and neck surgery increasingly over the last 2 decades although the pioneering works date to the 70's [1,4,19,20,45,46]. Because tumors that require a flap are usually large and of advanced T stage [47], they often require poRT. In our initial systemic review, we found abundant surgical grade B-C literature suggesting radiation-induced flap changes [34,38,39] and deteriorated functional outcomes [24,33,35–40]. Additional anecdotal (grade C) case studies reported flap loss after poRT. However, no references to flaps appear in the latest postoperative radiotherapy recommendations [11,47]. This reflects heterogeneity in practice but also that the management of flaps during radiotherapy is an area of high ambiguity [2].

Our stepwise consensus-building approach among an international community of head and neck experts, mostly radiation oncologists, was able to generate novel recommendations regarding the importance of surgeons reporting on clip placement and operating procedures more accurately. However, due to continuing knowledge gaps concerning flap definition on imaging and more importantly flaps as possible routes for tumor dissemination, there were major uncertainties that translated into significant variability at the international reviewing phase.

Our international panel could not agree on in-flap tumor spread patterns and could not determine whether a flap should be considered as part of the clinical target volume. There was no agreement on risk based on tumor site, tumor histology, or flap components as factors influencing tumor spread patterns. There was also lack of agreement on whether the whole flap (+/- its vascular anastomosis) should be included or only its area next to the flap-tissue junction as suggested by one team based on their practice rather than evidence [42–44]. There is concern about irradiation of large pedicled flaps, such as pectoralis major flaps, as including the whole flap in the CTV can inflate irradiated normal tissue volumes significantly and result in more toxicities [25].

The international group agreed on the concern about radiation-induced fibrosis and atrophy which might affect function. Therapeutic recommendations were to achieve flap and vascular pedicle dose avoidance through steep gradients potentially using complex fluence modulation. The surgical literature mostly reports small surgical series of fibrosis and atrophy.

As the true prevalence of flap atrophy of large fatty flaps is unknown, this is an area requiring further future assessment. There is limited but higher-quality literature (grade B-C) concerning functional outcomes following flap irradiation, which underscores the importance of defining the volumes and doses given to these flaps to better study their effects. There remains a need for better reports of literature and experience-based knowledge of functional outcomes following flap irradiation.

Items regarding the management of metal materials for bone flaps were controversial from scratch and could not reach the review phase.

An important factor in variability, and a potential limitation of this process, is shown by the 11 items that passed the initial rating phase but were rejected by the international group. While in part due to a lack of published evidence or data, there may also be variable experience with postoperative radiotherapy across countries, or even individual centers. There may be various strategies regarding the use of surgery followed by radiotherapy or upfront radiotherapy and consequently the management of flaps [48].

Conclusion

The major internationally validated consensus statements were that the flap-tissue junction should be considered at higher risk of tumor spread compared to other areas of the flap and that postoperative planning should be based on a contrast-enhanced CT. Surgeons should report the placement of flaps more accurately and consider clip placement to guide radiotherapy planning. It was also recommended to consider the risks of radiation-induced atrophy, fibrosis, and osteoradionecrosis and limit the maximum and mean doses during the radiotherapy planning process. There remain substantial knowledge gaps and as result, large areas of international variability. Patterns of tumor spread, and the results of dose-avoidance should be analyzed prospectively with assessment of functional outcomes and quality of life.

References

[1] Urken ML. Advances in head and neck reconstruction. The Laryngoscope 2003;113:1473–6. https://doi.org/10.1097/00005537-200309000-00008.

[2] Thariat J, Leleu T, Micault E, Gery B, Bastit V, Jeanne C, et al. [Ten years of advances in head and neck surgery, how does this influence postoperative radiotherapy?]. Bull Cancer (Paris) 2020;107:823–9. https://doi.org/10.1016/j.bulcan.2020.04.011.

[3] Cormack GC, Lamberty BG. A classification of fascio-cutaneous flaps according to their patterns of vascularisation. Br J Plast Surg 1984;37:80–7. https://doi.org/10.1016/0007-1226(84)90049-3.

[4] Lamberty BG, Cormack GC. Progress in flap surgery: greater anatomical understanding and increased sophistication in application. World J Surg 1990;14:776–85. https://doi.org/10.1007/BF01670524.

[5] Bozec A, Demez P, Gal J, Chamorey E, Louis M-Y, Blanchard D, et al. Long-term quality of life and psycho-social outcomes after oropharyngeal cancer surgery and radial forearm free-flap reconstruction: A GETTEC prospective multicentric study. Surg Oncol 2018;27:23–30. https://doi.org/10.1016/j.suronc.2017.11.005.

[6] Grégoire V, Evans M, Le Q-T, Bourhis J, Budach V, Chen A, et al. Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines. Radiother Oncol J Eur Soc Ther Radiol Oncol 2018;126:3–24. https://doi.org/10.1016/j.radonc.2017.10.016.

[7] Chao KSC, Ozyigit G, Tran BN, Cengiz M, Dempsey JF, Low DA. Patterns of failure in patients receiving definitive and postoperative IMRT for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2003;55:312–21. https://doi.org/10.1016/s0360-3016(02)03940-8.

[8] Grégoire V, Eisbruch A, Hamoir M, Levendag P. Proposal for the delineation of the nodal CTV in the node-positive and the post-operative neck. Radiother Oncol J Eur Soc Ther Radiol Oncol 2006;79:15–20. https://doi.org/10.1016/j.radonc.2006.03.009.

[9] Grégoire V, Levendag P, Ang KK, Bernier J, Braaksma M, Budach V, et al. CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC,RTOG consensus guidelines. Radiother Oncol J Eur Soc Ther Radiol Oncol 2003;69:227–36. https://doi.org/10.1016/j.radonc.2003.09.011.

[10] Cho Y, Yoon HI, Lee IJ, Kim JW, Lee CG, Choi EC, et al. Patterns of local recurrence after curative resection and reconstruction for oropharyngeal and oral cancers: Implications for postoperative radiotherapy target volumes. Head Neck 2019;41:3916–23. https://doi.org/10.1002/hed.25928.

[11] Evans M, Beasley M. Target delineation for postoperative treatment of head and neck cancer. Oral Oncol 2018;86:288–95. https://doi.org/10.1016/j.oraloncology.2018.08.011.

[12] Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck 2005;27:843–50. https://doi.org/10.1002/hed.20279.

[13] Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre J-L, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945–52. https://doi.org/10.1056/NEJMoa032641.

[14] Racadot S, Vérillaud B, Serre A-A, Le Guevelou J, Guzene L, Laude C, et al. [Impact of

reconstructive or minimal invasive surgery on the assessment of current definitions of postoperative clinical target volume for head and neck cancers]. Cancer Radiother J Soc Francaise Radiother Oncol 2020;24:649–57. https://doi.org/10.1016/j.canrad.2020.05.012.
[15] Le Guevelou J, Bastit V, Marcy PY, Lasne-Cardon A, Guzene L, Gerard M, et al. Flap delineation guidelines in postoperative head and neck radiation therapy for head and neck cancers. Radiother Oncol J Eur Soc Ther Radiol Oncol 2020;151:256–65. https://doi.org/10.1016/j.radonc.2020.08.025.
[16] Yi CR, Jeong WS, Oh TS, Koh KS, Choi J-W. Analysis of Speech and Functional Outcomes in Tongue Reconstruction after Hemiglossectomy. J Reconstr Microsurg 2020;36:507–13. https://doi.org/10.1055/s-0040-1709493.
[17] Pierre CS, Dassonville O, Chamorey E, Poissonnet G, Riss J-C, Ettaiche M, et al. Long-term functional outcomes and quality of life after oncologic surgery and microvascular reconstruction in patients with oral or oropharyngeal cancer. Acta Otolaryngol (Stockh) 2014;134:1086–93. https://doi.org/10.3109/00016489.2014.913809.
[18] Rihani J, Lee MR, Lee T, Ducic Y. Flap selection and functional outcomes in total glossectomy with laryngeal preservation. Otolaryngol--Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg 2013;149:547–53. https://doi.org/10.1177/0194599813498063.
[19] Bozec A, Poissonnet G, Chamorey E, Laout C, Vallicioni J, Demard F, et al. Radical ablative surgery and radial forearm free flap (RFFF) reconstruction for patients with oral or oropharyngeal cancer: postoperative outcomes and oncologic and functional results. Acta Otolaryngol (Stockh) 2009;129:681–7. https://doi.org/10.1080/00016480802369260.
[20] Bozec A, Poissonnet G, Chamorey E, Casanova C, Vallicioni J, Demard F, et al. Free-flap head and neck reconstruction and quality of life: a 2-year prospective study. The Laryngoscope 2008;118:874–80. https://doi.org/10.1097/MLG.0b013e3181644abd.
[21] Bozec A, Poissonnet G, Chamorey E, Casanova C, Laout C, Vallicioni J, et al. Quality of life after oral and oropharyngeal reconstruction with a radial forearm free flap: prospective study. J Otolaryngol - Head Neck Surg J Oto-Rhino-Laryngol Chir Cervico-Faciale 2009;38:401–8.
[22] Zhang X, Li M-J, Fang Q-G, Sun C-F. A comparison between the pectoralis major myocutaneous flap and the free anterolateral thigh perforator flap for reconstruction in head and neck cancer patients: assessment of the quality of life. J Craniofac Surg 2014;25:868–71. https://doi.org/10.1097/SCS.0000000000000443.
[23] van Hinte G, Wetzels J-WGH, Merkx MAW, de Haan AFJ, Koole R, Speksnijder CM. Factors influencing neck and shoulder function after oral oncology treatment: a five-year prospective cohort study in 113 patients. Support Care Cancer Off J Multinatl Assoc Support Care Cancer 2019;27:2553–60. https://doi.org/10.1007/s00520-018-4534-1.
[24] Shin YS, Koh YW, Kim S-H, Jeong JH, Ahn S, Hong HJ, et al. Radiotherapy deteriorates postoperative functional outcome after partial glossectomy with free flap reconstruction. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 2012;70:216–20. https://doi.org/10.1016/j.joms.2011.04.014.
[25] Gérard M, Le Guevelou J, Jacksic N, Lequesne J, Bastit V, Géry B, et al. Postoperative radiotherapy after flap reconstructive surgery in patients with head and neck cancer: A retrospective monocentric study with flap delineation to assess toxicity and relapse. Cancer Radiother J Soc Francaise Radiother Oncol 2020;24:851–9. https://doi.org/10.1016/j.canrad.2020.06.024.
[26] Las DE, de Jong T, Zuidam JM, Verweij NM, Hovius SER, Mureau MAM. Identification of independent risk factors for flap failure: A retrospective analysis of 1530 free flaps for

breast, head and neck and extremity reconstruction. J Plast Reconstr Aesthetic Surg JPRAS 2016;69:894–906. https://doi.org/10.1016/j.bjps.2016.02.001.
[27] Ooishi M, Motegi A, Kawashima M, Arahira S, Zenda S, Nakamura N, et al. Patterns of failure after postoperative intensity-modulated radiotherapy for locally advanced and recurrent head and neck cancer. Jpn J Clin Oncol 2016;46:919–27. https://doi.org/10.1093/jjco/hyw095.
[28] Halle M, Eriksson BO, Docherty Skogh A-C, Sommar P, Hammarstedt L, Gahm C. Improved Head and Neck Free Flap Outcome-Effects of a Treatment Protocol Adjustment from Pre- to Postoperative Radiotherapy. Plast Reconstr Surg Glob Open 2017;5:e1253. https://doi.org/10.1097/GOX.0000000000001253.
[29] Choi S, Schwartz DL, Farwell DG, Austin-Seymour M, Futran N. Radiation therapy does not impact local complication rates after free flap reconstruction for head and neck cancer. Arch Otolaryngol Head Neck Surg 2004;130:1308–12. https://doi.org/10.1001/archotol.130.11.1308.
[30] Jones J, Hunter D. Consensus methods for medical and health services research. BMJ 1995;311:376–80. https://doi.org/10.1136/bmj.311.7001.376.
[31] French Haute autorité de santé. Elaboration de recommandation de bonne pratique - Recommandations par consensus formalisé 2010.
[32] Tai H-C, Hsieh C-H, Chao KSC, Liu S-H, Leu Y-S, Chang Y-F, et al. Comparison of radiotherapy strategies for locally advanced hypopharyngeal cancer after resection and ileocolic flap reconstruction. Acta Otolaryngol (Stockh) 2009;129:311–7. https://doi.org/10.1080/00016480802163366.
[33] Haymerle G, Enzenhofer E, Lechner W, Stock M, Schratter-Sehn A, Vyskocil E, et al. The effect of adjuvant radiotherapy on radial forearm free flap volume after soft palate reconstruction in 13 patients. Clin Otolaryngol Off J ENT-UK Off J Neth Soc Oto-Rhino-Laryngol Cervico-Facial Surg 2018;43:742–5. https://doi.org/10.1111/coa.13042.
[34] Yamazaki M, Suzuki T, Hiraga C, Yoshida Y, Baba A, Saitou H, et al. Effect of postoperative radiotherapy for free flap volume changing after tongue reconstruction. Oral Radiol 2020. https://doi.org/10.1007/s11282-020-00489-0.
[35] Winter SCA, Cassell O, Corbridge RJ, Goodacre T, Cox GJ. Quality of life following resection, free flap reconstruction and postoperative external beam radiotherapy for squamous cell carcinoma of the base of tongue. Clin Otolaryngol Allied Sci 2004;29:274–8. https://doi.org/10.1111/j.1365-2273.2004.00812.x.
[36] Leu Y-S, Hsiao H-T, Chang Y-C, Yang C-C, Lee J-C, Chen Y-J, et al. Ileocolic free flap reconstruction, concomitant chemotherapy and radiotherapy and assessment of speech and swallowing function during management of advanced cancer of the larynx and hypopharynx: preliminary report. Acta Otolaryngol (Stockh) 2005;125:642–6. https://doi.org/10.1080/00016480510027457.
[37] Airoldi M, Garzaro M, Raimondo L, Pecorari G, Giordano C, Varetto A, et al. Functional and psychological evaluation after flap reconstruction plus radiotherapy in oral cancer. Head Neck 2011;33:458–68. https://doi.org/10.1002/hed.21471.
[38] Higgins KM, Erovic BM, Ravi A, Yeung R, Lee JW, Yao C, et al. Volumetric changes of the anterolateral thigh free flap following adjuvant radiotherapy in total parotidectomy reconstruction. The Laryngoscope 2012;122:767–72. https://doi.org/10.1002/lary.22509.
[39] Tarsitano A, Battaglia S, Cipriani R, Marchetti C. Microvascular reconstruction of the tongue using a free anterolateral thigh flap: Three-dimensional evaluation of volume loss after radiotherapy. J Cranio-Maxillo-Fac Surg Off Publ Eur Assoc Cranio-Maxillo-Fac Surg

2016;44:1287–91. https://doi.org/10.1016/j.jcms.2016.04.031.
[40] Lilja M, Markkanen-Leppänen M, Viitasalo S, Saarilahti K, Lindford A, Lassus P, et al. Olfactory and gustatory functions after free flap reconstruction and radiotherapy for oral and pharyngeal cancer: a prospective follow-up study. Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg 2018;275:959–66. https://doi.org/10.1007/s00405-018-4883-x.
[41] Fleury B, Thariat J, Barnoud R, Buiret G, Lebreton F, Bancel B, et al. [Microscopic extensions of head and neck squamous cell carcinomas: impact for clinical target volume definition]. Cancer Radiother J Soc Francaise Radiother Oncol 2014;18:666–71. https://doi.org/10.1016/j.canrad.2014.04.006.
[42] Bittermann G, Wiedenmann N, Bunea A, Schwarz SJ, Grosu A-L, Schmelzeisen R, et al. Clipping of tumour resection margins allows accurate target volume delineation in head and neck cancer adjuvant radiation therapy. Radiother Oncol J Eur Soc Ther Radiol Oncol 2015;116:82–6. https://doi.org/10.1016/j.radonc.2015.04.025.
[43] Bittermann G, Voss P, Duttenhoefer F, Zimmerer R, Vach K, Metzger MC. The validity of surgical clips as radiographic markers for the tumour resection cavity in head and neck cancer treatment. J Cranio-Maxillo-Fac Surg Off Publ Eur Assoc Cranio-Maxillo-Fac Surg 2015;43:758–62. https://doi.org/10.1016/j.jcms.2015.04.005.
[44] Bittermann G, Wiedenmann N, Voss P, Zimmerer R, Duttenhoefer F, Metzger MC. Marking of tumor resection borders for improved radiation planning facilitates reduction of radiation dose to free flap reconstruction in head and neck cancer surgery. J Cranio-Maxillo-Fac Surg Off Publ Eur Assoc Cranio-Maxillo-Fac Surg 2015;43:567–73. https://doi.org/10.1016/j.jcms.2015.02.021.
[45] Jose B, Banis J, Flynn M, Lindberg R, Spanos WJ, Paris K, et al. Irradiation and free tissue transfer in head and neck cancer. Head Neck 1991;13:213–6. https://doi.org/10.1002/hed.2880130308.
[46] Nakamizo M, Yokoshima K, Yagi T. Use of free flaps for reconstruction in head and neck surgery: a retrospective study of 182 cases. Auris Nasus Larynx 2004;31:269–73. https://doi.org/10.1016/j.anl.2004.03.003.
[47] Margalit DN, Sacco AG, Cooper JS, Ridge JA, Bakst RL, Beadle BM, et al. Systematic review of postoperative therapy for resected squamous cell carcinoma of the head and neck: Executive summary of the American Radium Society appropriate use criteria. Head Neck 2021;43:367–91. https://doi.org/10.1002/hed.26490.
[48] Culié D, Garrel R, Viotti J, Schiappa R, Chamorey E, Fakhry N, et al. Impact of HPV-associated p16-expression and other clinical factors on therapeutic decision-making in patients with oropharyngeal cancer: A GETTEC multicentric study. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol 2018;44:1908–13. https://doi.org/10.1016/j.ejso.2018.05.022.

Figures and Tables legend

Figure 1 **consensus methodology** (adapted from the French Heath authorities 'recommendation, https://www.has-sante.fr/upload/docs/application/pdf/2011-06/guideline_by_formal_consensus_quick_methodology_guide_110531.pdf) GORTEC Groupe d'Oncologie Radiotherapie des tumeurs de la Tete Et du Cou, HNFIG Head and Neck French InterGroup, international Head and Neck Cancer experts.

Figure 2 **Analysis of items** that passed the initial rating phase but were rejected by the international review group, with voting by country.

Table 1 **Criteria for acceptance of proposals** based on median value and distribution of ratings.

Table 2 **Proposals submitted and rated** across successive rounds.

Table 1: Criteria for acceptance of proposals based on median value and distribution of ratings.

Proposal evaluation		**Median value**	**Distribution of responses**
Appropriate	Strong agreement	≥ 7	All between [7- 9]
	Relative agreement	≥ 7	All between [5- 9]
Inappropriate	Strong agreement	≤ 3	All between [1- 3]
	Relative agreement	≤ 3.5	All between [1- 5]
Uncertain	Indecision	4 ≤ median ≤ 6,5	All between [1-9]
	Lack of consensus	All others	

For a group of more than 15 experts, analysis in the second round allowed exclusion of a missing value or a value opposite to that dominant group.

Table 2: Proposals submitted and rated across successive rounds.

		GORTEC Rating Committee		External Review group
Item	Proposals established by a GORTEC steering committee and present at:	Round 1	Round 2	Round 3
	Flap Delineation			
1	It is not well defined how to identify the flap contours on a planning CT	NC [6]	RA [7]	NC
2	It is difficult to identify the components of a flap according to their density on the planning CT	NC [7]	SA [7]	NC
3	The junction area (as defined by Bittermann) is difficult to define on a postoperative CT scan	NC [7]	SA [8]	NC
4	Surgeons should report on the position of the flap with respect to the native anatomy following tumor resection in their operating report	NC [8]	SA [8]	FR
5	It is important that surgeons report whether they used clips for hemostasis in the flap area	NC [5]	RA [7]	FR
6	It is important that surgeons report on using clips to define areas of questionable (dubious R0 or R1) resection	NC [5]	SA [8]	FR
7	The placement of clips around the tumor bed should be standardized between surgeons and described in the operating report	NC [8]	SA [8]	FR
8	The use of clips does not induce significant artifacts and should not interfere with delineation and dose calculation	NC [6.5]	SA [8]	FR
9	It is important that the planning CT be contrast enhanced to better visualize the flap	NC [7.5]	SA [8]	FR
10	It is important that the planning CT be contrast enhanced so as not to ignore an early evolution or a macroscopic postoperative tumor residue	SA [9]		FR
11	It is important to contour the flap	NC [5]	NC [7]	
12	It is not necessary to contour the flap because it is systematically positioned in an area to be irradiated (in the primary CTV T or in the prophylactic lymph node volumes N)	NC [5]	NC [3]	
13	It is important for surgeons to describe in their operating report whether they are using clips to show the junction area between the flap and native tissues remaining after tumor resection	NC [5]	NC [7]	
14	It is important to inject the planning CT to visualize the vascular pedicle	NC [7]	NC [7]	

15	Postoperative MRI might be helpful to improve visualization of the flap	NC [6]	NC [6]	
16	The recommendations for delineating CTVs are applicable whether there is a flap in the operating area or not (recommendations of Evans 2018 postoperatively)	NC [6]	NC [5]	
17	It is essential to carry out the delineation in the presence of the surgeon	NC [4]	NC [3]	
	Tumor spread pattern in a flap			
18	Coregistration of the preoperative imaging with the postoperative CT scan should be performed systematically to define the postoperative CTV	NC [8]	RA [8]	NC
19	Coregistration uncertainties (of the preoperative imaging with postoperative planning CT) should be compensated by expanding larger margins (than recommended for postoperative radiotherapy) around the preoperative GTV	NC [6]	NC [5]	
20	"Direct" postoperative modifications (edema, hematoma, lymphocele) of the flap should be included in the CTV	NC [7]	SA [7]	NC
21	The risk of microscopic tumor spread is centrifugal from the junction area to the depth of the remaining native tissues	NC [7]	SA [8]	NC
22	The risk of spreading microscopic disease is centrifugal from the junction area to the “mucous or cutaneous” surface of the flap	NC [4.5]	NC [5]	
23	The risk of microscopic diffusion into the flap may vary depending on the histology (squamous cell carcinoma and variants, adenoid cystic carcinoma, adenocarcinoma...)	NC [5]	NC [6]	
24	The risk of microscopic diffusion into the flap may vary depending to the tumor location (parotid vs pharynx vs sinus)	NC [6.5]	NC [6]	
25	The junction area between the native tissues (remaining after tumor resection) and the deep part of the flap is an area at higher risk of cancer	SA [8]		FR
26	The junction area is an area of the order of 6 mm thick in the depth of the flap as described by Bittermann (2015)	NC [6]	RA [7]	NC
27	The junction area at risk is about 10 mm thick in the depth of the flap	NC [5.5]	NC [5]	
28	The junction area varies in thickness depending on the nature of the components of the flap (mucosa / skin, fat, muscle / fascia, bone)	NC [7]	SA [7]	NC
29	The body of the flap (including all the rest of the flap beyond the junction area) should be irradiated entirely in the low-risk area	NC [4]	NC [3]	

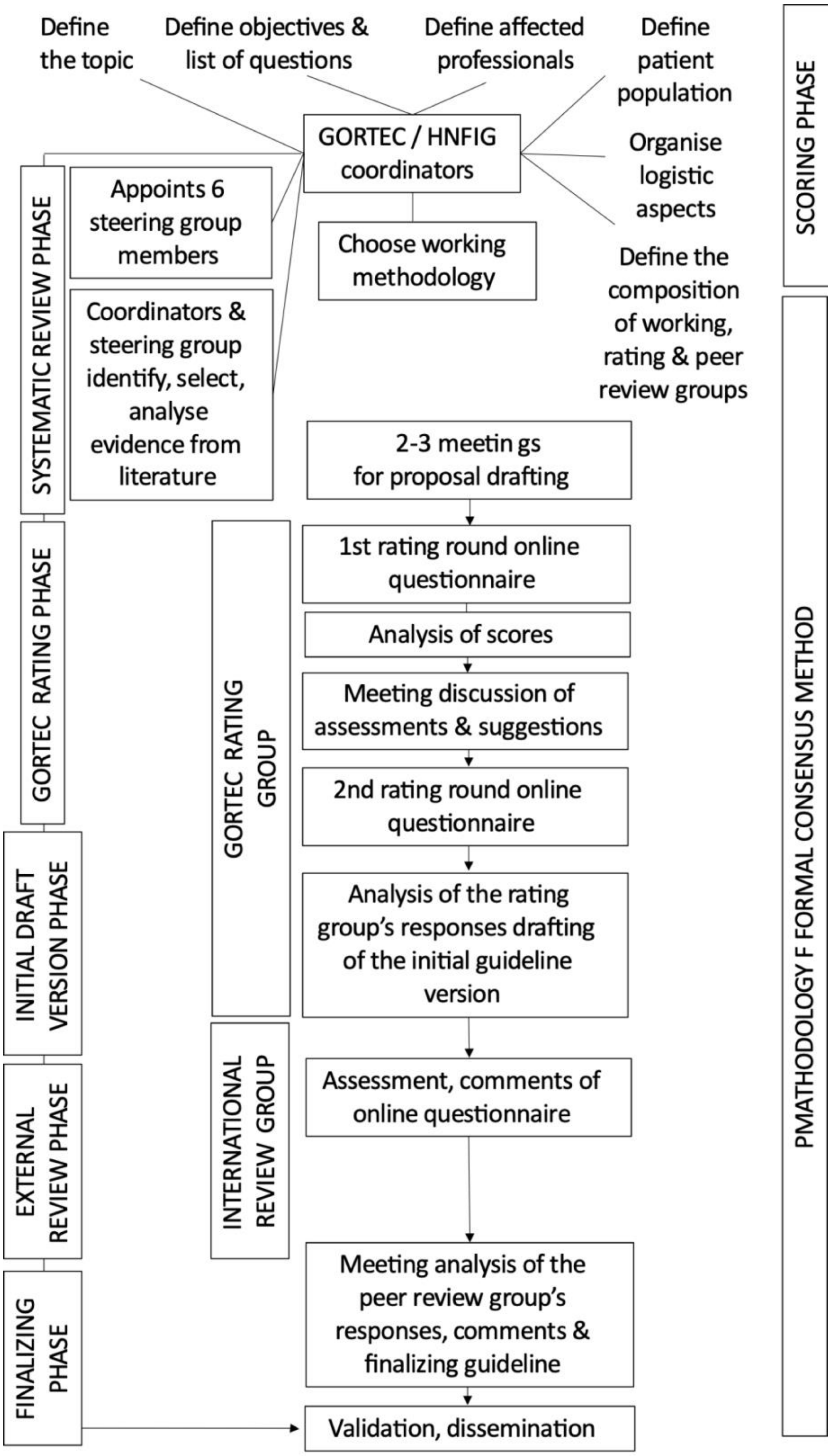
30	When the flap is very large, some of the flap body may not be included in the low-risk area	NC [6.5]	SA [8]	NC
31	The delineation uncertainties are so great in the postoperative situation that it is better to irradiate wide even if it means including the entire flap	NC [4.5]	NC [7]	
32	For pedicled flaps, it is not useful to include the vascular pedicle in the CTV. Its tumor colonization is unlikely, and its distal part is far from the operating bed of the primary patient	NC [4.5]	NC [7]	
33	For free flaps, vascular anastomosis is not a way of tumor dissemination	NC [5]	NC [7]	
34	The dose level delivered to the junction area corresponds to primary low-risk CTV if the resection is R0	NC [7.5]	RA [8]	NC
35	The dose level delivered to the junction area corresponds to primary high-risk CTV if the final quality of the resection is dubious R0 or R1 or R2	SA [8]		FR
	Functional flap outcomes			
36	Flap necrosis occurs in early postoperative (vessel quality, morbidity, technical procedure) and radiotherapy does not induce any specific risk	NC [7]	SA [8]	FR
37	Irradiation of the vascular pedicle of a flap induces a risk of necrosis of the flap that is negligible (=unlikely) (strong agreement)	NC [7]	SA [8]	FR
38	The dose received at the vascular anastomosis is not correlated with an increased risk of vascular thrombosis	NC [7]	RA [8]	FR
39	Irradiation of the vascular pedicle from a free flap is at higher risk of necrosis than irradiation of a vascular pedicle from a pedicled flap (no consensus)	NC [5]	NC [5]	
40	Radiotherapy alters the flexibility of the flap	NC [7]	SA [8]	FR
41	Radiotherapy can alter the functional results (swallowing, phonation) of the flap	NC [7]	SA [7]	FR
42	Irradiation of a bone flap is at risk of radionecrosis of the flap	NC [7]	SA [8]	FR
43	Atrophy of the fat flaps is possible spontaneously even in the absence of radiotherapy	NC [7]	SA [8]	FR
44	The risk of atrophy of the flap fat increases with radiotherapy	NC [8]	SA [8]	FR
45	Flap fat atrophy is associated with deterioration of functional results	NC [5.5]	NC [5]	
46	Flap fat atrophy MUST BE anticipated by surgeons by overcompensating tissue / flap thickness	NC [7]	NC [7]	
47	The radiation-induced atrophy of the fatty component of the flaps is related to the dose received	NC [5]	NC [7]	
48	Fibrosis changes of flaps are possible spontaneously even in the absence of radiotherapy	NC [6]	RA [7]	FR

49	Fibrosis of the muscle flap component can be favored by radiotherapy (significantly more than surgery alone)	NC [7]	SA [7]	FR
50	Radiation-induced flap fibrosis increases with dose	NC [7]	SA [7]	FR
	Technical IMRT feasibility (dose painting for structure avoidance)			
51	For thin flap, it may not be possible to achieve sufficiently steep gradients to spare the flap of the part	NC [7.5]	SA [8]	FR
52	Limiting the average dose to the flap could limit the risk for fatty atrophy and muscle fibrosis	NC [6]	RA [7]	FR
53	Limiting the average dose to the bone of the flap could limit the risk for flap osteoradionecrosis	NC [7]	RA [7]	FR
54	Limiting the maximum dose to the bone flap could limit the risk for osteoradionecrosis	NC [8]	SA [8]	FR
55	In the case of a bone flap, the presence of titanium, or other metal, in the irradiation area induces an increased risk of osteoradionecrosis	NC [7.5]	NC [6]	
56	In the case of a bone flap, avoid irradiating the titanium plate fixing the flap allows to reduce the risk of osteoradionecrosis	NC [4.5]	NC [3]	
57	In the case of a bone flap, titanium-type materials must be substituted to reduce the risk of osteoradionecrosis	NC [4.5]	NC [5]	
58	Limiting the maximum dose (hot spots) to the vascular pedicle seems feasible technically if the pedicle is delineated	NC [7]	SA [7]	FR
59	Limiting the maximum dose (hot spots) to the vascular pedicle would reduce the risk of necrosis of the flap	NC [5]	NC [6]	

Legend: SA strong agreement, RA relative agreement, NC no consensus, FR final recommendation; GORTEC steering committee and GORTEC rating committee are independent; median is indicated between brackets (median = 7-9 is required but ≥ 2 eliminating grades qualify items as NC for the first two rounds).

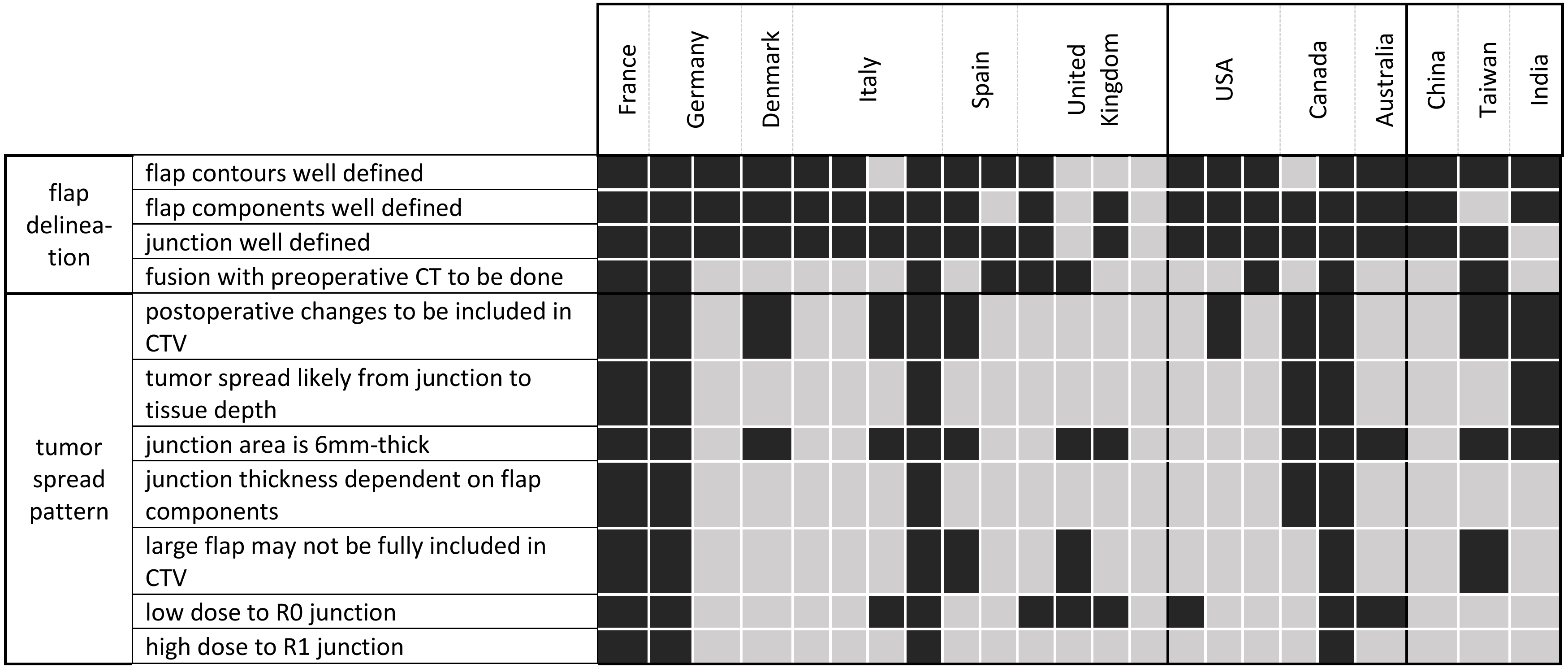
Figure 1: consensus methodology

(adapted from the French Heath authorities 'recommendation, https://www.has-sante.fr/upload/docs/application/pdf/2011-06/guideline_by_formal_consensus_quick_methodology_guide_110531.pdf)



Legend: GORTEC Groupe d'Oncologie Radiotherapie des tumeurs de la Tete Et du Cou, HNFIG Head and Neck French InterGroup, international Head and Neck Cancer experts.

Figure 2: Analysis of items that passed the initial rating phase but were rejected by the international review group, with voting by country.



CONFLICT OF INTEREST

Title page : **Recommendations for postoperative radiotherapy in head & neck squamous cell carcinoma in the presence of flaps: a GORTEC internationally-reviewed consensus**

Florent Carsuzaa[1], Michel Lapeyre[2], Vincent Gregoire[3], Philippe Maingon[4], Arnaud Beddok[5], Pierre-Yves Marcy[6], Julia Salleron[7], Alexandre Coutte[8], Severine Racadot[3], Yoann Pointreau[9], Pierre Graff[10], Beth Beadle[11], Karen Benezery[12], Julian Biau[2], Valentin Calugaru[5], Joel Castelli[13], Melvin Chua[14], Alessia Di Rito[15], Melanie Dore[16], Pirus Ghadjar[17], Florence Huguet[18], Pauline Jardel[19], Jorgen Johansen[20], Randall Kimple[21], Marco Krengli[22], Sarbani Laskar[23], Lachlan Mcdowell[24], Anthony Nichols[25], Silke tribius[26], Izaskun Valduvieco[27], Chaosu Hu[28], Xavier Liem[29], Antoine Moya-Plana[30], Ida D'onofrio[31], Upendra Parvathanen[32] , Vinita Takiar[33], Ester Orlandi[34], Amanda Psyrri[35], George Shenouda[36], David Sher[37] , Conor Steuer[38], Xu Shan Sun[39], Yungan Tao[30], David Thomson[40], Mu-Hung Tsai[41] , Noemie Vulquin[42], Philippe Gorphe[30], Hisham Mehanna[43], Sue S. Yom[44], Jean Bourhis[45], Juliette Thariat[46]

Conflict of Interest: no conflicting relationship exists for any author.