Review

# Removing the Taboo on the Surgical Violation (Cut-Through) of Cancer

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**IMPORTANCE** The surgical dictum of en bloc resection without violating cancer tissue has been challenged by novel treatments in head and neck cancer.

**OBSERVATIONS** An analysis of treatment outcomes involving piecemeal removal of sinonasal, laryngeal, oropharyngeal, and hypopharyngeal cancer shows that it did not compromise tumor control. The rationale for the evolution toward use of this technique is outlined.

**CONCLUSIONS AND RELEVANCE** While complete resection with clear margins remains a key end point in surgical oncology, we believe it is time to acknowledge that this time-honored dictum of avoiding tumor violation is no longer valid in selected situations.

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Surgical training has traditionally incorporated time-honored rules that are fundamental in providing best-practice approaches in oncology. Of utmost importance is the goal of completely removing the cancer because positive margins of surgical resection contribute to increased local recurrence and decreased survival rates.[1] Also, emphasis is given to the careful handling of the cancerous lesions and the surrounding tissues, primarily to minimize dispersion of cancer cells. However, what has come under recent scrutiny is the longstanding dictum not to surgically violate visible tumor during the extirpative process. It has been taught that cutting through gross tumor during an operation increases the risk of spreading viable cancer cells beyond the tumor and into the surrounding normal tissue. Such a maneuver may cause cancer cells to adhere to surgical instruments and subsequently become inadvertently implanted into the surrounding tissue by means of direct contact of the contaminated object. While documentation of this phenomenon is not prominent in the literature, in the head and neck literature a case report alludes to surgical implantation–related chest wall tumor following pectoralis major flap reconstruction for a pharyngeal cancer defect.[2] Presumably, tumor cells can be seeded by contaminated instruments used in the extirpative process within the adjacent donor site created to reconstruct a defect following cancer resection. Such events, albeit anecdotal, underscore the importance of the concept for en bloc resection, which for more than a century has remained a widely accepted principle in surgical oncology.

Although the principle of en bloc resection remains important, its application for surgical extirpation of cancer within some sites of the head and neck is not always feasible. For example, within the nasopharynx, anterior and lateral skull base, and sinonasal region, surgeons often find it difficult to adhere to this rule. Knowing that the fundamental premise is to remove the tumor with clear margins, head and neck surgeons have traditionally strived to achieve such resections for removing tumors as single intact specimens. However, too often the pathologist receives specimens that have been removed in multiple pieces. With some reservations, it is likely that such experiences have led to the acceptance of piecemeal removal of cancer in select situations when monobloc resection is not feasible or practical and as long as complete resection is achieved with clear margins.

Exactly when the attitude of accepting piecemeal removal of cancer began remains unclear. The evidence points to a gradual evolution. The early examples of tumor cut-through evolved under circumstances that were more subtle. For example, the surgical technique of Mohs for cutaneous malignant neoplasms has been practiced by dermatologists for more than half a century. In principle, this technique involves serial excisions parallel to the tumor margins until there is clearance of cancer cells. Although the intent is not to deliberately cut through gross disease, the approach does increase this risk because of the narrow margin being attempted to conserve tissue.[3] Justification of this narrow-margin approach rather than committing to the traditional wide margin is based on the judicious use of "real-time" histologic analysis by the dermatologic surgeon using frozen section technique to serially assess all surgical margins. In other words, because the margins were taken tangentially rather than perpendicularly, and examined personally by the surgeon at the time of the excision, the proportion of the total margin being examined under the microscope approached 100%. Also, it should be noted that the technique of Mohs surgery was originally designed for relatively indolent basal cell carcinomas of the skin. Later he applied it to other types of skin cancer using the original fixed-tissue technique for extensive, complicated cancers that

invade into or around bony structures, for cancers invading the erectile tissues of the penis, and for melanoma. The fresh-tissue technique was recommended for almost all other cutaneous cancers.[4] Nonetheless, it could be argued that Mohs chemosurgery and its subsequent modifications does represent an early example of cancer surgery in which the basic principle of avoiding tumor cut-through was not the strategy for complete tumor extirpation. Frozen sections of surgical margins are also used in management of mucosal malignant neoplasms, particularly in oral and pharyngeal cancer. However, unlike the smaller cutaneous cancers, margin analysis of these lesions requires a systematic evaluation of larger surfaces usually comprising submucosal tissue and musculature in addition to the mucosal epithelium. While tangential section has some role to play in the process, most pathologists find it more practical to sample select margins of larger specimens using perpendicular sectioning. Hence, the proportion of the total margin examined under the microscope is less than in the Mohs approach. Reassuring for the techniques of margin analysis, 1 study reported that patients with positive margins who underwent immediate repeated resection seemed to have the same survival rate as patients who had negative margins after the first monobloc tumor resection.[5]

## Treatment Outcomes

With regard to the seminal publications in which planned surgical transgression of tumor-bearing tissue is routinely used, an important example is sinonasal cancer, in which novel protocols have been developed that incorporated tumor debulking.[6] Sato et al[6] pioneered a "trimodality" protocol for advanced sinonasal cancer. Although the regimen included 3 treatment modalities, the surgical component involved debridement of tumor from the maxillary sinus rather than the standard treatment of en bloc resection. Among the 57 cases of carcinoma treated, 22 patients required no further treatment at the end of the protocol. Among the 19 patients with persisting tumor at the end of the therapy, partial resection of the maxilla or intracavitary radiation therapy was effective in eradicating the residue of the tumor in all of them. Total resection of the maxilla was not required even in the advanced cases, which increased the number of patients who were rehabilitated successfully. Compared with a prior group of patients, this therapy reduced the rate of local recurrences and consequently improved the survival rate. More recent reports using variations of the trimodality therapy approach with piecemeal removal of residual cancer have also shown improved results in terms of disease control, as well as organ preservation.[7,8] Whereas the more recent studies used modifications involving different chemotherapy agents and methods of infusion, the techniques for piecemeal removal have also evolved from debulking to systematic and comprehensive piecemeal removal using frozen section control to ensure clear margins.[8]

Realizing that en bloc removal of advanced sinonasal cancers involving the anterior cranial base is impractical in some cases, other investigators began to change the surgical technique for exposing such tumors using approaches that were transfacial or transcranial only. In a transfacial series[9] of 308 patients who had undergone craniofacial resection for sinonasal neoplasia, the subset with malignant disease had a 5-year actuarial survival of 59% at 5 years. In a case series reported by Blacklock et al,[10] 9 patients underwent transcranial-only surgery for malignant tumors, all of whom remained free of disease during the follow-up period. Furthermore, this approach proved to be an effective technique for reconstruction without the need for free-tissue transfer.

Although the piecemeal resection technique was viewed as nonconventional and not widely accepted at the time as standard of care, such procedures subsequently proved to be an effective treatment for selected patients with sinonasal cancer in reports by others.[6,8,10]

Endoscopic sinus surgeons subsequently began to remove selected cancers of smaller volume using the transnasal approach, usually without facial incisions. Between 1989 and 1999, Stammberger et al[11] treated 43 patients with invasive and/or destructive tumors of the paranasal sinuses and the anterior skull base strictly using the endoscopic transnasal technique. Whereas the first patients were approached with a palliative intention, subsequently selected patients were treated with curative intention. Histologically, patients with various differentiated carcinomas were operated on (n = 18), as well as patients with malignant melanoma (n = 5), esthesioneuroblastoma (n = 8), clivus chordoma (n = 3), immature teratoma (n = 1), and leiomyosarcoma (n = 1). Their first results indicated that survival outcome was at least equal to that of standard external approaches but with excellent functional outcomes and significantly better overall quality of life.

In a larger endoscopic sinus series, Lund and Wei[12] reported their experience with 140 patients with a mean follow-up of 60 months. Eighteen different malignant histopathologic subtypes were represented, with olfactory neuroblastoma (n = 36), malignant melanoma (n = 33), and adenocarcinoma (n = 19) being the commonest. Additional radiotherapy was given in 95 cases and chemotherapy in 49. The overall survival was 84% at 5 years and 69% at 10 years.

The larynx represents another site in which piecemeal tumor removal was developed. Steiner[13] published treatment outcomes of 240 patients treated between 1979 and 1985 with curative intent for cancer of the larynx through a transoral laser resection approach. There were 159 patients with glottic cancer (Tis, 29; T1, 96; T2, 34). The local recurrence rate was only 6%, with 1 patient needing a total laryngectomy. The overall 5-year survival rate was 86.5%. Among the 81 patients with supraglottic tumors, 58 patients were in tumor category pT2 (38 with glottic extension), 17 patients had pT3, and 6, pT4 tumors. The 5-year overall survival for supraglottic cancers was 59%, with 22% local recurrence and 6 cases of total laryngectomy.

In a concurrent study, Rudert and Werner[14] reported 47 patients with variously sized supraglottic tumors and 114 patients with early glottic cancers treated between 1979 and 1993. Although 10 patients with glottic tumors developed recurrences, curative treatment was possible with either repeated laser surgery (3 cases), radiation therapy (3 cases), or salvage laryngectomy (3 cases). Among the 30 patients with supraglottic lesions treated for cure, 24 remained free of disease, 2 patients died from secondary cancers, and 3 patients died from their tumors.

The same investigators who began using transoral laser microsurgery with its piecemeal technique for excising carcinomas of the larynx subsequently extended its application to the hypopharynx, oropharynx, and oral cavity. Documentation of its suitability for these additional sites is strongest in the oropharynx. Steiner et al[15] reported the outcomes of 48 previously untreated patients with base-of-tongue squamous cell carcinoma treated in this manner. The

distribution of the T categories was T1, 2%; T2, 25%; T3, 15%; and T4, 58%; and 94% had stage III to IVa disease. Selective neck dissection was performed in 43 patients; 23 patients underwent postoperative radiotherapy with or without simultaneous chemotherapy. The Kaplan-Meier 5-year local control rate was 85%. There was no local recurrence in T1 and T2 lesions, but there was a 20% local recurrence rate in T3 and T4 tumors. The 5-year recurrence-free and overall survival rates were 73% and 52%, respectively. The mean performance status scale scores were 92% for normalcy of diet and 88% for understandability of speech. Twenty-one patients survived at least 5 years after treatment with a functional larynx. A later prospective trial conducted by Haughey et al[16] provided confirmation of the transoral laser microsurgery approach for oropharyngeal cancer. The data included 204 patients with stage III to IV tonsil or tongue base cancer, treated between 1996 and 2006 at 3 centers. With a mean follow-up of 49 months, 79.4% of patients were alive. The 3-year overall survival, disease-specific survival, and disease-free survival rates were 86%, 88%, and 82%, respectively. The local control rate was 97%, while 87% of patients had normal swallowing or only episodic dysphagia. Thus, for oropharyngeal cancer, these 2 studies along with others have demonstrated that transoral laser microsurgery as a primary treatment for advanced oropharyngeal cancer confers excellent survival and swallowing proficiency.

In the hypopharynx, Steiner et al[17] treated 129 patients with carcinoma of the piriform sinus with transoral laser microsurgery between 1981 and 1996. Among them, 24 patients had pT1, 74 had pT2, 17 had pT3, and 14 had pT4 disease. Node status was positive in 68% of patients. Seventy-five percent of patients had stage III or IV disease. Forty-two percent of the patients were treated solely with surgery, and 58% underwent surgery and postoperative radiotherapy. With a median follow-up of 44 months, 87% of the patients achieved local control of disease. The 5-year overall survival rate was 71% for stage I and II and 47% for stage III and IV disease. The 5-year recurrence-free survival rates were 95% and 69%, respectively.

## Discussion

The aforementioned treatment outcomes for patients with sinonasal, laryngeal, oropharyngeal, and hypopharyngeal cancer in which piecemeal removal was used support the use of surgical techniques that involve tumor transgression in select situations. Of particular advantage for patients with sinonasal cancer is the endoscopic approach, which involves the progressive removal of the lesion while maintaining a clear perspective of the boundaries between normal and diseased structures. The endoscopic intervention typically starts with tumor debulking with the intent to define the possible site of origin of the lesion and its relationship with the anterior skull base.[18] In laryngeal cancer, the transoral laser microsurgery approach was based on the rationale that cutting through viable cancer with the laser did not carry the same risk of dispersing cancer cells as using a knife or scissors. Furthermore, the carbon dioxide laser may have the added benefit of sealing small lymphatic vessels when used to cut through viable cancer. Also, the approach using segmental resection allowed improved visualization of the tumor-host interface, which better ensured a margin of resection devoid of cancer. Thus, the piecemeal removal of cancers involving the glottis, supraglottis, and subsequently other upper aerodigestive tract sites has led to the development of what has now become modern endoscopic surgery for upper aerodigestive tract cancer.

It is important to remember that the word "piecemeal" should not be interpreted as the haphazard removal of pieces of tumor without regard to achieving completeness of removal. It should be interpreted to convey systematic and planned removal of segments of tumor for better visualization, to facilitate complete resection, which is the ultimate goal of the operation. The use of labeled "maps" and differentially colored inked margins is essential to facilitate communication between surgeon and pathologist in identification of margin specimens. Based on treatment results, it appears that margin control equivalent to traditional techniques of serial sectioning of en bloc specimens can be achieved as long as the surgeon is careful to submit a complete representation of the tumor-host interface for comprehensive histologic examination of all surfaces.

While the modifications of the en bloc resection of sinonasal cancers and other skull base malignant tumors represented a gradual change in practice, the acceptance of tumor cut-through for transoral resection of laryngeal cancer seems to have evolved over a shorter time frame. In retrospect, one could argue that this modification, considered bold at the time, precipitated a paradigm shift for treating this site-specific cancer. Prior to transoral laser surgery, the principles of laryngeal cancer excision emphasized the traditional en bloc technique, whether in the context of conservation surgery (partial laryngectomy) or whole-organ resection (total laryngectomy). Of particular note, when endoscopic laryngeal laser surgery was being pioneered, the initial strategy was to excise the lesion as a single specimen and avoid tumor cut-through. As a result, the application of the approach as a primary treatment was limited to low-volume disease, primarily T1 to T2 of the vocal cord.[19] It was only when colleagues in Germany deviated from the traditional principle and began to violate the tumor with multiple laser cuts that it became possible to excise tumors of higher volume within the glottis and supraglottis.[13,14] In addition, Haughey et al[16] and others have taken advantage of this strategy to excise advanced-stage lesions of the oropharynx using the transoral laser microsurgery exposure.

When analyzing the treatment results of therapies for advanced disease that rely on piecemeal removal, one must keep in perspective the use of adjuvant therapies such as radiation and chemoradiation.[20] When surgical principles for oncology evolved during the late 19th and early 20th centuries, such adjuvant treatment modalities did not exist. The principles were based on the reliance on surgery alone for providing the best chance for cure. Thus, the surgical violation of gross tumor portending a worse outcome was of great concern. Although the evolution of combined treatment modalities may have served to mitigate these concerns, it should be emphasized that their advent was never intended to change the principle of achieving complete tumor resection. When complete tumor resection is achieved, similar oncologic results have been demonstrated in both en bloc and piecemeal resections of advanced laryngeal tumors, irrespective of the administration of adjuvant treatment.[21] Suffice it to say that adjuvant therapies do not make up for incompletely removed tumors.

Relative to surgery as it was practiced a century ago, it is important to note that surgical decision making has been improved because of technical advances in many medical fields,

including diagnostics and therapeutic modalities. Clearly, the availability to the head and neck surgeon of instruments to conduct endoscopic surgery, laser microsurgery, and robotics has revolutionized the field. Advances in tumor imaging now permit surgical planning that essentially eliminates unexpected intraoperative findings and allows the surgeon to accurately plan approaches for removing the disease.

## Conclusions

The time-honored rule of never purposefully cutting through cancer has changed, but the fundamental concept of completely removing the tumor with clear margins stands, even if it is not in continuity. Whether the tumor is removed as a monobloc specimen or in a systematic comprehensive piecemeal fashion is not important, as long as complete removal is accomplished. However, in select circumstances the advantages of tumor cut-through outweigh the adverse possibilities. This has been demonstrated in the treatment of sinonasal, laryngeal, oropharyngeal, and hypopharyngeal cancer. For lesions that are locally advanced, the appropriate use of adjuvant treatment modalities such as postoperative radiation therapy remains an important consideration. Advances in diagnostic techniques and therapies have paved the way for surgeons to approach lesions using new strategies. Finally, credit should be given to the ingenuity of surgeons who were willing to break away from traditional concepts and set new paradigms that ultimately benefited patients.

### ARTICLE INFORMATION

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### REFERENCES

1. Hinni ML, Ferlito A, Brandwein-Gensler MS, et al. Surgical margins in head and neck cancer: a contemporary review. *Head Neck*. 2013;35(9):1362-1370.

2. Robbins KT, Woodson GE. Chest wall metastasis as a complication of myocutaneous flap reconstruction. *J Otolaryngol*. 1984;13(1):13-14.

3. Mohs FE. Chemosurgical treatment of cancer of the ear; a microscopically controlled method of excision. *Surgery*. 1947;21(5):605-622.

4. Mohs FE. Chemosurgery. *Clin Plast Surg*. 1980;7(3):349-360.

5. Kwok P, Gleich O, Hübner G, Strutz J. Prognostic importance of "clear versus revised margins" in oral and pharyngeal cancer. *Head Neck*. 2010;32(11):1479-1484.

6. Sato Y, Morita M, Takahashi HO, Watanabe N, Kirikae I. Combined surgery, radiotherapy, and regional chemotherapy in carcinoma of the paranasal sinuses. *Cancer*. 1970;25(3):571-579.

7. Knegt PP, Ah-See KW, vd Velden L-A, Kerrebijn J. Adenocarcinoma of the ethmoidal sinus complex: surgical debulking and topical fluorouracil may be the optimal treatment. *Arch Otolaryngol Head Neck Surg*. 2001;127(2):141-146.

8. Samant S, Robbins KT, Vang M, Wan J, Robertson J. Intra-arterial cisplatin and concomitant radiation therapy followed by surgery for advanced paranasal sinus cancer. *Arch Otolaryngol Head Neck Surg*. 2004;130(8):948-955.

9. Howard DJ, Lund VJ, Wei WI. Craniofacial resection for tumors of the nasal cavity and paranasal sinuses: a 25-year experience. *Head Neck*. 2006;28(10):867-873.

10. Blacklock JB, Weber RS, Lee YY, Goepfert H. Transcranial resection of tumors of the paranasal sinuses and nasal cavity. *J Neurosurg*. 1989;71(1):10-15.

11. Stammberger H, Anderhuber W, Walch C, Papaefthymiou G. Possibilities and limitations of endoscopic management of nasal and paranasal sinus malignancies. *Acta Otorhinolaryngol Belg*. 1999;53(3):199-205.

12. Lund VJ, Wei WI. Endoscopic surgery for malignant sinonasal tumours: an eighteen year experience. *Rhinology*. 2015;53(3):204-211.

13. Steiner W. Results of curative laser microsurgery of laryngeal carcinomas. *Am J Otolaryngol*. 1993;14(2):116-121.

14. Rudert HH, Werner JA. Endoscopic resections of glottic and supraglottic carcinomas with the CO2 laser. *Eur Arch Otorhinolaryngol*. 1995;252(3):146-148.

15. Steiner W, Fierek O, Ambrosch P, Hommerich CP, Kron M. Transoral laser microsurgery for squamous cell carcinoma of the base of the tongue. *Arch Otolaryngol Head Neck Surg*. 2003;129(1):36-43.

16. Haughey BH, Hinni ML, Salassa JR, et al. Transoral laser microsurgery as primary treatment for advanced-stage oropharyngeal cancer: a United States multicenter study. *Head Neck*. 2011;33(12):1683-1694.

17. Steiner W, Ambrosch P, Hess CF, Kron M. Organ preservation by transoral laser microsurgery in piriform sinus carcinoma. *Otolaryngol Head Neck Surg*. 2001;124(1):58-67.

18. Nicolai P, Castelnuovo P, Bolzoni Villaret A. Endoscopic resection of sinonasal malignancies. *Curr Oncol Rep*. 2011;13(2):138-144.

19. Zeitels SM, Koufman JA, Davis RK, Vaughan CW. Endoscopic treatment of supraglottic and hypopharynx cancer. *Laryngoscope*. 1994;104(1, pt 1):71-78.

20. Robbins KT. The evolving role of combined modality therapy in head and neck cancer. *Arch Otolaryngol Head Neck Surg*. 2000;126(3):265-269.

21. Cabanillas R, Rodrigo JP, Llorente JL, Suárez C. Oncologic outcomes of transoral laser surgery of supraglottic carcinoma compared with a transcervical approach. *Head Neck*. 2008;30(6):750-755.