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Histosurgical mapping of endoscopic endonasal surgery of sinonasal tumours to improve radiotherapy guidance

Cartographie histochirurgicale utilisée en chirurgie endonasale endoscopique des tumeurs nasosinusiennes pour améliorer la qualité de la radiothérapie

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Running title: Radiotherapy of sinonasal tumours after endonasal surgery

Abstract

Purpose: Endoscopic endonasal surgery (EES) is becoming a standard for most malignant sinonasal tumours. Margin analysis after piecemeal resection is complex and optimally relies on accurate histosurgical mapping. Postoperative radiotherapy may be adapted based on margin assessment mapping to reduce the dose to some sinonasal subvolumes. We assessed the use of histosurgical mapping by radiation oncologists (RO).

Material and methods: a French practice survey was performed across 31 ENT-expert RO regarding implementation of EES, quality of operative and pathology reports and modalities of radiotherapy through an electronic questionnaire.

Results: EES was ubiquitously performed in France. Operative and pathology reports yielded accurate description of EES samples according to 66.7% of interviewed RO. Accuracy of margin assessment was however insufficient according to more than 40.0% of RO. Additional margins / biopsies of the operative bed were available in 55.2% (16/29) of the centres. In the absence of additional margins, quality of resection after EES was considered as microscopically incomplete in 48.3% or dubious in 48.3% of RO. As performed, histosurgical mapping allowed radiotherapy dose and volumes adaptation according to 26.3% of RO only.

Conclusions: Standardized histosurgical mapping with margin and additional margin analysis could be more systematic. Advantages of accurate EES reporting could be dose-painting radiotherapy to further decrease morbidity in sinonasal tumours.

Keywords

cancer, sinonasal, endoscopic endonasal surgery, margins, radiotherapy

Résumé

Objectif de l'étude : La chirurgie endonasale endoscopique est à ce jour standardisée pour la plupart des tumeurs nasosinusiennes malignes. L'analyse des marges à la suite d'une résection fragmentaire est complexe et s'appuie de manière optimale sur une cartographie histochirurgicale précise. La radiothérapie postopératoire peut être adaptée en fonction de l'analyse des marges de la cartographie afin de réduire la dose à certains sous-volumes nasosinusiennes. Nous avons effectué une étude sur l'utilisation de la cartographie histochirurgicale chez les radiothérapeutes.

Matériel et méthodes : Un sondage a été réalisé en France, avec l'aide d'un questionnaire électronique, auprès de 31 experts radiothérapeutes équirépartis en France sur la mise en place de la chirurgie endonasale endoscopique, la qualité des comptes rendus opératoires et médicaux, ainsi que les modalités de la radiothérapie en découlant.

Résultats : La chirurgie endonasale endoscopique était omniprésente en France. Les comptes rendus opératoires et médicaux ont fourni une description précise des échantillons de la chirurgie endonasale endoscopique selon 66,7 % des oncologues radiothérapeutes interrogés. La précision de l'évaluation des marges était cependant insuffisante selon plus de 40,0 % des oncologues radiothérapeutes. Des marges / biopsies supplémentaires étaient disponibles dans 55,2% (16/29) des centres. En l'absence de marges supplémentaires, la qualité de la résection après la chirurgie endonasale endoscopique a été considérée comme microscopiquement incomplète pour 48,3% ou discutable pour 48,3% des oncologues radiothérapeutes. Telle qu'elle est réalisée, la cartographie histochirurgicale a permis une adaptation des doses et volumes de radiothérapie selon 26,3% des oncologues radiothérapeutes uniquement.

Conclusion : L'utilisation d'une cartographie histochirurgicale normalisée avec analyse des marges pourrait être plus systématique afin de guider finement la radiothérapie.

Mots clés

Cancer, nasosinusienne, chirurgie endonasale endoscopique, marge chirurgicale, chirurgie, radiothérapie

INTRODUCTION

Surgery is the gold standard for the treatment of sinonasal malignancies. It involves macroscopic tumour removal with free margins. Historical external approaches have been gradually replaced since the end of the 1990s by endoscopic endonasal approaches due to advances in optics and instrumentation. Because of the narrowness of the sinonasal cavities and the complexity of the three-dimensional sinonasal anatomy, endoscopic endonasal surgery (EES) has caused a shift in the concept of monobloc resection toward piecemeal resection. This leads to more uncertainty in margin analysis and postoperative management. This has already been described in early laryngeal tumours [2].

There is growing evidence that EES is a safe technique as it shows equivalent results in overall survival and lower complication rates in ethmoid adenocarcinomas and squamous cell carcinomas, as well as melanomas or adenoid cystic carcinomas [3-10]. Postoperative irradiation is frequently indicated in sinonasal tumours [11-13] as it reduces the risk of local relapse. It usually consists of high

dose irradiation, of 50 to 66 Gy, depending on residual tumour bulk, delivered to a large tumour bed that is located near critical organs. Such organs include the optic nerve, chiasma, retina, pituitary gland and brain structures which tolerate lower dose constraints (<54 Gy) than the dose required to eradicate the tumour. Thereby, radiotherapy can be responsible for high rates of late complications such as sensory or endocrine toxicities or cognitive sequelae [14]. Radiotherapy dose has also been found responsible for acute or prolonged nasal mucositis [15,16].

It is important to understand that the necessary radiotherapy dose varies with the quality of resection from 50 Gy for safe margins to 66 Gy for microscopically incomplete resection or 70 Gy for residual macroscopic disease. Because EES relies on piecemeal resection, with many tissue or tumour fragments from various sites of a complex anatomic region, detailed operative and pathological reports are essential to assess both local tumour extensions and quality of resection [17]. Accurate position, size, orientation, relation and margin of each sample of the sinonasal tumour anatomy, is critical to guide radiotherapy, and a comprehensive discussion about anatomical and tumoral description between surgeons and radiation oncologists is necessary.

Because of the low prevalence of sinonasal malignancies and the recent development of EES, there is a lack of recommendation on how to assess margins, and guide definitions of dose and volumes in post-EES radiotherapy. The aim of this study was to assess the use of EES and understanding by radiation oncologists of EES for postoperative radiotherapy practice in malignant sinonasal tumours knowing that accurate histosurgical mapping can be done. The current survey was designed to assess radiation oncology practices in France in the context of evolving surgical practices in sinonasal tumours using EES.

MATERIAL AND METHODS

An electronic questionnaire (www.easy-crf.com/sinocaRT) was designed and aimed to assess:

- management of sinonasal malignancies with respect to implementation of EES;
- information contained in operative and pathology reports in case of EES;
- modalities of postoperative radiotherapy with respect to EES.

This questionnaire was sent to 31 French ENT-expert radiation oncologists, chosen to have a geographically ubiquitous representation of centres performing EES in France. One radiation oncologist was interviewed per centre. Radiation oncologists had to quote their access to information or practice semi-quantitatively using always/systematically, often/frequently, rarely, never. In case when systematically represented less than 10% of cases in retrospect, systematically and frequently were grouped as one item “frequently”. Figures and percentages are therefore provided for the total number of centres.

RESULTS

Twenty-nine questionnaires out of 31 (93,5%) were filled in by ENT radiation oncologists from various health care institutions (private practice and academic centres) in France. Their mean experience was 10 years (range: 1-39 years). Mean yearly number of ENT cancers treated per radiation oncologist was 115, including 9.2 patients with sinonasal cancers, which represented 52.8% of sinonasal cancers treated at their respective centre. The following answers are provided by the interviewed radiation oncologists. EES and open surgery were both performed in all 29 centres at the time of study (2019). EES was performed for ethmoid adenocarcinomas in 93.1% (27 out of 29) or for any histology in 86.2% (26 out of 29) of the centres. Median year of introduction of EES (regardless of whether it was first used for benign or malignant tumours) was 2010 (1990-2017).

Information contained in operative and pathology reports and their interpretation of margins for radiotherapy guidance is presented in Table 1.

Unless biopsies / additional margins of the tumour bed were explicitly reported, the quality of resection after EES was systematically considered as R1 (microscopic residual tumour) by 48.3% of the interviewed radiation oncologists (14 out of 29). It was considered as dubious R0 (no microscopic residual tumour but close margins) by 48.3% (14 out of 29). It was considered as true R0 margins in 3.4% (1 out of 29). None of them considered R2 (macroscopic residual tumour). The quality of margins was not considered differently with respect to a haemorrhagic aspect of the tumour by 69.0% (20 out of 29). Median dose delivered in case of R0 resection assessed by biopsies / additional margins of the tumour bed was 57 Gy (range: 50-60 Gy), 60 Gy (range: 50-60 Gy) for close/dubious R0 and 66 Gy (range: 66 Gy) for R1 resection. When available, additional margins, interviewed radiation oncologists adapted their radiotherapy volumes in 21.1% (4 out of 19).

Flaps used during reconstructive surgery were included in the radiotherapy volume by 79.3% (23 out of 29) of radiation oncologists after open resection and 86.2% (25 out of 29) after EES.

DISCUSSION

Because evolutions of surgery may influence the way radiotherapy is delivered [1, 2], our survey assessed how the use of EES of sinonasal tumours was addressed among ENT expert radiation oncologists in French health care institutions. Not only can mini-morbid surgery influence the dose to be delivered to a given area but also the volumes of irradiation, which include the resected tumour (i.e. macroscopic tumour volume) and surrounding areas at risk for microscopic tumour cell spread. The topic is timely because of the increasing use of EES in ENT oncology and because radiotherapy can now be optimized technically to achieve very steep dose gradients. The management of sinonasal tumors is highly transversal and advances in one given treatment may influence the way to deliver the others.

We showed that assessment of margins was unevenly reported after EES and that operative / pathological reports were not always standardized. About half the radiation oncologists considered that EES intrinsically achieved close/dubious R0 margins while the other half adopted a worst-case scenario of R1 margins. This translated in a significant difference in dose of 6 Gy. Some also considered EES as achieving true R0 resection based on operative report only, with a corresponding mean dose of about 57 Gy (range: 50-60 Gy). However, operative reports can only state on the absence of macroscopic residual tumour but not on microscopic residual tumour. The lack of systematic tumour bed biopsies or additional margins on pathology reports, here described in more than a third of cases, likely contributed to this highly variable interobserver (radiation oncologists) assessment of the quality of resection on joint operative / pathologic reports. If piecemeal resection no longer appears as a major prognostic factor [18], free margins are significantly associated with a higher probability of local relapse and poor survival [19, 20]. The poorer prognosis of R1 resection is partially compensated by increased radiation dose in the order of 66 Gy [21]. However, increasing the dose in the tumour also translates in increased dose (and higher risk of toxicities) to normal tissues surrounding the tumour bed. Thus, accurate description of the quality of resection is critical for radiation dose guidance. It appears, through this survey, that both the operative procedure and the reporting may be improved to better analyse margins and define more precisely radiotherapy volumes and dose prescription. Although, histosurgical mapping appeared [22] standardized among surgeons and between surgeons and pathologists, there seems to be residual gaps to make histosurgical mapping fully interpretable by radiation oncologists. It is recommended that histosurgical mapping be systematically used.

Other trivial aspects for a surgeon are not straightforward for radiation oncologists. For example, sinonasal tumours often develop from a thin tumour implantation basis, that is easily perioperatively. However, radiation oncologists refer to preoperative imaging in addition to histosurgical reports. Imaging overestimates tumour extensions in pedicled tumours in cases where the full cavities are filled in (but not involved by) by the tumour. Similarly, because margins may be even more difficult to assess perioperatively for friable and haemorrhagic tumours. In these situations, systematic tumour bed biopsies or additional margins may be even more critically for radiation oncologists to adapt the dose to a given sinonasal area.

Accurate histosurgical mapping reports in the radiotherapy field may be used to adapt radiotherapy by more selectively deliver the dose spatially and by reducing high dose volumes and toxicity. Mini-morbid radiotherapy intensity modulated radiation therapy (IMRT, tomotherapy) with dose-painting strategies on areas at risk and hadrontherapy [23-29] could be used following mini-morbid surgery to maximize the therapeutic index. The intriguing low rate of adaptation of radiotherapy volumes and doses despite access to histosurgical mapping in our study may be explained by the fact that radiotherapy is not yet routinely done with dose-painting approaches. Dose-painting approaches

theoretically consist in modulating the dose at the voxel level to escalate the dose to twice or thrice in hypoxic voxels based on functional imaging of hypoxia. However, such orders of magnitude are too high to be technically robust and safe. In contrast, dose painting may be applied more realistically to centimetric subvolumes based on histosurgical mapping to standard dose levels from 50 to 66 Gy, which may be proposed in the following years (Figure 1).

One limitation of our study is its declarative aspect, radiation oncologists described information contained in operative and pathology reports in their respective centre. Thereby, surgical practices in French centres may differ slightly. Implementation of dose painting radiotherapy will have to be further evaluated once histosurgical mapping is optimally implemented by surgeons and pathologists and further discussed between those and the radiation oncologists.

CONCLUSION

EES is commonly and increasingly performed in France (and worldwide). Standardization of operative and pathology reports and multidisciplinary discussions may contribute to more accurate definitions of radiotherapy doses to sinonasal subvolumes and are a pre-requisite toward mini-morbid postoperative radiotherapy.

CONFLICT OF INTEREST

No conflict of interest.

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Table 1. Use of histosurgical mapping of endoscopic endonasal surgery of sinonasal tumours in routine radiation oncology practice in 2019, a survey of 29 French ENT experts: Information availability in operative and pathology reports and interpretation of margins for radiotherapy guidance.

	Information availability
<i>Information contained in operative reports</i>	
Non standardized reporting	27.6% (8/29)
Macroscopic aspect of the tumour (haemorrhagic, friable, etc.)	82.7% (24/29)
Tumour epicentre	68.0% (20/29)
Presence of a tumoral pedicle / implantation base	75.9% (22/29)
Tumour extensions	86.2% (25/29)
Perioperative complications	86.2% (25/29)
Reconstructive surgery	93.3% (28/29)
Quality of resection - perioperative assessment of margins	62.0% (18/29)
Accurate histosurgical mapping	62.0% (18/29)
Biopsies of the operative bed	55.2% (16/29)
<i>Information contained in pathology reports</i>	
Pathological analysis based on surgical sampling	Systematic 62% (18/29) or frequent 27.5% (8/29)
Accurate surgical mapping	68.7% (20/29)
Accurate reporting of margins	58.6% (17/29)
Histoprognostic factors such as vascular emboli	93.1% (27/29)
Histoprognostic factors such as perineural invasion,	89.6% (26/29)
Histoprognostic factors such as grade	82.7% (24/29)
Histoprognostic factors such as specific classifications	68.9% (20/29)
<i>Interpretation of margins for radiotherapy guidance</i>	
In the absence of reporting of biopsies / additional margins, quality of resection after EES interpreted as R1, dubious R0 (no microscopic residual tumour but close margins), true R0 margins	48.3% (14/29), 48.3% (14/29), 3.4% (1/29)
Quality of margins unchanged in case of haemorrhagic tumour	69.0% (20/29)
Median dose delivered in case of R0, dubious R0 or R1 resection assessed by additional margins	57 Gy (50-60), 60 Gy (50-60), 66 Gy (66 Gy)
Radiotherapy volumes adapted based on additional margins	21.1% (4/19)
Flaps included in the radiotherapy volume after open resection	79.3% (23/29)
Flaps included in the radiotherapy volume after EES	86.2% (25/29)

EES: endonasal surgery.

Legend Figure 1

Schematic example of using histosurgical mapping for dose-painting radiotherapy in a 56 y.o woodworker operated for an adenocarcinoma of ethmoid.

A : Corotal T1-weighted preoperative MRI.

B-C : Postoperative histosurgical mapping. Invaded structures are completely filled (1-3) while non-invaded resected structures are filled with hatching. 1 – Right (R) anterior ethmoidal cells (EC), 2- R posterior EC, 3-R superior turbinate, 4-R middle turbinate, 5-R uncinata process, 6-R anterior wall of sphenoid sinus, 7-R nasal septum mucosa, 8-R olfactory cleft mucosa with cribriform plate (CP) 9-R Mucosa of ethmoid roof 10-R dura of the R CP and R olfactory bulb.

D : Radioterapy delineation on postoperative planning CT.

E : Dose distribution in standard radiotherapy.

F : Dose distribution using dose painting radiotherapy based on histosurgical mapping.

