

Recent Advances in the Treatment of Head and Neck Cancer: A Patient Care Perspective

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1.2 CONTACT HOURS

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Epidemiology

Head and neck cancer is a relatively uncommon malignancy, accounting for approximately 4% of all cancers in the United States (Shaha & Strong, 1995). However, in other parts of the world, it is one of the most common types of cancer. For example, nasopharyngeal cancer is common in southern China, North Africa, and the Middle East (Ali & Al-Sarraf, 1999). The prevalence of cancer of the cheek is high in India, where it is common practice to chew a betel nut and tobacco leaf mixture and hold it inside the cheek, much the way some Americans hold chewing gum or chewing tobacco in the mouth (Shaha & Strong, 1995).

Head and neck cancer is potentially devastating. In the year 2000, an estimated 10,100 new cases of laryngeal cancer were diagnosed and 3,900 Americans died from the disease (American Cancer Society, 2000). Head and neck cancer is much more common in men than in women, although the incidence is gradually increasing in women as a result of behavioral factors (Shaha & Strong, 1995). The two most important risk factors for most head and neck tumors (nasopharyngeal cancer is an exception) are heavy alcohol and tobacco use (Shaha & Strong, 1995). A history of alcohol and tobacco use is reported in 80% to 85% of patients with head and neck tumors (Shaha & Strong, 1995). The two factors appear to be synergistic.

Other factors thought to contribute to head and neck cancer are listed in Table 1. A genetic susceptibility has been theorized to explain head and neck cancer in patients who do not use alcohol or tobacco (Shaha & Strong, 1995). Occupational exposure to asbestos has been linked with laryngeal cancer (Shaha & Strong, 1995). Tumors have been observed in the floor of the mouth due to mechanical irritation from dentures with an improper fit. It is speculated that mechanical irritation from the studs that many young people now wear in their tongues could affect the incidence of tongue cancer decades from now.

Chronic viral infection appears to play a role in head and neck cancer, especially nasopharyngeal cancer. Epstein-Barr virus has been found in nasopharyngeal tumor tissues, and patients with these tumors have high levels of antibodies to the virus (Shaha & Strong, 1995). Nasopharyngeal cancer also is associated with a diet rich in heavily salted fish (Ali & Al-Sarraf, 1999). Genetic as well as environmental factors are thought to contribute to this type of tumor (Ali & Al-Sarraf, 1999).

Treatment

Tumors of the head and neck are a heterogeneous group involving a variety of sites, including the oral cavity (anterior tongue, floor of the mouth, cheeks), oropharynx (soft palate and tonsils), hypopharynx (area below the oropharynx), nasopharynx, maxillary sinus, and larynx (including the epiglottis and vocal cords). This article will focus on the treatment of squamous cell tumors because they comprise the majority of head and neck

tumors. Adenocarcinomas are relatively rare and may be associated with salivary gland tumors (Shaha & Strong, 1995).

Head and neck tumors differ from other types of malignancies in that they tend to spread to distant sites relatively late in the course of the disease (Shaha & Strong, 1995). Recurrent local or regional disease is the primary concern in treating head and neck cancer because it is the common pattern of failure despite recent improvements in treatment (Schantz, Harrison, & Forastiere, 1997). The goals of treatment for head and neck cancer (Table 2) include enhanced local and regional control. The advanced age of and many comorbid conditions (often resulting from a lifetime of heavy alcohol and tobacco use) in the patient population may make improved overall survival difficult to achieve.

The National Comprehensive Cancer Network (NCCN), a group of experts from leading cancer centers, has developed oncology practice guidelines for managing various tumors, including head and neck tumors (Forastiere, Goepfert, Goffinet, Hong, Laramore, Mittal, et al., 1998). These guidelines are complex because of the heterogeneity of head and neck cancer. According to NCCN, the stage at the time of diagnosis is the factor most predictive of survival (Forastiere, Goepfert, Goffinet, Hong, Laramore, Mittal, et al., 1998). Mischaracterization of an advanced tumor as one at an early stage puts the patient at risk for a poor outcome. The use of endoscopy and computed tomography scanning is recommended in staging tumors.

Table 1.**Risk Factors for Head and Neck Cancer (Shaha & Strong, 1995)**

- Chronic viral infection (especially Epstein-Barr virus)
- Diet (heavily-salted fish)
- Genetic susceptibility
- Heavy alcohol use
- Mechanical irritation
- Occupation
 - exposure to asbestos
 - exposure to textile fibers
 - nickel refining
 - woodworking
- Tobacco use

Table 2.**Goals of Treatment for Head and Neck Cancer**

- Enhanced local and regional control
- Reduced treatment-related morbidity
- Improved relapse-free survival
- Improved overall survival

Standard therapy for head and neck tumors is surgery, radiation therapy, or a combination of the two modalities (Forastiere, Goepfert, Goffinet, Hong, Laramore, Mittal, et al., 1998). The use of a single modality (i.e., surgery or radiation therapy) is preferred for early-stage tumors. However, combined modality therapy often is required for advanced (i.e., stage III or IV) tumors.

Treatment for patients with advanced tumors often involves many different health-care professionals and specialties (e.g., medical oncologists, dental and oral surgeons, and speech therapists as well as nurses, surgeons, and radiation therapists). Nurses need to be involved early in the treatment planning process because of the vital role that they play in coordinating and providing care. Finally, patients need to be encouraged to participate in clinical trials as appropriate, because insight from clinical trials has led to many recent advances in the treatment of head and neck cancer.

Advances in Surgery

Surgery has been the cornerstone of treatment for head and neck cancer in some practices. It is considered the standard against which other treatments are measured. The functional and cosmetic results from surgery for many early stage lesions are preferable to the outcomes from other therapies, including radiation therapy. A potential disadvantage of radiation therapy is the loss of salivary gland function and dry mouth (Schantz, Harrison, & Forastiere, 1997).

Various new surgical approaches have met with success. These approaches include improved techniques for reconstruction, such as the use of vascularized bone grafts (to replace excised bone) and free tissue grafts (Foster, Anthony, Sharma, & Pogrel, 1999). Laser surgery is particularly useful for early lesions on the vocal cords (Delsupehe, Zink, Lejaegere, & Bastian, 1999). Partial laryngectomies may preserve speech (Rebeiz, Wang, Annino, McGilligan, & Shapshay, 2000). There is considerable interest in organ preservation (especially laryngeal preservation) for patients

with head and neck cancer. Surgery for advanced tumors must be extensive (and sometimes mutilating) because the head and neck area has a rich lymphatic supply that facilitates rapid local spread of malignancies arising in this area. Therefore, surgeons must usually remove a lot of tissue.

Advances in Radiation Therapy

Advances in radiation therapy include improved localization of tumors using computed tomography and magnetic resonance imaging (Shaha & Strong, 1995). This approach minimizes damage to normal tissues and is particularly helpful for tumors at the base of the skull or in the sinuses.

Hyperfractionation (delivery of radiation twice a day instead of once daily, as is done with conventional radiation therapy, to improve tumor control) may now be the standard for radiation therapy of patients with head and neck cancer. Studies have shown that various new accelerated hyperfractionation regimens in which the radiation is delivered over a shorter period (less than 6 weeks versus 7 to 9 weeks) improve local and regional disease control (Fu, Pakak, Trotti, Jones, Spencer, Phillips, et al., 2000; Leborgne, Zubizarreta, Fowler, Ortega, Mezzera, Deus, et al., 2000).

Other new forms of radiation therapy (e.g., fast neutron therapy, which is the treatment of choice for inoperable or recurrent salivary gland tumors) have been developed but they are not widely available in the United States (Potter, Prott, Micke, Haverkamp, Wagner, & Willich, 1999). Proton

beam therapy improves local control of tumors at the base of the skull (Tatsuzaki, & Urie, 1991). It is available on a limited basis.

Chemotherapy

Chemotherapy has been integrated into standard therapy for head and neck cancer in various ways. Induction (neoadjuvant) chemotherapy is given before standard therapy, although this approach lengthens the duration of therapy. Alternatively, chemotherapy may be given concurrently with radiation therapy (standard or accelerated hyperfractionation regimens). Chemotherapy has been given both before and concomitantly with radiation therapy, an approach in which there is currently a lot of interest.

Induction chemotherapy was first used with standard therapy roughly two decades ago in an attempt to improve local and regional control in patients with advanced disease (Hong, Shapshay, Bhutani, Craft, Ucmakli, Yamaguchi, et al., 1979). Early studies of induction chemotherapy included patients with little chance of disease control from standard therapy. Chemotherapy was given for 6 to 9 weeks; the surgical margins were not changed at the time of surgery regardless of response to chemotherapy. Nevertheless, the response to chemotherapy was rapid and impressive (Fountzilias, Nicolaou, Sridhar, Sideras, Haritanti, Anastasakis, et al., 1989). Complete or nearly complete disappearance of the tumor can be expected from the 6- to 9-week induction chemotherapy regimens used today (two or three courses of cisplatin and fluorouracil at 3-week intervals) in

90% of patients (Spaulding, Fischer, & Wolf, 1994). The likelihood of distant metastasis is reduced (The Department of Veteran Affairs Laryngeal Cancer Study Group, 1991). However, a survival advantage from induction chemotherapy prior to standard therapy has never been demonstrated, perhaps owing to flaws in study design.

Advantages of induction chemotherapy include the rapid, dramatic tumor response, lack of an increase in the rate of complications from surgery, good patient compliance, and possible avoidance of surgery (Jacobs, Pajak, Kinzie, Al-Sarraf, Davis, Hanks, et al., 1987). Disadvantages include the acute toxicity (e.g., mucositis), 6 to 9 week delay in definitive therapy, loss of tumor margins (difficulty in determining what tissue to excise), and lack of a demonstrated survival advantage. The response to induction chemotherapy in many cases is so good that the patient opts for radiation therapy but refuses surgery. In other cases, the surgeon is reluctant to excise tissue that looks normal.

Concurrent chemotherapy and radiation therapy is a rational approach because the two modalities have an additive effect in killing cancer cells. Certain chemotherapeutic agents (e.g., the radiosensitizers cisplatin, carboplatin, paclitaxel, gemcitabine, fluorouracil, bleomycin) have an effect that might be synergistic with that of radiation therapy (Vokes, 1998). The use of concurrent therapy avoids the delay in definitive therapy associated with induction chemotherapy and shortens the overall duration of treatment. Concurrent therapy can enhance local dis-

ease control. However, it also increases the severity of acute local toxicity from radiation therapy (e.g., mucositis) (Al-Sarraf, LeBlanc, Giri, Fu, Cooper, Vuong, et al., 1998).

This toxicity can require the interruption of treatment and prolong therapy. Whether concurrent therapy increases long-term toxicity from radiation therapy (e.g., fibrosis) is unknown. If salvage surgery is required (i.e., if the response to concurrent therapy is less than desired), the morbidity from surgery is increased by concurrent therapy.

Quality of Life and Organ Preservation

Organ preservation and quality of life have been the focus of recent research, especially in patients undergoing laryngectomy for tumors of the larynx, hypopharynx, or base of the tongue because of the tremendous potential impact on quality of life from the loss of the vocal cords (Harwood, & Rawlinson, 1983). The incidence of laryngeal cancer in the United States is high, with 10,000 to 11,000 new cases annually (American Cancer Society, 2000). As with most other types of head and neck tumors, laryngeal cancer occurs predominantly in men and is associated with heavy alcohol and tobacco use (Sessions, Harrison, & Forastiere, 1997). The surgical management of advanced laryngeal cancer involves removal of the voice box and a portion of the pharyngeal wall followed by reconstruction and creation of a tracheal stoma. In most cases, the lateral neck muscles are removed. The consequences of these changes with respect to quality of life can be dramatic. It is impossible to swim or take a bath and

showering is made difficult by the presence of an open tracheostomy. Expressing anger is difficult because it is not possible to raise one's voice. Similarly, it is difficult to laugh. The sense of taste is affected because it requires the sense of smell, which is impaired by the inability to sniff due to the loss of the epiglottis. Loss of the lateral neck muscles can affect the ability to play golf and bowl.

The need to learn a new means of communication because of the loss of the vocal cords is a big problem because it is difficult to accomplish, and requires considerable dedication and support. Less than 20% of the patient population at Dr. Spaulding's VA facility learn esophageal speech (the use of the walls of the esophagus and pharynx to create sounds).

Laryngeal cancer was the focus of organ preservation research because of its prevalence and the fact that although the cure rate in advanced disease is higher with surgery than with radiation therapy alone, surgery can have a negative impact on quality of life. In an early quality of life study, attitudes toward the quality and quantity of life were explored in 37 healthy volunteers, including 25 upper management executives and 12 firefighters, in a hypothetical situation (McNeil, Weichselbaum, & Pauker, 1981). The subjects were asked to choose among several treatment options (surgery or radiation therapy alone or radiation therapy followed by surgery if necessary) in the event that they developed laryngeal cancer. The advantages and disadvantages of the options (loss of normal speech but a longer life expectancy with surgery) were explained to the subjects, who listened to good

examples of esophageal speech. On average, the firefighters were willing to trade 6% of their life expectancy to retain normal speech (i.e., avoid laryngectomy). In contrast, executives were willing to trade an average of 17% of their life expectancy. When the assumed survival rate after radiation therapy was increased, the percentage of subjects in each group who were willing to gamble (i.e., consider options other than surgery) also increased. Although the results of this study may not accurately reflect the decisions that patients with diagnosed disease face, it prompted researchers to further explore organ preservation issues.

Landmark VA Laryngeal Trial

Thirteen VA hospitals participated in a trial coordinated by the VA Cooperative Studies Program. Patients with advanced laryngeal carcinoma were randomized to receive (1) standard therapy (surgery followed by radiation therapy) or (2) induction chemotherapy (cisplatin and fluorouracil) followed by radiation therapy for responders (non-responders with less than a 50% tumor response underwent surgery followed by radiation therapy) (Spaulding, Fischer, & Wolf, 1994; The Department of Veterans Affairs Laryngeal Cancer Study Group, 1991). Salvage laryngectomy was performed if signs of recurrence were observed in the chemotherapy group. Patient accrual was difficult because of the randomization (many patients preferred the chemotherapy plus radiation therapy arm to avoid surgery). There was no difference between treatment groups in disease-free survival or overall survival (Spaulding, Fischer, & Wolf, 1994; The Department of Veterans

Affairs Laryngeal Cancer Study Group, 1991). About two-thirds of patients in each group remained alive 5 years later (The Department of Veterans Affairs Laryngeal Cancer Study Group, 1991). The results of this study demonstrate that preservation of the larynx is feasible without a loss of survival time.

The feasibility of preserving the larynx without jeopardizing survival was also demonstrated in patients with cancer of the pyriform sinus (i.e., hypopharynx) in a phase III trial conducted by the European Organization for Research and Treatment of Cancer (Lefebvre, Chevalier, Luboinski, Kirkpatrick, Collette, & Sahmoud, 1996). Patients were randomized to undergo immediate surgery followed by radiation therapy or to receive induction chemotherapy followed by radiation therapy for responders (or surgery followed by radiation therapy for non-responders). Salvage surgery was performed in patients who relapsed after chemotherapy and radiation therapy. There was no difference between treatment groups in survival.

It seems intuitive that laryngectomy adversely affects quality of life. In fact, the initial impact of laryngectomy on speech and quality of life was great in the VA laryngeal trial (Hillman, Walsh, Wolf, Fisher, & Hong, 1998). However, in a long-term follow-up study of these patients more than 10 years after study entry (long after the completion of post-laryngectomy rehabilitation), there was no difference between groups in the ability to communicate. The laryngectomized patients had adjusted well to the loss of their natural voice. Measures of anxiety and depression were high among laryngectomized patients,

although the difference between treatment groups was not large. A surprisingly high number of patients (three-fourths of those with an intact larynx) continued to use alcohol and tobacco.

Laryngeal preservation may be accompanied by unanticipated long-term adverse effects on quality of life. Radiation therapy to the hypopharynx and parts of the oropharynx and larynx can cause fibrosis that interferes with swallowing, and the use of chemotherapy in combination with radiation therapy adds to the problem. Contraction of the muscles involved in swallowing becomes sluggish and uncoordinated. Swallowing can be incomplete, which increases the risk of aspiration. Weight loss can occur because of inadequate dietary intake. Some patients require feeding tubes. At the time of long-term follow-up, patients in the VA laryngeal trial who were treated with chemotherapy and radiation therapy had not recovered the weight loss associated with treatment to the same extent as patients who had been treated with surgery and radiation therapy. Whether the benefits of laryngeal preservation outweigh the long-term adverse effects on quality of life requires additional study.

Nasopharyngeal Cancer

Nasopharyngeal cancer differs from other types of head and neck cancer in that: it is not clearly associated with heavy alcohol or tobacco use; the likelihood of advanced disease and systemic metastases at the time of diagnosis is higher; and, the cells are histopathologically different and more sensitive to radiation therapy and chemotherapy than squamous cell tumors (Ali & Al-Sarraf,

1999). Nasopharyngeal cancer typically is not amenable to surgical intervention because of its location near the base of the skull, the lack of defined margins, and the high likelihood that metastases are present. Standard treatment has been radiation therapy to the nasopharynx and bilateral cervical nodes. Most head and neck tumors spread to lymph nodes in the anterior cervical area. In contrast, nasopharyngeal tumors tend to spread to posterior cervical nodes. Therefore, the area treated with radiation is large.

The use of radiation therapy in combination with chemotherapy was explored in patients with nasopharyngeal cancer because the incidence of local and regional failure after radiation therapy is high and distant metastases are common (Ali & Al-Sarraf, 1999). In a phase III randomized trial, radiation therapy plus cisplatin followed by three courses of cisplatin plus fluorouracil (i.e., chemotherapy was given both concurrent with radiation therapy and adjuvantly after combination therapy) was compared with radiation therapy alone (Al-Sarraf, LeBlanc, Giri, Fu, Cooper, Vuong, et al., 1998). The goal for patient accrual was 270 but the study was terminated early because of the dramatic benefit of chemotherapy in combination with radiation therapy. The 3-year survival rate was 47% with radiation therapy alone and 78% with chemotherapy plus radiation therapy. The 3-year progression-free survival rate also was significantly higher with combination therapy (69% versus 24% with radiation therapy alone). Local, nodal, and distant recurrences were more common in patients receiving radiation alone. Combination therapy became the standard because of the results of this study. However,

treatment-related toxicities (acute skin changes, weight loss, and grades 3 and 4 nausea, vomiting, and mucositis) were more common with combination therapy than with radiation therapy alone.

Ameliorating Treatment-Related Morbidity

Several new interventions are available to reduce treatment-related morbidity. Amifostine is a radioprotective agent that is administered intravenously to minimize the severity and duration of mucositis associated with radiation therapy (Bourhis, DeCrevoisier, Abdulkarim, Deutsch, Lusinchi, & Luboinski, et al., 2000). The uptake of amifostine is much more efficient in normal cells than in malignant cells because of pH differences (tumors typically are acidic). The drug has a selective protective effect against radiation-induced damage in normal cells. The topical “swish and swallow” administration of certain growth factors may be beneficial for the same reason.

Improved antibiotics help patients tolerate the myelosuppression associated with chemotherapy or radiation therapy. Modifying radiation therapy fractionation schedules also can minimize morbidity.

New Approaches

New approaches to treating head and neck cancer include the use of new chemotherapeutic agents (e.g., the taxanes paclitaxel and docetaxel, and the topoisomerase inhibitors topotecan and irinotecan). The availability of oral fluoropyrimidines (e.g., fluorouracil) may offer patients convenience (a continuous intravenous infusion of fluorouracil over a period of 5 days

has been required) (Humerickhouse, Dolan, Haraf, Brockstein, Stenson, Kies, et al., 1999).

Local therapy for recurrent local or regional disease is a new approach that involves direct intralesional injection of chemotherapy, mutant viruses, or gene therapy (Clayman & Dreiling, 1999). The propensity of head and neck tumors to recur locally, where they are accessible by intralesional injection, allows the use of this approach. A mutant virus known as ONYX-15 selectively grows in and kills cells lacking a functional p53 protein (Ganly, Soutar, & Kaye, 2000). The p53 protein is made by a tumor suppressor gene that is absent from most head and neck cancers, especially those that are particularly virulent. Tumor regression has been demonstrated in head and neck cancers after intralesional injection of ONYX-15 (Ganly, Eckhardt, Rodriguez, Soutar, Otto, Robertson, et al., 2000; Heise, Sampson-Johannes, Williams, McCormick, Von Hoff, & Kirn, 1997; Khuri, Nemunaitis, Ganly, Arseneau, Tannock, Romel, et al., 2000). Studies of the combination of ONYX-15 and systemic chemotherapy are under way and appear promising. This research is particularly exciting because clinicians have had little to offer patients with recurrent disease other than temporary palliative measures.

Gene therapy involves the transfer of therapeutic genes to target cells (Clayman & Dreiling, 1999). Delivery vehicles include viruses and plasmid-liposome complexes. Therapeutic genes might include the p53 gene that is missing from cancer cells, a suicide gene that causes the death of cancer cells, or genes that encode immunotherapies that result in local cell death (e.g., the gene for

interleukin-2 production) (Ganly, Eckhardt, Rodriguez, Soutar, Otto, Robertson, et al., 2000). These approaches are still highly experimental and years away from routine therapeutic use.

Summary

Head and neck cancer is a devastating malignancy that usually is preventable. Treatment of advanced disease involves multiple healthcare professionals, and nurses play a crucial role in coordinating as well as providing care. Improvements continue to be made in the standard treatment modalities. The use of chemotherapy makes organ preservation feasible without jeopardizing survival but raises concerns about treatment-related toxicity and quality of life. Intralesional injection therapies appear promising because of the tendency for most head and neck cancers to recur locally. The role of these investigational therapies remains to be clarified in randomized clinical trials.

References

- Ali, H., & Al-Sarraf, M. (1999). Nasopharyngeal cancer. *Hematol Oncol Clin North Am*, 13, 837-847.
- Al-Sarraf, M., LeBlanc, M., Giri, P.G., Fu, K.K., Cooper, J., Vuong, T. et al. (1998). Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized Intergroup study 0099. *J Clin Oncol*, 16, 1310-1317.
- American Cancer Society (2000). Laryngeal and hypopharyngeal cancer. Available: http://www3.cancer.org/cancerinfo/load_cont.asp?st=wi&ct=23&Language=ENG LISH#stats. Accessed October 2, 2000.
- Bourhis, J., De Crevoisier, R., Abdulkarim, B., Deutsch, E., Lusinchi, A., Lubinski, B., et al. (2000). A randomized study of very accelerated radiotherapy with and without amifostine in head and neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys*, 46, 1105-1108.
- Clayman, G.L., Dreiling, L.K. (1999). Injectable modalities as local and regional strategies for head and neck cancer. *Hematol Oncol Clin North Am*, 13, 787-810.
- Delsupehe, K.G., Zink, I., Lejaegere, M., & Bastian, R.W. (1999). Voice quality after narrow-margin laser cordectomy compared with laryngeal irradiation. *Otolaryngol Head Neck Surg*, 121, 528-533.
- Forastiere, A., Goepfert, H., Goffinet, D., Hong, K.W., Laramore, G., Mittal, B., et al. (1998). NCCN practice guidelines for head and neck cancer. National Comprehensive Cancer Network. *Oncology*, 12(7A), 39-147.
- Foster, R.D., Anthony, J.P., Sharma, A., Pogrel, M.A. (1999). Vascularized bone flaps versus nonvascularized bone grafts for mandibular reconstruction: An outcome analysis of primary bony union and endosseous implant success. *Head and Neck*, 21, 66-71.
- Fountzilas, G., Nicolaou, A., Sridhar, K., Sideras, T., Haritanti, A., Anastasakis, C., et al. (1989). Induction chemotherapy with cisplatin, 5-fluorouracil, bleomycin, mitomycin C and hydroxyurea for previously untreated locally advanced squamous cell carcinomas of the head and neck. *Arch Otorhinolaryngology*, 246, 373-377.
- Fu, K.K., Pajak, T.F., Trotti, A., Jones, C.U., Spencer, S.A., Phillips, T.L., et al. (2000). A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: First report of RTOG 9003. *Int J Radiat Oncol Biol Phys*, 48, 7-16.
- Ganly, I., Eckhardt, S.G., Rodriguez, G.I., Soutar, D.S., Otto, R., Robertson, A.G., et al. (2000). A phase I study of Onyx-015, an E1B attenuated adenovirus, administered intratumorally to patients with recurrent head and neck cancer. *Clin Cancer Res*, 6, 798-806.
- Ganly, I., Soutar, D.S., Kaye, S.B. (2000). Current role of gene therapy in head and neck cancer. *Eur J Surg Oncol*, 26, 338-343.
- Harwood, A.R., & Rawlinson, E. (1983). The quality of life of patients following treatment for laryngeal cancer. *Int J Radiat Oncol Biol Phys*, 9, 335-338.
- Heise, C., Sampson-Johannes, A., Williams, A., McCormick, F., Von Hoff, D.D., Kirn, D.H. (1997). ONYX-015, an E1B gene-attenuated adenovirus, causes tumor-specific cytolysis and antitumor efficacy that can be augmented by standard chemotherapeutic agents. *Nat Med*, 3, 639-645.

- Hillman, R.E., Walsh, M.J., Wolf, G.T., Fisher, S.G., & Hong, W.K. (1998). Functional outcomes following treatment for advanced laryngeal cancer. Part I-Voice preservation in advanced laryngeal cancer. Part II-Laryngectomy rehabilitation: The state of the art in the VA System. Research Speech-Language Pathologists. Department of Veterans Affairs Laryngeal Cancer Study Group. *Ann Otol Rhinol Laryngol Suppl*, 172, 1-27.
- Hong, W.K., Shapshay, S.M., Bhutani, R., Craft, M.L., Ucmakli, A., Yamaguchi, K.T., et al. (1979). Induction chemotherapy in advanced squamous head and neck carcinoma with high-dose cis-platinum and bleomycin infusion. *Cancer*, 44, 19-25.
- Humerickhouse, R.A., Dolan, M.E., Haraf, D.J., Brockstein, B., Stenson, K., Kies, M., et al. (1999). Phase I study of eniluracil, a dihydropyrimidine dehydrogenase inactivator, and oral 5-fluorouracil with radiation therapy in patients with recurrent or advanced head and neck cancer. *Clin Cancer Res*, 5, 291-298.
- Jacobs, J.R., Pajak, T.F., Kinzie, J., Al-Sarraf, M., Davis, L., Hanks, G.A., et al. (1987). Induction chemotherapy in advanced head and neck cancer. A Radiation Therapy Oncology Group Study. *Arch Otolaryngol Head Neck Surg*, 113, 193-197.
- Khuri, F.R., Nemunaitis, J., Ganly, I., Arseneau, J., Tannock, I.F., Romel, L., et al. (2000). A controlled trial of intratumoral ONYX-015, a selectively-replicating adenovirus, in combination with cisplatin and 5-fluorouracil in patients with recurrent head and neck cancer. *Nat Med*, 6, 879-885.
- Leborgne, F., Zubizarreta, E., Fowler, J., Ortega, B., Mezzera, J., Deus, J.L., et al. (2000). Improved results with accelerated hyperfractionated radiotherapy of advanced head and neck cancer. *Int J Cancer*, 90, 80-91.
- Lefebvre, J.L., Chevalier, D., Luboinski, B., Kirkpatrick, A., Collette, L., & Sahnoud, T. (1996). Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. *J Natl Cancer Inst*, 88, 890-899.
- McNeil, B.J., Weichselbaum, R., & Pauker, S.G. (1981). Speech and survival: Tradeoffs between quality and quantity of life in laryngeal cancer. *N Engl J Med*, 305, 982-987.
- Potter, R., Prott, F.J., Micke, O., Haverkamp, U., Wagner, W., & Willich, N. (1999). Results of fast neutron therapy of adenoid cystic carcinoma of the salivary glands. *Strahlenther Onkol*, 175(suppl 2), 65-68.
- Rebeiz, E.E., Wang, Z., Annino, D.J., McGilligan, J.A., & Shapshay, S.M. (2000). Preliminary clinical results of window partial laryngectomy: A combined endoscopic and open technique. *Ann Otol Rhinol Laryngol*, 109, 123-127.
- Schantz, S.P., Harrison, L.B., & Forastiere, A.A. (1997). Tumors of the nasal cavity and paranasal sinuses, nasopharynx, oral cavity, and oropharynx. In V.T. DeVita, S. Hellman, & S.A. Rosenberg (Eds.), *Cancer: Principles & Practice of Oncology* (5th ed.), (pp. 741-801). Philadelphia, PA: Lippincott-Raven Publishers.
- Sessions, R.B., Harrison, L.B., & Forastiere, A.A. (1997). Tumors of the larynx and hypopharynx. In V.T. DeVita, S. Hellman, & S.A. Rosenberg (Eds.), *Cancer: Principles & Practice of Oncology* (5th ed.), (pp. 802-829). Philadelphia, PA: Lippincott-Raven Publishers.
- Shaha, A.R., & Strong, E.W. (1995). Cancer of the head and neck. In *American Cancer Society Textbook of Clinical Oncology* (2nd ed), (pp. 355-377). Atlanta, GA: American Cancer Society.
- Spaulding, M.B., Fischer, S.G., & Wolf, G.T. (1994). Tumor response, toxicity, and survival after neoadjuvant organ-preserving chemotherapy for advanced laryngeal carcinoma. The Department of Veterans Affairs Cooperative Laryngeal Cancer Study Group. *J Clin Oncol*, 12, 1592-1599.
- Tatsuzaki, H., & Urie, M.M. (1991). Importance of precise positioning for proton beam therapy in the base of skull and cervical spine. *Int J Radiat Oncol Biol Phys*, 21, 757-765.
- The Department of Veterans Affairs Laryngeal Cancer Study Group. (1991). Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med*, 324, 1685-1690.
- Vokes, E.E. (1998). Head and neck cancer. In A.S. Fauci, E. Braunwald, K.J. Isselbacher, et al (Eds.), *Harrison's Principles of Internal Medicine* (14th ed.), (pp. 549-552). New York: McGraw-Hill Health Professions Division.

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