

TITLE: Laryngeal Conservation

SOURCE: Grand Rounds Presentation, UTMB, Dept. of Otolaryngology

DATE: February 9, 2005

RESIDENT PHYSICIAN: Sarah Rodriguez, MD

FACULTY PHYSICIAN: Shawn Newlands, MD, PhD, MBA

SERIES EDITORS: Francis B. Quinn, Jr., MD and Matthew W. Ryan, MD

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Approximately 9500 new cases of laryngeal cancer are diagnosed each year in the United States. Early glottic cancer is a curable disease; with single modality therapy of surgery or radiation the five year survival rate is 80 to 90%. More advanced stage disease has traditionally been treated with more aggressive surgery, most likely total laryngectomy, and post-operative radiation therapy. Several randomized trials have demonstrated the feasibility of organ preservation in patients with advanced laryngeal and hypopharyngeal cancer through the increasingly sophisticated use of chemotherapy and altered fractionation radiotherapy schedules. Many novel therapeutic agents are being investigated which may promise even higher rates of organ preservation in those patients with advanced squamous cell carcinoma of the larynx.

INDUCTION CHEMOTHERAPY:

The Department of Veterans Affairs Laryngeal Cancer Study Group (1991)

This study investigated whether induction chemotherapy and definitive radiation therapy with laryngectomy reserved for salvage represented a better initial treatment approach for patients with stage 3 or 4 laryngeal cancer than total laryngectomy with post-operative radiation therapy (PORT). This randomized clinical trial had two arms: the experimental arm consisted of three cycles of induction cisplatin and fluorouracil. Physical exam after the second cycle determined progression. Those found to have a complete or partial response (50% reduction in size of the primary) continued on to receive the third cycle of chemotherapy and subsequent radiation therapy. Those found not to have at least a partial response received laryngectomy and post-operative radiation therapy. For those in the experimental arm completing all three cycles of induction chemotherapy, endoscopy and biopsies were obtained to confirm the clinical impression of complete or partial response. These patients then proceeded to radiotherapy. The control arm consisted of patients receiving total laryngectomy with post-operative radiation therapy. There were a total of 332 patients enrolled and divided between groups.

This study documented that 64% of those assigned to the experimental arm retained their larynx at 2 years with no decrement in two year survival as compared with the control arm. Of the patients in the experimental arm, 59 underwent salvage laryngectomy (30 prior to XRT and

29 after radiation). Late salvage surgery required in 11 additional patients (80% of these occurred in the year after treatment). Salvage laryngectomy was required more often in those with glottic vs supraglottic CA (43 vs 31%); fixed vs mobile vocal cords (41 vs 29%); gross cartilage involvement vs no cartilage involvement (41 vs 35%)--but these results were not statistically significant. Significantly, salvage surgery was required in 44 % of patients with stage IV cancers as compared with 29% of patients with stage 3 cancer and 56% of patients with T4 cancers as compared with 29% of patients with smaller primaries. The author concluded that induction chemotherapy enhanced the effectiveness of definitive XRT; however, the author also noted that a direct comparison was not made between induction chemotherapy with radiation therapy and radiation therapy alone. Therefore, the role of chemotherapy remained somewhat uncertain.

Another finding of the study was that local recurrence was more common and distant metastases less frequent in the chemotherapy group. It was proposed that chemotherapy may prevent or at least delay distant metastases.

A follow-up to the 1991 study reported more details regarding the tumor response, toxicity and survival in the patients receiving chemotherapy. 155 patients received two cycles of chemotherapy; 116 patients went on to receive all three cycles of induction chemotherapy. One patient was removed for renal impairment. Twelve patients had transient increases in creatinine and received reduced doses of cisplatin. Fifty-two patients had mild renal impairment. One patient died of a suspected electrolyte imbalance. Four patients experienced grade 4 myelotoxicity; two of these developed pulmonary infections leading to death. Four patients had grade 3 mucositis; four patients had grade 4 mucositis. Twenty-seven patients experienced severe nausea and vomiting. Overall, 78% of patients completed therapy with only minimal toxicity.

In terms of response to chemotherapy, 84% had at least a partial response after two cycles of chemotherapy; 31% had a complete response. Twenty-four patients failed to have at least a partial response after two cycles of chemotherapy and were treated with surgery. After three cycles of chemotherapy, 42% had a complete response at both the primary and the cervical nodes. Only two patients were felt to have tumor progression after three cycles and were referred for surgical treatment. A total of 117 patients were evaluated by endoscopy and biopsy after the third cycle of chemotherapy. Sixty four patients had no tumor in their specimen.

European Organization for Research and Treatment of Cancer (EORTC) Cooperative Group (1996)

This study was conducted to compare the results of treating patient with T2-T4, N0-N2b squamous cell carcinoma of the pyriform sinus or aryepiglottic fold with either induction chemotherapy followed by radiation to standard surgical therapy (total laryngectomy, partial pharyngectomy) and post-operative radiation therapy. One hundred and ninety-four eligible patients were enrolled with 94 in the immediate-surgery arm and 100 in the induction-chemotherapy arm. Patients were to receive either two or three cycles of induction cisplatin and fluorouracil. Patients with progressive disease after one cycle were referred for surgery. After the second cycle, those with progressive disease or no change were surgically treated. Patients with a complete response after two cycles were treated with radiation therapy. Patients with a partial

response after two cycles received a third cycle; complete responders went on to radiation therapy, all others received surgical treatment.

Ninety-seven patients started chemotherapy as randomized. Sixty of these patients progressed to complete chemotherapy and radiation therapy. Eight of these required surgical salvage. The other 52 patients had a 3 and 5 year estimate of having a functional larynx of 64 and 58% respectively. If the analysis includes all 100 patients randomized to the chemotherapy arm, the estimated rate of larynx preservation at 3 and five years is 28 and 17% respectively. Chemotherapy complete responders were more frequent among those with T2 disease (82%) than those with T3 (48%) or T4 (0%) disease. Nonresponders did not appear to experience a decrement in survival in comparison to chemotherapy responders.

At three years the survival rate seemed superior for the chemotherapy-arm patients (57%) than for the surgery arm (43%); however, at five years there was no difference in survival although this comparison is based on small number of patients at risk.

No difference between groups was noted with respect to locoregional failure or occurrence of second primaries. Distant metastases developed in 36% of the surgery arm compared to 25% of the chemotherapy arm.

The above trials both suggest that organ preservation is possible without compromising survival in advanced squamous cell carcinoma of the larynx or hypopharynx; however, the precise role of chemotherapy fails to be elucidated. The rate of laryngeal retention in the VA study for the patients treated with induction chemotherapy is within the range of what is reported in the literature for radiation therapy alone. Both studies suggest that distant metastases may be delayed or suppressed with the addition of chemotherapy and that squamous cell carcinoma of the head and neck is very sensitive to cisplatin and fluorouracil. Additionally, both studies demonstrate lower rates of organ preservation with more advanced tumors. Based on these efforts, further studies to elucidate the role of chemotherapy in organ preservation were conducted.

CONCURRENT CHEMOTHERAPY AND RADIOTHERAPY

Radiation Therapy Oncology Group Trial 91-11

The role of chemotherapy in the treatment of laryngeal cancer with the goal of organ preservation was evaluated in this randomized prospective trial. Patients with stage 3 or 4 squamous cell carcinoma of the larynx were randomized to one of three treatment arms. An important exclusion criteria was significant tongue base involvement or destruction of cartilage (markers of high-volume T4 disease). Patients in the first arm received 2 cycles of cisplatin and fluorouracil and were examined. Nonresponders underwent salvage total laryngectomy and post-operative radiotherapy. Responders underwent a third cycle of chemotherapy and then completed radiation therapy. Patients in the second arm received concomitant chemoradiotherapy with cisplatin. Patients in arm 3 were treated with conventionally fractionated radiation therapy. Aside from the patients in arm 1 who did not respond after two cycles of chemotherapy, other indications for laryngectomy were biopsy-proven disease at primary site at least 8 weeks after radiation therapy, laryngeal dysfunction with aspiration or laryngeal necrosis. 173 patients were

in arm one and 172 patients were in arm 2 and 3 each. Salvage laryngectomy was performed on 28% of patients in arm one, 16% of patients in arm 2 and 31% of patients in arm 3. The rate of laryngeal preservation at a median follow-up of 3.8 years was significantly higher among patients receiving concurrent chemoradiotherapy (84%) than among those receiving induction chemotherapy (125/173) or radiotherapy alone (116/173). In fact, induction chemotherapy followed by radiotherapy when compared to radiotherapy alone, did not significantly improve the rate of laryngeal preservation.

Other findings in this trial include: the overall 2 and 5 year survival estimates show no significant difference among treatment groups, with a 2 year survival of 76%; local-regional control is significantly better for patients treated with concurrent chemoradiotherapy compared with induction chemotherapy or radiotherapy alone; chemotherapy significantly reduces distant metastases compared with radiotherapy alone.

An update of this same trial later in 2003 reported more information on the toxicities of the different treatment arms and more quality of life information. It was found that the grade and frequency of toxic acute effects was similar in the induction chemotherapy and standard radiotherapy arms and consisted of mostly grade 3 in-field effects on skin and mucous membranes. Patients receiving concurrent chemoradiotherapy had chemotherapy-related toxic acute effects such as neutropenia and severe nausea and vomiting as well as increased rates of severe radiation-related mucosal, pharyngeal and esophageal effects. Rates of late toxic effects were similar among groups.

This study also noted a decrease in the rate of distant metastases at five years for the patients receiving either induction chemotherapy or concurrent chemoradiotherapy versus standard radiotherapy.

This trial clearly demonstrates that induction chemotherapy is inferior to concurrent chemoradiotherapy in terms of local control and laryngeal preservation. Multiple non site-specific trials to further investigate the role of chemoradiation in treatment of advanced head and neck squamous cell carcinoma and organ preservation have been completed and are ongoing. Cisplatin and fluorouracil continue to be identified as promising agents in management of head and neck squamous cell carcinoma. Other chemotherapeutic agents such as the taxanes are also being investigated.

Varying radiation schedules are also being studied with the goal of increasing local control and organ preservation. Hyperfractionation is smaller radiation doses given two or more times a day but keeping the overall treatment time the same or slightly reduced. The use of smaller fractions increases the tolerance of late-reacting tissues such that the total radiation dose can be increased by about 10 to 15% without worsening of late complications. Recent trials studying patients with head neck cancer (non site specific) with sufficient follow up show a moderate but consistent improvement in local control with hyperfractionated schedules. The incidence of late toxicity with hyperfractionation in these trials appears to be the within the range observed with conventional fractionation schedules. Accelerated fractionation shortens the duration of therapy to less than the seven weeks of conventional radiotherapy; this reduction is accomplished by increasing the number of fractions per week. The total dose remains the same. However, an overall time reduction of more than 1.5 weeks without a decrease in the total dose

induces intolerable acute mucosal toxicity; delivery of more than 2 fractions per day can cause a higher incidence of late toxicity. Non site-specific trials studying accelerated schedules show an average magnitude of locoregional improvement of 10 to 15 %.

Molecular targets have been identified which may hold promise in the treatment of head and neck squamous cell carcinoma. Overexpression of epidermal growth factor receptor is recognized in more than 80% of squamous cell carcinomas. The epidermal growth factor receptor and its ligands, epidermal growth factor and transforming growth factor alpha are important in cell proliferation, adhesion, invasion and angiogenesis. Administration of the epidermal growth factor receptor monoclonal antibody (cetuximab) has been shown to increase radiosensitization, decrease tumor cell line growth and increase apoptosis. Other novel chemotherapeutics include agents to inhibit tyrosine kinase, angiogenesis inhibitors, and agents that have selective toxicity to hypoxic cells.

Increasing research has been directed at determining the quality of life and functional outcomes of those patients being treated for advanced laryngeal cancer. In a follow up to the VA Study, Terrell reported the results of various quality of life assessments for patients in both study arms. The SF-36 general health measure, HNQOL Instrument, and Beck Depression Inventory were administered to 65 surviving patients. Baseline demographics as well as data on alcohol, smoking, speech and swallowing were gathered. 25 patients from the surgery/radiotherapy group and 21 patients from the induction chemotherapy group completed the surveys; they did not differ in terms of demographics, original tumor classification or performance status aside from the patients in the induction chemotherapy arm being significantly older.

Patients who had successful organ preservation tended to have better scores on all domains of the SF-36 when compared with patients who had undergone laryngectomy. Patients who retained their larynx scored significantly better on the bodily pain and mental health domain of the SF-36. Patients who retained their larynx also scored significantly better on the emotion domain and their impression of their response to treatment on the HNQOL survey. At long-term follow up, 10 of 45 patients had BDI scores consistent with moderate or severe depression. Nine of those 10 had undergone laryngectomies.

When compared with the US population aged 55 to 64 years, patients with intact larynges had similar scores in the social functioning, role emotional and mental health domain suggesting that these patients (1) did not experience more problems with work or other daily activities because of emotional problems, (2) did not have more problems with social activities because of physical and emotional conditions and (3) did not have more feelings of nervousness or depression than the US male population aged 55 to 64 years. When the same comparison was done for patients who had undergone laryngectomy, these patients had significantly lower scores on all domains in comparison to US males aged 55 to 64 years.

Chronic pain appears to be a significant problem in the patients who underwent laryngectomy. These patients had dramatically poor bodily pain scores when compared to US men aged 55 to 64 years, indicating a great degree of pain or limitations because of pain.

Results from two additional quality of life studies suggest that those patients that undergo laryngectomy, when compared with patients who have undergone organ preservation are more

depressed and socially isolated.

● Lee-Preston

- 36 patients surveyed 3-12 months after with radiotherapy only (24), or total laryngectomy + PORT/salvage laryngectomy after XRT (12)
- Functional Assessment of Cancer Therapy (FACT) with head and neck subscale, Nottingham Health Profile and the Hospital Anxiety and Depression Scale
- Combined therapy patients had lower FACT head and neck scores (poorer QOL) with identified problems of dry mouth, swallowing, breathing and communication
- The two treatment groups showed no difference in anxiety but there was a trend towards greater depression in the combined therapy group
- Results of the NHP show that scores were worse for those in the combined therapy group in all domains except pain. The differences were statistically significant in the emotional reaction and social isolation subscales.

● Hanna

- EORTCQOL administered to 42 patients treated either with concurrent chemoradiation or surgery and PORT for stage 3 or 4 laryngeal cancer
- No statistically significant differences in overall QOL scores
- Subscale analysis revealed a trend for pts in the surgery group to experience greater difficulties with social functioning relative to the chemoradiation group
- Surgery pts reported significantly greater sensory disturbances, use of painkillers, and coughing
- Chemoradiation patients reported significantly greater problems with dry mouth

Impacting quality of life for patients undergoing organ preservation attempts is post-treatment speech and swallowing. The fact that the larynx has been preserved does not coincide with preservation of laryngeal function. A follow up of the VA study reported outcomes in the domains of speech/communication and swallowing. Patients who retained their larynx fared significantly better from the standpoint of speech communication. At two years post-treatment, patients with successful organ preservation had regained their pretreatment level of functioning for two of the three measures tested (intelligibility and reading rate) and exceeded pretreatment performance on the third (a communication profile used to assess general communication status). The patients in this study who received laryngectomy and post-operative radiotherapy had a decrease in all three speech communication-related measures despite availability of all modes of speech rehabilitation and therapy. Measures of swallowing dysfunction were similar between the patients who retained their larynx and those who underwent laryngectomy.

In the EORTC study, of the 52 patients who received induction chemotherapy and radiation and did not require salvage, seven had a tracheotomy tube during the follow-up period and five patients had a gastrostomy. Duration of time with either a tracheotomy or gastrostomy was not reported. In terms of speech, there was no difference among the treatment groups at either 12 or 24 months of follow-up. The reporting of moderate or worse speech impairment was reported as 6, 11 and 13% at one year and 3, 6 and 8 percent at two years. In terms of

swallowing, 23 percent of those assigned to concurrent chemoradiotherapy could swallow only soft foods or liquids at one year and three percent could not swallow at all. In contrast, of the patients assigned to induction chemotherapy, 9% were limited to soft foods or liquids at one year and none were unable to swallow. These patients did not differ significantly from the standard radiotherapy group in terms of swallowing. At two years out, there was not a statistically significant difference between all three groups in terms of swallowing with 14-16% of patients reporting difficulty swallowing.

Staton recently identified 45 patients available for follow-up 6 months after treatment with intra-arterial cisplatin and concurrent radiotherapy for stage 3 or 4 laryngeal cancer. These patients were all disease free. Sixteen patients required a feeding tube and/or tracheostomy (tracheostomy 13, gastrostomy 13, both 10) 6 months after treatment. Pre-treatment variables analyzed included T and N classification, neck dissection, massive cartilage invasion, subsite, age, pulmonary status and vocal cord paralysis/fixation. The only variable found to impact subsequent tracheostomy and feeding tube requirement at 6 months was vocal cord fixation. T4 status and massive cartilage invasion both trended toward an association with laryngeal dysfunction. The presence of pulmonary disease alone did not correlate with the outcome measures of tracheostomy or gastrostomy; however, when combined with vocal cord fixation, the likelihood of poor function was particularly high.

Lazarus studied nine patients treated with radiation therapy and adjuvant chemotherapy for advanced stage head and neck squamous cell carcinoma. All subjects underwent videofluorographic examination of their swallowing. All nine patients demonstrated reduced swallow efficiency when compared with age-matched normal subjects. All patients experienced tongue base and laryngeal movement disorders during swallowing. The observed swallowing disorders appeared to be due to sluggish contraction of the affected muscles, which makes timing uncoordinated and some movements incomplete.

Gillespie recently reported a survey of pts 12 months or more out from treatment of stage 3 or 4 SCCA of the oropharynx, larynx or hypopharynx. 19 patients were in the larynx/hypopharynx category. 11 of these were treated with surgery + PORT; 8 were treated with concurrent chemoXRT. All were administered the MD Anderson Dysphagia Inventory. There was no difference in scores between treatment type. All pts in study had scores 25-50% worse than the general population

Carrara de Angelis reports speech and swallow evaluations of 19 patients who underwent concurrent chemoradiation with paclitaxel and cisplatin for laryngeal or hypopharyngeal. The analysis took place 2-9 months post-treatment. Eleven patients required tracheostomy and 14 patients required feeding tube at some point in treatment. At the time of analysis, 6 still had tracheostomy and 6 were still using a feeding tube. Results of voice analysis showed 40% of patients with moderate dysphonia, 27% severe dysphonia. Results of swallow analysis showed 5 patients with silent aspiration. Functional swallowing was present in 3 patients; mild dysphagia in 7, mild or moderate dysphagia in 2 and severe dysphagia in 2.

Another concern about organ preservation attempts is the potential surgical morbidity for those who fail initial treatment and require salvage. The Danish Society for Head and Neck Oncology conducted a nationwide survey in 1998 to determine the surgical outcome of salvage

laryngectomy after radiation alone. The specific outcome measured was development of pharyngocutaneous fistula. Data from a total of 472 patients was analyzed from a period of 1987-1997. A total of 89 fistulae lasting more than 2 weeks developed and this corresponded to an overall fistula rate of 19%. The number of performed laryngectomies per year decreased linearly (from 58 to 37), whereas the annual number of fistulae increased slightly (from 7 to 11). This corresponded with a risk of fistula in 1987 of 12% and a risk of fistula in 1997 of 30%. The increased fistula rate over time was attributed to two factors: higher stages of laryngeal cancer were offered radiotherapy as definitive treatment over the period of the study and the individual surgical experience with laryngectomy decreased over the study time. Other significant risk factors for fistulae included younger patient age, primary advanced T and N stage, and nonglottic primary site. The relative risk of fistulae was twice as high for patients with initial T3-4 tumors compared with T1-2 tumors. Patients with nonglottic tumors had a fistulae odds ratio of 2.08.

In the EORTC trial in which patients were randomized into three arms (induction chemotherapy plus radiotherapy, concurrent chemoradiotherapy, and radiotherapy alone), surgical complication rates were low. Surgical complications were defined as systemic or wound related and further classified as major (significantly prolonging hospitalization or life-threatening) or minor (self-limited, managed with local wound care and did not significantly prolong hospitalization). There were no significant differences in frequency of systemic complications across the three treatment arms. Pharyngocutaneous fistulas occurred in 25%, 30% and 15% of patients in treatment arms 1, 2 and 3 respectively. The incidence of complications across the three arms was independent of the time from the end of the treatment to laryngectomy.

Lavertu compared the surgical complications encountered between a group of patients treated for stage 3 or 4 head and neck squamous cell carcinoma who were treated initially either with radiotherapy alone or chemoradiation who subsequently required neck dissection or salvage at the primary site. Fifty-four patients underwent 59 surgical procedures. Twenty-nine planned neck dissections and 30 salvage operations were performed. Total laryngectomy was part of the salvage procedure in 14 of the radiation alone patients and 7 of the chemoradiation patients. Modified radical neck dissection was performed in 16 of the radiation only patients and 15 of the chemoradiation patients. Four of the chemoradiation patients required bilateral neck dissections. For the neck dissections, there was one major complication consisting of a chyle leak which did not resolve spontaneously in a radiation only patient. The minor complications of neck dissection were chyle leak (one in a radiation only patient), skin incision breakdown (one in a radiation only patient and 5 in chemoradiation patients) and C. difficile colitis (one in a radiation only patient). Major complications of salvage surgery were carotid artery rupture, pharyngocutaneous fistula, bleeding duodenal ulcer (one each of these three in a radiation-only patients), sepsis, stroke and pharyngeal stenosis (one each of these last three in chemoradiation patients). Minor complications of salvage surgery included skin incision breakdown, granulation tissue at tracheostoma, hypothyroidism and partial small bowel obstruction. These minor complications were not numerous and did not differ between groups. Lavertu concluded that neither major nor minor complications differed between treatment groups and that surgical morbidity rates for salvage surgery after aggressive organ-preservation protocols was acceptable. Interestingly, Lavertu noted a trend in the chemoradiation group whereby the patients with complication after salvage surgery had completed treatment a mean time of 18.3 weeks prior to surgery; the patients without complications had completed treatment a mean time of 64.5 weeks prior to surgery.

In conclusion, patients with increasingly advanced disease can enjoy organ preservation. Many new therapies are under investigation that would increase the rates of organ preservation and decrease the toxicity of these methods. Functional and quality of life outcomes are important and more work should be done to assist in identifying the best treatment plan for the individual patient. As organ preservation becomes more prevalent, the surgeon will be faced with more challenging salvage surgery.

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