Surgical Margins in Transoral Robotic Surgery for Oropharyngeal Squamous Cell Carcinoma

Consensus update and recommendations, 2018

Head and Neck Steering Committee

P. Gorphe *, F. Nguyen, Y. Tao, P. Blanchard, O. Casiraghi, A. Ben Lakhdar, F. Bidault, J. Guerlain, D. Hartl, F. Janot, H. Mirghani, A. Moya-Plana, S. Temam, I. Breuskin Institut Gustave Roussy, Villejuif, France



* Synthesis

BACKGROUND margins in Head and Neck surgery

QUESTION sufficient margins in Head and Neck surgery

REVIEW margins for oropharyngeal carcinoma in the literature

CONSENSUS surgical margins in TORS for oropharyngeal squamous cell carcinoma

BACKGROUND margins in Head and Neck surgery





Perfect goal of surgery in oncology

Comprehensive resection, without either macroscopic or microscopic residual disease (R0)







Surgical resection macroscopically complete with security margins of cancer-free tissues

- Decrease as much as possible the risk of microscopic residual disease Vs.
- > Limitation of the major morbidity associated with large resections in Head and Neck

HN Cancer biologically associated with a high risk of microscopic residual disease (high rates of diffuse spreading, perinervous invasion, lympho-vascular invasions, lymph node invasion)

Standard of care : postoperative adjuvant high-dose radiotherapy

BACKGROUND margins in Head and Neck surgery

How are defined the margins ?

UICC/AJCC definitions

R categories for the primary tumor site

- R0 no residual tumor
- R1 microscopic residual tumor
- R2 macroscopic residual tumor
- RX presence of residual tumor cannot be assessed

Margin status

- Negative margins (tumor not present at the surgical margin)
- Microscopic positive margin (tumor present microscopically at the margin)
- Macroscopic positive margin (tumor identified grossly at the margin)
- Margin not assessed



Cancer Staging

Manual

Eighth Edition



How are defined the margins ?

The presence of residual tumor may

- 1. Indicate the effect of therapy
- 2. Influence further therapy
- 3. Be a strong predictor of prognosis



1. Indicate the effect of therapy ?

Pathological features associated with the risk of primary microscopic residual disease

- Size and local invasions of the primary tumor
- Quality of surgical margins
- Presence and intensity of perinervous invasion
- Lympho-vascular invasions





1. Indicate the effect of therapy ?

Pathological features associated with the risk of primary microscopic residual disease

- Size and local invasions of the primary tumor
- Quality of surgical margins
- Presence and intensity of perinervous invasion
- Lympho-vascular invasions

Surgical margin: only feature that the surgeon can influence

> Major criterion of quality assurance in surgical oncology



BACKGROUND margins in Head and Neck surgery

2. Influence further therapy ?

Therapeutic intensification

 Very high risk of microscopic residual disease (microscopic positive margins OR lymph node extracapsular extension)
 Concurrent chemotherapy with postoperative adjuvant radiotherapy (Cisplatine 100mg/m² *3)

Therapeutic deflation

Very low risk of microscopic residual disease
 (sufficient large resection AND no PNI/LVI AND early-stage pT1-2 pN0)
 No postoperative adjuvant radiotherapy





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BACKGROUND margins in Head and Neck surgery



3. Be a strong predictor of prognosis?

Microscopic positive margins are associated with decreased

- ✓ Local control
- ✓ Locoregional control
- ✓ Disease-free survival
- ✓ Overall survival



Kaplan-Meier Curves for overall survival (OS) and disease-free survival (DFS) in 268 patients with pT1-2 oral tongue SCC AJCC 8th edition, according to the R0 versus R1 status (R1: margins \leq 1mm) A study of the Institut Gustave Roussy, 2018, Submission process



□ The status R does not indicates the margins but the risk of microscopic residual disease

Goal: to decrease as much as possible the risk of microscopic residual disease (status R1)

□ The status of margins must be reported and identified along with the evaluation of the status *R*

□ The risk of status R1 is to be evaluated according to the risk factors of microscopic residual disease



□ The risk of status R1 (microscopic residual disease) is deemed very high when a margin is microscopic positive (or ≤ 1mm, for most of teams)

□ The risk of R1 decreases with the size of the security margin of cancer-free tissues

□ The risk of R1 is deemed very low when cancer-free margins are large :

« sufficient margins »





« security margins of cancer-free tissues »

Sufficient resection: Is there a definition ?



« security margins of cancer-free tissues »

Sufficient resection: Is there a definition ?

- Positive surgical margin
- Close surgical margin
- Negative surgical margin



Qualitative evaluation Vs. Quantitative (mm)

The quantitative definition of sufficient margins depends on

- 1. The size and extents of the primary tumor
- 2. The anatomical boundaries of the primary site





1. The size and extents of the primary tumor

- Risks of inadequate margins in deep connective tissue > mucosal margins
- Visibility Vs. Very limited palpation in TORS

Characteristic

Negative

Intraoperative margins

• Bulky and superficial tumors Vs. Deep infiltrating tumors

BOT (n = 51)

32

%

62.75

Positive	18	35.29	11	12.36		
Persky et al. Positive marains b	v oropharvnaeal subsite in tr	ansoral robotic suraerv	for T1/T2 sauamous cell	carcinoma. Otolarvnaoloav –	Head and Neck Surgery 2018 158	3(4) 660-666

Primary Surgery

n

73

Tonsil (n = 89)

82.02

P Value

.002





1. The size and extents of the primary tumor

- Risks of inadequate margins in deep connective tissue > mucosal margins
- Visibility Vs. Very limited palpation in TORS
- Bulky superficial tumors Vs. Deep infiltrating tumors

TORS: mainly for limited and resectable T1-2 tumors

Size and extents of the primary tumor should not be limitations for adequate margins







2. The anatomical boundaries of the primary site

- Tonsil fossa
- Base of tongue
- Posterior pharyngeal wall



2. The anatomical boundaries of the primary site

- Tonsil fossa
- Base of tongue
- Posterior pharyngeal wall

- > Deep margins are anatomically limited by the parapharyngeal space
- Size (mm) of deep margins will not exceed the thickness of the superior constrictor





2. The anatomical boundaries of the primary site

- Tonsil fossa
- Base of tongue
- Posterior pharyngeal wall

- > Deep margins are not anatomically limited by deep muscles structures
- Size (mm) of deep margins are expected to be at least as large as for oral tongue





- 2. The anatomical boundaries of the primary site
- Tonsil fossa
- Base of tongue
- Posterior pharyngeal wall

- > Deep margins are anatomically limited by the retropharyngeal space
- Invasion of the constrictor muscles in the most of cases









In Oropharyngeal carcinoma





ORAL ONCOLOGY

http://intl.elsevierhealth.com/journals/oron/

A histopathological appraisal of surgical margins in oral and oropharyngeal cancer resection specimens

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Received 6 May 2005; accepted 7 June 2005

status				рТ рN					pStage				
status		T1	T2	Т3	T4	N0	N1	N2b	N2c	I	Ш	Ш	IV
Clear	14	3	7	1	3	9	2	3		3	3	2	6
Close	16 ^a	3	4	4	5	4		9	2		2	1	13
Involved	18	2	1	4	11	7	3	5	3	1	2	3	12
	Clear Close Involved	Clear 14 Close 16 ^a Involved 18	Clear 14 3 Close 16 ^a 3 Involved 18 2	Clear1437Close16a34Involved1821	Clear 14 3 7 1 Close 16 ^a 3 4 4 Involved 18 2 1 4	Clear 14 3 7 1 3 Close 16 ^a 3 4 4 5 Involved 18 2 1 4 11	Clear 14 3 7 1 3 9 Close 16 ^a 3 4 4 5 4 Involved 18 2 1 4 11 7	Clear 14 3 7 1 3 9 2 Close 16 ^a 3 4 4 5 4 Involved 18 2 1 4 11 7 3	Clear 14 3 7 1 3 9 2 3 Close 16 ^a 3 4 4 5 4 9 Involved 18 2 1 4 11 7 3 5	Clear 14 3 7 1 3 9 2 3 Close 16 ^a 3 4 4 5 4 9 2 Involved 18 2 1 4 11 7 3 5 3	Clear 14 3 7 1 3 9 2 3 3 Close 16 ^a 3 4 4 5 4 9 2 1 1 1 7 3 5 3 1 Involved 18 2 1 4 11 7 3 5 3 1	Clear 14 3 7 1 3 9 2 3 1 2 1 1 7 3 5 3 1 2 1 1 1 7 3 5 3 1 2 1 1 1 7 3 5 3 1 2 1 1 1 7 3 5 3 1 2 1 1 1 7 3 5 3 1 2 1 1 1 7 3 5 3 1 <td>Clear 14 3 7 1 3 9 2 3 3 3 2 Close 16^a 3 4 4 5 4 9 2 2 1 Involved 18 2 1 4 11 7 3 5 3 1 2 3</td>	Clear 14 3 7 1 3 9 2 3 3 3 2 Close 16 ^a 3 4 4 5 4 9 2 2 1 Involved 18 2 1 4 11 7 3 5 3 1 2 3

Analysis of margin status according to

- Localization
- Anatomical extensions
- Stage

Involved defined <1mm

Critics: mainly focused on oral cancer, did not consider Cis on margins, definition of close not reported ++





Available online at www.sciencedirect.com

ScienceDirect

British Journal of Oral and Maxillofacial Surgery 49 (2011) 172-175



Involved surgical margins in oral and oropharyngeal carcinoma—an anatomical problem?

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Accepted 21 February 2010 Available online 31 July 2010

Margins status in OPSCC T1-4, n=78 Invaded margin defined ≤1mm

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invaded margins OPSCC 37%, deep n=21 and mucosal margin n=7 (3 both)

Critics: analysis of surgical margin improvement between two audit



Specifically in Transoral Surgery



Transoral Lateral Oropharyngectomy for Squamous Cell Carcinoma of the Tonsillar Region

II. An Analysis of the Incidence, Related Variables, and Consequences of Local Recurrence

Ollivier Laccourreye, MD; Stéphane Hans, MD; Madeleine Ménard, MD; Dominique Garcia, MD; Daniel Brasnu, MD; F. Christopher Holsinger, MD

Arch Otolaryngol Head Neck Surg. 2005;131:592-599

Induction Chemo (n=131) + TO lateral Oropharyngectomy (n=166)+/- PORT (n=51) for T1-3 OPSCC

Margins positive 7.8%, close 4.8%, negative 85.5% Positive margins associated with increased risk of local failure

Critics: landmark publication for development of TORS, but close margins are not defined



Transoral Robotic Surgery

Radical Tonsillectomy

Gregory S. Weinstein, MD; Bert W. O'Malley Jr, MD; Wendy Snyder, BS; Eric Sherman, MD; Harry Quon, MD, MS

Arch Otolaryngol Head Neck Surg. 2007;133(12):1220-1226

TORS for T1-3 tonsil carcinoma n=27

9 patients with frozen sections: final margins negative in 8, uncertain in 1 (cautery artifact) 18 patients without frozen sections: 17 negative margins, 1 « questionable margins »

PORT n=9, CRT n=15, chem alone n=1 (history of RT for lymphoma)

Critics: landmark publication, but no definition nor discussion of margins

The Laryngoscope © 2013 The American Laryngological, Rhinological and Otological Society, Inc.

Margin Mapping in Transoral Surgery for Head and Neck Cancer

Michael L. Hinni, MD; Matthew A. Zarka, MD; Joseph M. Hoxworth, MD

T1-4 tonsil SCC treated by transoral laser microsurgery and margin mapping, n=128 (n=99 primary treatment) Closest deep and peripheral margins, related to study of OP dimensions MRI in healthy patients

> Average closest margin 2mm deep and 2.82mm peripheral Mean minimal thickness of the constrictor 2.4mm 5-y LC 99%, DFS 94.5%, OS 76%

Conclusion: margin mapping satisfactory, wide margins unobtainable in tonsil

Critics: 5-y DFS 94.5% and OS 76% ??? Big problem in statistics





Impact of positive margins on outcomes of oropharyngeal squamous cell carcinoma according to p16 status

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Head & Neck 2017;39:1680-1688



T1-T2 OPSCC, Tonsil and BOT ++ and soft palate, n=55 (p16+ n=29, p16- n=26) Impact of positive margins on DSS according to p16 status

P16+: 12 positive margins, 13 close 1-5mm, 1 clear >5mm, postoperative RT, no impact P16-: 9 positive margins, 12 close 1-5mm, 5 clear>5mm, worse DSS with positive margins

Conclusion: p16+ positive margins have low risk of recurrence despite PORT alone

Critics: small sample, bias of nodal status



Positive Margins by Oropharyngeal Subsite in Transoral Robotic Surgery for TI/T2 Squamous Cell Carcinoma

Michael J. Persky, MD¹, William G. Albergotti, MD², Tanya J. Rath, MD³, Mark W. Kubik, MD², Shira Abberbock, MS⁴, Mathew Geltzeiler, MD², Seungwon Kim, MD², Umamaheswar Duvvuri, MD, PhD², and Robert L. Ferris, MD, PhD² Orbaryngology-Head and Neck Surgery 2018, Vol. 158(4) 660-666 © American Academy of Otolaryngology-Head and Neck Surgery Foundation 2017 Reprints and permission: sagepub.com/journalsPermissions.nav DOI: 10.1177/0194599817742852 http://otojournal.org

> T1-2 tonsil and BOT, n=140, 88% p16+ Positive versus definitive negative margin Intraoperative versus final margin

Conclusion: Positive margin more likely in BOT compared to tonsil

Critics: definition of definitive margins





Transoral robotic surgery-based therapy in patients with stage III-IV oropharyngeal squamous cell carcinoma

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Oral Oncology 75 (2017) 16-21

T1-4a OPSCC, n=80, tonsil n=66, tongue base n=13, soft palate n=1, p16+ n=47 Neodjuvant chemo PF n=49 Negative margin n=66, positive margin n=14 (17.5%) S alone n=13, PORT n=28, CRT n=39

Critics: neoadjuvant chemo, PF not standard in HN, margins positive or negative (no close definition)

Transoral robotic surgery for oropharyngeal carcinoma: Surgical margins and oncologic outcomes

Eric J. Moore MD¹ Hathryn M. Van Abel MD¹ Haniel L. Price MD¹ Christine M. Lohse MS² Kerry D. Olsen MD¹ Ryan S. Jackson MD³ Eliot J. Martin PA-C¹ Head & Neck. 2018;40:747-755

TORS +/- adjuvant for OPSCC (T1-2 87%) n=314 (tonsil n=204, BOT n=110), p16+ 93%

Adjuvant RT for ≥N2b, final positive margins, T4 Close, but negative margins: not indications for adjuvant therapy Adjuvant CRT for pathological ECS

No. of attempts for a negative margin (0-5)

Conclusion: final free margins 98%. No of attempts for a negative margin associated with local or regional recurrence, death due to disease, and death from any cause

Critics: good methodology, but final take-home message should rather be : « final negative margins » have limited value





QA in Clinical Trials

A Phase II Randomized Trial for Early-Stage Squamous Cell Carcinoma of the Oropharynx: Radiotherapy vs. Trans-Oral Robotic Surgery (ORATOR)

Principal Investigators

Dr. David Palma Radiation Oncologist OICR Clinician Scientist London Regional Cancer Program Dr. Anthony Nichols Head and Neck Surgical Oncologist Clinician Scientist London Regional Cancer Program

Circumferential margins sent for frozen section analysis, until negative margins obtained

If positive or close margin on final pathology: attempt to clear the margin transorally within four weeks

RT for ≥pN1, LVI+, pT3-4, close margins (<2mm) CRT for positive margins, ECE, ≥3 N+

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NRG ONCOLOGY RTOG 1221

RANDOMIZED PHASE II TRIAL OF TRANSORAL ENDOSCOPIC HEAD AND NECK SURGERY FOLLOWED BY RISK-BASED IMRT AND WEEKLY CISPLATIN VERSUS IMRT AND WEEKLY CISPLATIN FOR HPV NEGATIVE OROPHARYNX CANCER

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology, ECOG-ACRIN Medical Research Foundation, Inc., and SWOG.

Study Tea	am (8/19/14)
Principal Investigator/Surgery	Radiation Oncology Co-Chair
Floyd Christopher Holsinger, MD, FACS	Wade L. Thorstad, MD
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Resection should provide complete removal of the primary lesion with negative gross margins Assessment of margins by frozen sections is preferred

Tonsillar carcinoma: ≥3mm microscopic margins required; exception: deep margins (superior constrictor), binary: negative, or positive Tongue base carcinoma: ≥ 3mm microscopic margins required

Positive margin on final pathology after negative frozen sections: deemed RO « close » if additional negative tissus surrounding and deep

CRT for positive surgical margins, ECE, ≥5 N+

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EORTC Avenue E. Mounier 83/11 1200 Brussels Belgium Tel: +32 2 774 1611 Email: eortc@eortc.be www.eortc.org

Study information			Outline form				
Title	Phase III study assessing The "best of" radiotherapy compared to the "best of" surgery (trans-oral surgery (TOS) in patients with T1-T2, N0 oropharyngeal carcinoma						
Short title (max 50 characters)	"Best of" Radiotherapy vs "Best of" Surgery						
Study Number	EORTC -1420-HNCG-ROG	Leading Group	EORTC				
Study Coordinator	Name: Christian Simon	Institution: 457 - CHUV/UI	NIL, Lausanne, Switzerland				
Study co-Coordinator	Jean Bourhis (GORTEC) Name: Frank Zimmermann (SAKK)	Institution:					

Surgical margin defined to be clear (R0) if ≥3mm, except deep margin for tonsillar resection that is either R1 or R0 Close margin ≥1mm and <3mm

Involved margin (R1) <1mm in the final specimen

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GRAND PARIS

Any R1 margin should lead to a re-resection in operating room





Code Promoteur de l'étude : CSET 2017-2617

N° ID-RCB : 2017-A02253-50

Etude prospective comparative non randomisée entre IMRT et chirurgie transorale première dans le traitement des carcinomes épidermoïdes de stade local précoce de l'oropharynx

Acronyme: TORPHYNX

Version finale nº 1.0 du 21/08/2017

INVESTIGATEUR COORDONNATEUR	Nom : GORPHE Philippe Adresse: Département de Cancérologie Cervico-Faciale Gustave Roussy, 114 rue Edouard Vaillant 94800 Villejuif Tei. : 01 42 11 45 86 philippe.gorphe@gustaveroussy.fr
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Microscopic positive margin : carcinoma or Cis <1mm Clear margins: mucosa 4mm, deep margins in BOT 3mm, deep margins in tonsil 2mm

Positive margin on specimen with negative additional resection: deeemed R0 close

PORT : pN+, pT3-4a, close margins CRT: positive margins, ECS; discussed for ≥2N+, or at least 2 criteria within: N+, PNI, LVI, pT3-T4a



Synthesis

• Very limited level of evidence in oropharyngeal cancer

• Heterogeneous local standards and trial QA

CONSENSUS surgical margins in TORS for oropharyngeal squamous cell carcinoma





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Tonsil

When the constrictor muscles are not invaded:

- ➤ Microscopic positive margins (R1) are ≤ 1mm (deep and superficial)
- Close margins (R0 close) are
 >1mm and < 2-3mm deep
 >1mm and <5mm superficial
- Clear « sufficient » margins are ≥ 2-3m ≥ 5mm
- >1mm and <5mm superior
 - ≥ 2-3mm deep ≥ 5mm superficial

CONSENSUS surgical margins in TORS for oropharyngeal squamous cell carcinoma



Tonsil

- Sparing of postoperative adjuvant radiotherapy should be considered in pT1T2 tonsil carcinoma that do not pathologically involve the constrictor muscles, without adverse pathological features
- Postoperative adjuvant radiotherapy should be considered whenever constrictor muscles are pathologically invaded, even without other adverse pathological features
- TORS should not routinely be considered when the carcinoma penetrates through constrictor muscles and invades the parapharyngeal space (prefer a cervical-transoral robotic oropharyngectomy with free flap reconstruction if possible)



Base of tongue

When the constrictor muscles are not invaded:

- ➤ Microscopic positive margins (R1) are ≤ 1mm (deep and superficial)
- Close margins (R0 close) are
 > 1mm and < 3-5mm deep
 > 1mm and < 5mm superficial
- Clear « sufficient » margins are ≥ 3-5mm deep
 ≥ 5mm superficial



Base of tongue

Sparing of postoperative adjuvant radiotherapy should be considered in pT1T2 tongue base carcinoma without adverse pathological features

TORS should not routinely be considered when the carcinoma penetrates deeper than 10-15mm into the extrinsic muscles (prefer a radical cervical-transoral robotic basiglossectomy with free flap reconstruction if possible)



Posterior oropharyngeal wall

When the constrictor muscles are not invaded:

- ➤ Microscopic positive margins (R1) are ≤ 1mm (deep and superficial)
- Close margins (R0 close) are
 > 1mm and < 2-3mm deep
 > 1mm and < 5mm superficial
- Clear « sufficient » margins are ≥ 2-3mm deep
 ≥ 5mm superficial

CONSENSUS surgical margins in TORS for oropharyngeal squamous cell carcinoma



Posterior oropharyngeal wall

When the constrictor muscles are invaded:

Microscopic deep margins are positive (R1), or negative (R0 close)



Posterior oropharyngeal wall

- Sparing of postoperative adjuvant radiotherapy should be considered in pT1 carcinoma of the posterior oropharyngeal wall without invasion of the superior constrictor muscle and without any other adverse pathological features
- PORT should be considered in any other situations, with or without concurrent chemotherapy according to the general status of the patient and the adverse pathological features

Surgical Margins in Transoral Robotic Surgery for Oropharyngeal Squamous Cell Carcinoma

Consensus update and recommendations, 2018

Head and Neck Steering Committee

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* Synthesis