What Is the Role of Primary Surgery in the Treatment of Laryngeal and Hypopharyngeal Cancer?

Hayes Martin Lecture

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The improvement of XRT techniques and imaging reliability, surgical advances (classical partial procedures and radical surgery), and the appearance of active chemotherapeutic regimens have shifted many paradigms. In particular, a tendency to avoid removing the entire larynx led many teams to assess preservation strategies using chemotherapy as first-line therapy to select candidates for either subsequent XRT or subsequent surgery. Encouraging results have been published. This does not, however, signify that the new standard is to initiate the treatment of any larynx or hypopharynx squamous cell carcinoma (SCC) with chemotherapy and/or XRT and to consider surgery only as a salvage treatment in nonresponders to chemotherapy or for persistent or recurrent diseases after XRT.

The aim of this review is to clarify, at the turn of the millennium, the current place of primary surgery in larynx and hypopharynx SCC.

HISTORY OF LARYNX AND HYPOPHARYNX SURGERY

Since the beginning of the 19th century there are articles mentioning laryngeal surgery. In the absence of pathological evaluation it is impossible to assert that all procedures were performed to remove malignant tumors. However, it is indisputable that from the beginning of this surgical research to date, laryngologists have been paying attention both to cure patients and to preserve as often as possible laryngeal function.

The key date in larynx surgery is December 31, 1873, when Theodore Billroth performed the first total laryngectomy. In 1914, Gluck and Sørensen reported a success rate of 72 of 172 patients treated with total laryngectomy, while Tapia reported in 1922 a 3-year survival rate of 75 of 107 patients after total laryngectomy and in 1929 a postoperative death rate of 12 of 190 patients. Early in its history, total laryngectomy appeared to be both safe and efficient.

But as soon as larynx surgeons had at their disposal total laryngectomy for the treatment of larynx cancer, they tried to avoid performing such a mutilating surgery. (It must be underscored that this surgical approach began long before the appearance of active chemotherapeutic regimens in head and neck oncology.) There are references to partial surgery of the glottis using the term “laryngofissure,” by Desault (1801) and Bowes (1833). Sands proposed the term “partial laryngectomy” in 1863 and Billroth performed his first hemilaryngectomy in 1878, 5 years after the first total laryngectomy. In 1922, Saint Clair Thomson and Sebileau proposed an extended thyrotoomy, and Leroux Robert in 1948 performed a frontolateral laryngectomy. Partial surgery for the supraglottis appeared later in the literature. In 1938, Huet described a hyothyroepiglottectomy, Alonso published in...
1939 his report of a partial horizontal laryngectomy, and Leroux Robert described his experience with supraglottic laryngectomy in 1956. Larynx surgeons also used partial surgery for larynx and hypopharynx cancers. In 1904, Sebileau published his experience with a lateral retrothyroid pharyngectomy technique; Trotter, a lateral pharyngectomy in 1913; Andre, Pinel, and Lacroix, a hemilaryngopharyngectomy in 1962; and Ogura, an extended supraglottic laryngectomy in 1965.

In between classical partial procedures and total laryngectomy there was a gap that led some teams to explore the reliability of “subtotal” surgery. Foederl in 1906, Hoffman in 1950, and Majer in 1959 proposed a subtotal laryngectomy procedure. In 1970, Arslan and Serafini described a technique of subtotal laryngectomy with thyrohyoepiglottopexy, while Labayle proposed in 1971 a “reconstructive” technique with cricohyoidopexy. Piquet in 1972 pioneered this surgery, refining its technical aspects and indications. This was the beginning, in France, of the “cricos” experience with either cricohyo-oidopexy (CHP) or cricohyoidoepiglottopexy (CHEP). In the early 1980s, Laccourreye published these techniques in the English-language literature using the term “supracricoid laryngectomies.” In 1981, Pearson described his technique of subtotal laryngectomy. Briani in 1952, Conley in 1958, Azai in 1960, and Stafieri in 1971 had proposed to perform a total laryngectomy with a continent tracheopharyngeal fistula.

The larynx is certainly a unique example in the human body of such a small organ subject to so many surgical procedures. Larynx surgeons indeed have at their disposal an incredible arsenal allowing them to deal with about any kind of local extension. For supraglottic cancer, an endoscopic resection, a carbon dioxide laser resection or destruction, an epiglottectomy, a supraglottic laryngectomy, a subglossal-supraglottic laryngectomy, an extended supraglottic laryngectomy, a supracricoid laryngectomy with cricohyoidoepipexy, a total laryngectomy, or a subtotal total laryngectomy may be performed. For glottic cancer, an endoscopic resection, a carbon dioxide laser resection or destruction, a cordectomy, a frontolateral laryngectomy, a frontal anterior laryngectomy, various techniques of hemilaryngectomy, a glottectomy, a supracricoid laryngectomy with cricohyoidoepipexy or cricohyoidoepiglottopexy, or a total laryngectomy may be performed. For lateral epilarynx and hypopharynx cancers, an endoscopic resection, a carbon dioxide laser resection or destruction, an extended supraglottic laryngectomy, a hemilaryngopharyngectomy, a lateral hypopharyngectomy, a posterior retrothyroid hypopharyngectomy, a total laryngectomy with partial pharyngectomy, a circumferential pharyngolaryngectomy, or an esophagolaryngolaryngectomy may be considered.

The history of surgery for larynx and hypopharynx cancer should not ignore the history of other cancer treatments. In 1895, Roentgen discovered x-rays. In 1896, Despeignes proposed to use x-rays for therapeutic purposes, which was the beginning of XRT for cancer care, and in 1903 Schepperell used XRT for the treatment of a larynx cancer. Since the beginning of the 20th century, then, laryngologists have at their disposal the 2 major options for the treatment of larynx cancers—surgery and XRT. During the century both have been used according to institutional policies. To date, however, no randomized comparison of their efficacies in similar clinical cases have been conducted.

After the last world war, chemotherapy appeared to be a new tool against cancer. Up to the end of the 1970s there was no regimen effectively active against head and neck SCC. The appearance of platinum-based chemotherapy completely shifted paradigms. In previously untreated patients, impressive response rates as high as 80%, with 40% to 50% complete responses were observed. It was discovered that chemosensitive tumors were also radiosensitive in the large majority of cases. This had a notable impact on the “concept” of chemotherapy in head and neck SCC. Chemotherapy was for a long time considered as poorly active and was mainly used for palliation (advanced unresectable, recurrent, or metastatic diseases). The appearance of active drugs (in terms of response rates) led to the integration of chemotherapy in therapeutic protocols with curative intent (for advanced diseases or in high-risk patients). In both cases, the drugs’ cytotoxicity was the rationale for their use. With the concept of chemosensitivity and radiosensitivity, induction chemotherapy was used to separate patients into 2 groups—good responders and poor responders—to consider subsequent treatment. With such an approach, chemotherapy was mainly used as a selective tool, its cytotoxic effects being put aside. Chemotherapy was given with just the number of cycles sufficient to assess the responsiveness without delaying too much the subsequent treatment. This means that chemotherapy may have been used suboptimally and could not have a real impact on the outcome (except for quality of life). More recently, articles have been published on the use of chemotherapy in early stages of disease, which is an issue of debate. Indeed, in early larynx or hypopharynx cancers, conventional treatments (surgery, XRT, or both) are able to control most of the disease with few sequelae, the main risk being the appearance of metachronous cancers during follow-up. There are no convincing data in the literature supporting that chemotherapy decreases the incidence of such metachronous cancers. Thus, it may be asserted that if chemotherapy has had an impact on surgical indications for advanced diseases, it has no obvious role for early diseases.

**RESULTS OF LARYNX AND HYPOPHARYNX SURGERY**

There are many published series reporting the results of larynx and hypopharynx surgery, which are summarized below.

For the glottic larynx, partial surgery provides a 5-year local control ranging between 92% and 95% with 5-year larynx function preservation ranging between 95% and 100%, and for total laryngectomy a 5-year local control of 90% is observed. When conventional procedures are extended (for example, when a cordectomy or a frontolateral laryngectomy is extended to the arytenoid, both local control and functional results are poorer). This must lead to select a larger conventional procedure instead of extending a smaller one.
For the supraglottic larynx, partial surgery provides a 5-year local control ranging between 92% and 94% with a 5-year larynx function preservation ranging between 92% and 95%, and total laryngectomy yields a 5-year local control of 88%. Supraglottic laryngectomies may be extended superiorly (to the inferior part of the base of tongue) or laterally (to the upper part of the piriform sinus) without jeopardizing the results.

For the epilarynx and hypopharynx, partial surgery provides a 5-year local control ranging between 90% and 95% with a 5-year larynx function preservation ranging between 85% and 100%, and total laryngectomy with a partial pharyngectomy demonstrates a 5-year local control of 85%.

In general, carcinologic and functional failures may be explained by “preventable” causes. These mistakes may occur during decision making as a result of an inappropriate workup, resulting in an overestimation or underestimation of the tumor extension, an inappropriate patient selection (in particular regarding cardiovascular and, moreover, pulmonary functions), or an inappropriate surgical procedure selection. They may also occur during surgery as a result of a lack of expertise (in particular for large partial procedures such as supraccoidary laryngectomies), technical mistakes during the procedure (excessive tissue resection generating poor functional results or insufficient tissue resection causing local recurrences), or technical mistakes during closure.

Using these procedures, there are few local recurrences (less than 10% on average) and few nodal recurrences (ranging from 5% for glottic cancer to 10% for epilaryngeal and hypopharyngeal cancers). Larynx function is preserved in 5% to 10% of patients after partial surgery and never, by definition, after radical surgery but there are some possibilities for voice rehabilitation (esophageal voice or tracheoesophageal prostheses) although the effects of a permanent tracheostomy will impact on quality of life.

To assess the role of chemotherapy in improving these results, it is important to balance its disadvantages and advantages to overcome carcinologic or functional failures after surgery. In general, deaths due to toxic reactions after chemotherapy are reported to be less than 2% and progression of the disease during chemotherapy is reported between 3% and 5% (this means that a tumor initially amenable to partial surgery may be only eligible for a total laryngectomy in such a case after chemotherapy). Ten percent to 30% of patients are reported to be noncompliant with treatment after chemotherapy (ie, they do not follow the surgeon’s advice for subsequent treatment). Finally, if there are increasing data supporting the feasibility of partial surgery for salvage after XRT, we do not know how many cases are actually salvaged with a functional procedure and if this salvage is still feasible after chemo-XRT with a low morbidity. In early stages of disease there are few local, regional, or distant failures after surgery. It is unlikely that chemotherapy could improve these results. There are few functional problems, which often, like carcinologic failures, are due to a technical mistake either in the indication or in the performance of surgery. Good surgical training (and certainly not chemotherapy) may correct these mistakes. The main risk for these patients, when surgery has been properly selected and performed, is the development of metachronous cancers. To date there are no data supporting that chemotherapy could decrease their incidence. The real concern for these early diseases is the choice between partial surgery or definitive irradiation, which must be supported by a fair evaluation of the age and performance status of the patient, the patient’s occupation and compliance with treatment, the local and nodal extension, the patient’s wishes, and the surgeon’s and radiation therapist’s expertise. In advanced but resectable diseases, there are also very few local or nodal recurrences after radical surgery. On the contrary, there are numerous distant metastases, in particular for hypopharyngeal cancers, which may justify a chemotherapy-based clinical approach. The main concern for advanced diseases is the challenge of giving the patient the maximum chance for cure without loss of voice. It is important that the surgeon assess the value of the different larynx-preserving approaches and, more important, define which patients are suitable for larynx preservation and which patients must be definitively treated by radical surgery.

THE DILEMMA OF LARYNX PRESERVATION

Since the middle 1980s, larynx preservation has been mainly assessed in light of induction chemotherapy. Four randomized trials must be discussed. Three trials were based on a selection of patients to either surgery or irradiation according to tumor responsiveness, and the fourth on the systematic use of chemotherapy irrespective of the tumor response to induction chemotherapy. The first trial is the Veterans Affairs trial on larynx cancers. Three hundred thirty-two patients were randomly assigned to receive either “mutilating surgery” or chemotherapy with 2 cycles of cisplatin-fluorouracil followed, in responders (partial or complete responders), by a third cycle and XRT or by surgery in nonresponders. There was no significant difference in survival between both arms and, at 4 years, two thirds of the survivors in the chemotherapy arm had retained their larynx.

A French group (Groupe D’Etude des Tumeurs de la Tête et du Cou [GETTEC]) recently published another trial. Their patient selection was different from the Veterans Affairs study since all tumors were classified T3 and more cases were glottic or transglottic tumors. Patients were randomized to receive either the standard treatment (total laryngectomy) or 3 cycles of induction chemotherapy followed by XRT in cases of clinical response of greater than 80% or by total laryngectomy in the other cases. Locoregional control and survival were significantly higher in the surgery arm. However, only 68 patients were enrolled and computed tomographic scans were not routinely performed to assess the tumor extension nor was the tumor response to chemotherapy or XRT assessed, thus limiting the conclusions of this trial.

The third trial was conducted by the European Organization for Research and Treatment of Cancer (EORTC) in patients with hypopharynx tumors only eligible for total laryngectomy with partial pharyngectomy. Two hun-
dred two patients were enrolled, comparing the standard treatment (surgery and postoperative XRT) vs 2 or 3 cycles of chemotherapy followed by XRT at the primary site in clinically complete responders, or, for other patients, by the conventional treatment. There was no significant difference in survival, despite a notable difference in median survival favoring the experimental (chemotherapy) arm (44 months) when compared with the surgery arm (25 months). This difference in median survival was only explained by the fact that distant metastases appeared later after chemotherapy, leading to a better survival rate at 3 years that did not last any longer at 5 years. At 3 and 5 years, half the survivors in the chemotherapy arm had retained a functional larynx.

Since these 3 trials had similar design and used the same chemotherapy regimen (cisplatin-fluorouracil combination), they were combined in a specific subanalysis of a large meta-analysis carried out at Institut Gustave Roussy on about 10,000 randomized patients in trials comparing a standard treatment with the same treatment and chemotherapy (induction, adjuvant, or concurrent chemotherapy). It appeared for this subanalysis that there was a nonsignificant trend for a 6% poorer survival in the chemotherapy arms when pooled together and that these results varied according to the anatomic subsites. This was counterbalanced by a 58% larynx preservation rate.

The fourth trial compared, in resectable hypopharynx tumors only amenable to mutilating surgery, the outcome of patients randomly assigned to receive induction chemotherapy followed by surgery and postoperative XRT vs induction chemotherapy followed by XRT with surgery in reserve for salvage, in both arms irrespective of tumor response to chemotherapy. With a median follow-up of 92 months in the 92 randomized patients, there was a better 5-year survival (37%) and a better local control (63%) in the surgery arm compared with the XRT arm (19% and 39%, respectively). The comparison of the results of this trial with those of the EORTC trial suggests that the tumor chemosensitivity must be taken into account before deciding on subsequent XRT instead of surgery. Results suggested that 3 cycles of induction chemotherapy were unable to modify patient outcome.

In the first 3 first trials, chemotherapy was conceptually used only as a selection tool (in particular in the EORTC trial in which the patient received XRT as soon as a complete response was achieved). There are other possible tools to select tumors that are potentially chemosensitive or radiosensitive. In the Veterans Affairs study, a high proliferating cell nuclear antigen or p53 expression was predictive of chemosensitivity and ultimately of chances for larynx preservation. There are other articles showing that ploidy, c-myc, c-jun, c-raf could also be predictive factors. This could avoid using chemotherapy (which is both toxic and expensive) only for selection, and more as a real part of the treatment in patients predicted to receive benefit from chemotherapy. Finally, there are increasing published data showing that hyperfractionated or accelerated XRT could produce better results in advanced larynx and hypopharynx cancers.

If larynx preservation appears to be feasible with induction chemotherapy, it is clear that this is only an option among others and that, in some cases, mutilating surgery remains the most appropriate approach. There are many questions about the respective places of subtotal surgery, new XRT protocols, and different settings of chemotherapy, as well as about the precise role of biology, the best imaging tools to assess residual diseases, quality of life and quality of the “preserved” laryngeal function, which lead one to consider larynx preservation as investigational.

CONCLUSIONS

For partial surgery, the oncologic and the functional results are excellent when the surgical procedure has been properly selected. Failures are usually due to a technical mistake or to an inadequate evaluation of the local extension. Head and neck surgeons have at their disposal many procedures to address about any size tumor. Induction chemotherapy has not proved to improve the outcome of patients presenting with early larynx or hypopharynx SCC. Selection of patients to receive either functional surgery or XRT must be supported by a fair anticipation of functional and oncologic results, the wishes of the patient, and the expertise of radiation therapists and surgeons.

As far as “mutilating” surgery is concerned, it must be underscored that, in the vast majority of patients, this surgery can achieve control above the clavicles, but it is indisputable that the loss of normal speech and, moreover, the presence of a definitive tracheotomy have a deleterious impact on quality of life. Data from published trials and studies have shown that, globally, preserving approaches have not jeopardized survival and have allowed the preservation of the larynx but the analysis by subsets of patients (anatomic subsites, biological profiles, some tumor extensions, etc) suggests that results may vary according to these variables. To date, it is probable that surgery remains, in some cases, the best solution even if mutilating. If results of salvage surgery have been evaluated after conventional XRT, little is known about salvage after altered fractionation XRT or after concurrent chemo-XRT.

In summary, there is no reason to abandon surgery as the first treatment in all cases of larynx or hypopharynx SCC. The question is open only in the case of patients requiring a total laryngectomy. If there are converging data showing the feasibility of larynx-preserving approaches, there are also data showing that such approaches cannot be considered as a standard, and, therefore, remain in the field of clinical research.

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