Contemporary Management of Head and Neck Cancers

Ziv Gil MD PhD[1,2,3] and Dan M. Fliss MD[3]

[1]The Skull Base Surgery Service, [2]Laboratory for Translational Cancer Research, and [3]Department of Otolaryngology Head and Neck Surgery, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

ABSTRACT: Head and neck cancer is the sixth most common cancer worldwide. HNCs can originate in the skin or soft tissue, in the upper aerodigestive tracts (oral cavity, oropharynx, hypopharynx, larynx, nasopharynx, paranasal sinuses, salivary glands), or in the thyroid. In each of these sites, tumors vary not only by the primary site but also by pathophysiology, biological behavior, and sensitivity to radiotherapy or chemotherapy. Management should be planned according to the tumor's characteristics, patient factors and expertise of the medical team. The main goals of therapy are ablation of the cancer while minimizing morbidity and preserving function and cosmesis. A multidisciplinary team is needed to achieve these goals. Early-stage HNC (stage I and II) should be managed with a single modality, and advanced tumors (stage III and IV) with multimodality therapy. Treatment should be directed to the primary tumor and the area of its lymphatic drainage – the neck lymph nodes. Evidence of metastases in the neck necessitates comprehensive clearance of regional lymphatic basins. However, even if there is no evidence of lymph nodes metastases, when the risk for positive neck lymph nodes exceeds 15–20% elective neck dissection is indicated. Advances in minimally invasive techniques now enable reliable microscopic and endoscopic procedures that mimic the open approaches. Development of contemporary surgical techniques and reconstructive means will help improve the quality of life of patients and prolong survival.

IMAJ 2009;11:296–300

KEY WORDS: oral cavity, larynx, oropharynx, hypopharynx, squamous cell carcinoma

Head and neck cancers include various malignancies found in the upper aerodigestive tracts. The most common malignant tumors of the head and neck include squamous cell carcinomas and salivary gland and thyroid carcinomas. Demographic and geographic factors as well as exposure to different carcinogens (e.g., nicotine, alcohol, viruses) contribute to the differential incidence of these tumors [1]. Tumors originating at different sites also vary by pathophysiology, biological behavior, and sensitivity to radiotherapy and chemotherapy. Such factors play an important role in tailoring appropriate treatment for patients with HNC.

Over the past few decades the 5 year survival associated with squamous cell HNC has significantly increased from less than 50% in the 1960s to approximately 70% at the present time [2]. Improved survival and decreased incidence of head and neck cancer in the western world are likely due to greater emphasis on prevention, early diagnosis and development of new treatment modalities. While the incidence of head and neck squamous cell carcinoma has decreased, the incidence of thyroid carcinomas has increased in the last decade, mostly due to the widespread use of imaging modalities in modern medicine without significant impact on survival [3].

In this paper we review the current management of head and neck cancers in light of recent developments in surgical, medical and radiation oncology. The roles of new imaging modalities, minimally invasive surgery, reconstruction methods and adjuvant treatment are also discussed.

PREOPERATIVE MANAGEMENT

Physical examination and preoperative imaging are required for clinical staging and treatment planning. The nasopharynx, hypopharynx and larynx are evaluated with a flexible endoscope while the floor of mouth and base of tongue are better assessed by manual examination. Radiological evaluation of patients with HNC may include computed tomography scan of the head and neck while well-differentiated thyroid cancers are better evaluated using ultrasound. For skull base tumors or tongue cancers magnetic resonance imaging may offer better assessment of soft tissue invasion. Positron emission tomography or integrated PET-CT system offers a good assessment of locoregional and distance metastases [4]. A Panorex or dental CT scan is performed in case of mandibular invasion. Angiography and balloon occlusion test may be indicated in selected cases when involvement of the carotid artery is suspected.

TAILORING TREATMENT

During the last decade the management of HNC changed dramatically, mostly due to the organ-preservation approach [5]. Management of HNC should be tailored according to

HNC = head and neck cancer

PET = positron emission tomography

characteristics of the tumor and to patient and surgeon preferences. The most important tumor factors associated with prognosis are local invasion, neural infiltration, angioinvasion, lymphogenic dissemination and soft tissue extension. Patient factors include age, medical status, performance, access to medical care, and personal preferences. Factors related to the medical care provider include availability of a modern radiotherapy facility and surgical experience. The main goals of therapy are: a) ablation of cancer while minimizing morbidity, b) preservation or restoration of function, and c) improvement in the patient's quality of life. These goals are achieved by a multidisciplinary team including various specialists in head and neck surgery, reconstructive surgery, radiation oncology, medical oncology, dental surgery, prosthetics, HNC pathology, and rehabilitation medicine. Adjunctive teams including speech and swallowing, neurosurgery, psychiatry or addiction services may also participate in the management of these patients as indicated.

As a rule, early-stage (stage I and II) HNC should be managed with a single modality, while advanced tumors are managed with multimodality therapy [6]. Tumors originating in the salivary gland, oral cavity and paranasal sinuses require surgical ablation, while early cancers of the oropharynx, hypopharynx and larynx can be alternatively managed with primary radiation. Papillary, follicular and medullar thyroid cancers with or without neck metastases are managed surgically [7]. Advanced, nasopharyngeal, oropharyngeal, hypopharyngeal or laryngeal squamous cell carcinomas are preferentially managed by primary concurrent chemoradiation.

Head and neck cancer is the sixth most common cancer worldwide

PRINCIPLES OF SURGERY

The overall objective of all surgical oncology procedures is to excise all tumor extensions with sufficient surgical margins [8]. Tumors originating in the oral cavity and salivary glands, which are accessible and relatively non-sensitive to radiation, are managed surgically. Patients with distance metastases (positive M stage) are considered non-surgical candidates, with the exception of adenoid cystic carcinoma and well-differentiated thyroid cancers. The tumor should be resected if possible in an *en bloc* fashion in order to decrease the possibility of tumor spillage and to ensure the presence of negative margins. A 1.5–2 cm margin can be achieved in oral cavity and major salivary gland tumors; however, in cases of larynx cancers and skull base tumors, wide margins can lead to loss of vital functions and unequivocally should not be pursued [9].

Patients with HNC have a 4% risk per year of developing a second primary tumor even after complete tumor ablation. Prevention (smoking and alcohol cessation) and early detection should be a principal objective of postoperative patient care. Follow-up of patients with HNC is aimed at early detection of primary tumor recurrence, locoregional or distant metastases, or of a second primary tumor. Routine head and neck examination and yearly chest X-ray imaging are part of the management of these patients after surgery. Computed tomography, MRI and PET imaging can be used for early detection of recurrence in this population [4].

MANAGEMENT OF THE NECK

The type, grade, site and stage of the primary tumor determine the risk of cervical metastases and hence the type of treatment. In oral tongue carcinoma, the risk of neck metastasis is significantly associated also with the depth of tumor invasion [10]. The patterns of spread of cancer to cervical lymph nodes are predictable, based on the anatomical location of the primary tumor. Therefore, in the absence of clinical evidence of neck disease, the pathological features of the primary tumor along with its site of origin and clinical T stage are used to stratify the risk of positive neck metastases and, consequently, the need for a neck dissection. When the risk for positive neck lymph nodes exceeds 15–20%, elective neck dissection is indicated – not only as treatment but also to evaluate the need for adjuvant therapy. A selective neck dissection, directed to the basins at risk for lymphatic spread, is commonly used for this purpose. For example, resection of levels I-IV is performed for oral cavity cancers and of levels II-IV for cancers of the larynx and hypopharynx. Due to the rich lymphatic system of the supraglottis and the frequent involvement of multiple subsites, supraglottic tumors will necessitate bilateral neck dissection. Similarly, tongue and glottic tumors that cross the midline will also necessitate neck dissection bilaterally. Sentinel lymph node dissection is a technique commonly used for malignant melanoma and its use in other carcinomas of the head and neck awaits further studies [11]. The presence of palpable neck disease mandates comprehensive clearance of the lymphatic basins in the neck. Radical neck dissection was considered the primary modality for treatment of HNC with clinical evidence of cervical metastases. However, sacrificing vital structures during radical neck dissection causes severe disabilities in patients and a markedly reduced quality of life. Advances in the anatomic elucidation of the neck, enhanced understanding of the biological behavior of tumors, and improved surgical methods have contributed to the emergence of the functional neck dissection technique, resulting in excellent survival and functional outcome [6]. Exact knowledge of the anatomy of the neck and its adjacent structures and the risk and location of common cervical metastases is essential for the operative treatment of HNC. As a general principle, preservation of the accessory

nerve should be pursued even in the presence of positive neck disease without impairing the first goal of surgery – extirpation of the cancer. Although a selective neck dissection is generally performed in patients without clinical evidence of neck metastases, there is emerging data that selective neck dissection can be performed also in patients with positive lymph nodes that are anatomically amenable, provided an adequate surgical margin can be safely obtained [12]. Radical neck dissection is reserved for patients with clinical or radiological evidence of neck disease, when complete tumor removal is unattainable without sacrificing the cranial nerves, the internal jugular vein and the sternocleidomastoid muscle.

TREATMENT OF LARYNGEAL CANCERS

Owing to the development of organ preservation regimens for patients with laryngeal cancer, total laryngectomy is currently reserved for tumors with extensive cartilage erosion, for tumors with extra-laryngeal involvement, or as salvage therapy [13]. For these patients, tracheoesophageal prostheses have revolutionized the rehabilitation and restoration of speech and quality of life. Open surgical approaches that preserve laryngeal function may be indicated for selected patients failing radiation therapy [14]. These include: a) supraglottic partial laryngectomy, b) vertical partial laryngectomy, and c) supracricoid partial laryngectomy.

Early-stage cancer is managed with a single modality and advanced tumors with multimodality therapy

Advances in minimally invasive techniques have led to the development of reliable techniques for laryngeal surgery that mimic the open approaches. Trans-oral laser microsurgery is an established technique for management of early laryngeal and hypopharyngeal tumors with good functional and clinical outcomes [15]. Absolute contraindications for laryngeal microsurgery include significant invasion of the thyroid cartilage or extra-laryngeal sites. Results from laryngeal microsurgery have been reported by many centers and is considered an acceptable alternative to primary radiotherapy for early laryngeal cancer [5]. Trans-oral laser microsurgery for advanced laryngeal tumors can potentially offer curative outcome while conferring several intraoperative and postoperative surgical advantages over open surgery: namely, faster recovery and improved laryngeal function. On the other hand, the clinical outcomes of microscopic resection of advanced laryngeal cancers have been controversial and more data are required before its true clinical efficacy can be determined. Despite the success of minimally invasive techniques for the management of laryngeal tumors, patients who are poor surgical candidates and those with extra-laryngeal spread would benefit from non-surgical modalities or from total laryngectomy, respectively.

MINIMALLY INVASIVE SKULL BASE SURGERY

With the increasing development of endoscopic modalities in surgical oncology, advanced ablative and reconstructive procedures are being performed endoscopically mainly in the management of benign tumors arising in the paranasal sinuses or skull base. Future clinical studies are required to evaluate the role of endoscopic surgery to treat early-stage malignant tumors arising in the paranasal sinuses [16]. Head and neck surgeons trained to perform both open and endoscopic approaches can offer patients the best surgical treatment for their disease. Multidisciplinary teams of skull-base surgeons, with expertise in treating cancer patients, can choose the best ablative and reconstructive approaches for the tumor and are prepared to deal with intraoperative or postoperative complications that require immediate transition from an endoscopic to an open approach [17].

RECONSTRUCTION

Reconstructing the surgical defect is aimed at preservation of function and acceptable cosmesis [18]. Reconstruction after HNC resection is technically challenging and may be further complicated by several factors. First, there is a paucity of local tissue for transfer into the defect. Second, previous radiation treatment significantly reduces tissue perfusion and thus delays normal wound healing. Finally, many of these patients have undergone earlier surgeries prior to the index operation, increasing its complexity and decreasing tissue perfusion secondary to scar tissue formation.

Primary closure or a split-thickness skin graft is suitable for early tongue, buccal mucosa or floor of mouth tumors. Local flaps are often used for reconstruction of the lip or skin. Recent progress in microvascular and surgical techniques has enabled the development and implementation of free tissue transfer [19]. Following resection, free flaps may be used for restoration of speech and swallowing, to maintain patency of the upper aerodigestive tracts, and for occlusion of large surgical defects with excellent surgical results and low complication rates. Adequate reconstruction, however, should never be attained at the expense of incomplete tumor ablation or inadequate surgical margins. New reconstructive means for endoscopic resections are needed to allow full implementation of minimally invasive modalities [20].

THE NEED FOR ADJUVANT TREATMENT

As a general concept, a patient with an early-stage HNC can be adequately treated with surgery alone while those with advanced-stage cancer will require adjuvant therapy. The

patient's previous treatment and the pathological features of the tumor will determine the need for adjuvant treatment after surgery. Accurate tumor staging is crucial to determine the need and type of adjuvant therapy. Tumor factors that will have impact on the need for postoperative adjuvant treatment include tumor type, size and grade, depth of invasion, bone invasion, nerve invasion, status of cervical lymph nodes, extracapsular spread and status of surgical margins. For example, in oral tongue carcinoma, depth of invasion > 8 mm increases the mortality rate by > 20% compared to < 2 mm depth of invasion [21]. Similarly, positive margins are associated with a 30% decrease in disease-specific survival rate.

Treatment is directed to the primary tumor and to its lymphatic basins in the neck

Recent studies demonstrated a slight improvement in 5 year survival rates after adjuvant concurrent chemo-radiation therapy over radiotherapy alone for advanced HNC [22]. Due to the significant morbidity when adding chemotherapy to radiotherapy, significant controversy remains regarding the pathological factors requiring more aggressive adjuvant treatment [23]. A recent meta-analysis suggested that patients with extracapsular extension and microscopically involved surgical margins have a significantly poor outcome and therefore may benefit from concurrent chemotherapy and radiotherapy if they are medically fit [24].

LONG-TERM OUTCOME

The long-term prognosis of HNC has improved over the past decades mainly due to the popularization of postoperative adjuvant radiotherapy. Recent studies demonstrated 5 year survival rates of approximately 68% after curative resection of oral cavity cancer. In a subgroup of patients with lymph node and margin-negative tumors, 5 year survival of over 80% has been achieved [25]. Analysis of the patterns of treatment failure in patients with oral cancers reveals that 57% will reoccur at the site of the primary tumor, half will fail due to regional metastases and 9% due to distance metastases [26]. Sixteen percent of the patients will have recurrence at multiple sites. Similarly, positive margins are associated with poor survival in patients with skull base tumors including carcinomas and sarcomas [27].

Early identification, a multidisciplinary team approach and use of adjuvant radiation or chemo-radiation therapy have contributed to increased patient survival

NEW FRONTIERS IN HEAD AND NECK SURGERY

The new frontier in surgical treatment of HNC should be aimed at reducing the morbidity associated with tumor extirpation while maintaining the safety and efficacy of treatment. In the last decade, laparoscopic and robotic surgeries have become established procedures in multiple specialties of surgery. However, these technically challenging procedures have lagged behind surgical management of head and neck neoplasms. The development of new endoscopic instruments, intraoperative navigation and novel imaging modalities now allow the extirpation of HNC. Endoscopic and robotic techniques are under development for management of tumors that traditionally required open approaches, including those originating in the oropharynx, hypopharynx, sinuses and skull base. New lines of flexible fiber optic lasers, tissue-welding techniques and biomaterials warrant continued development and preclinical investigation and may provide a basis for new tools in the management of HNC.

An ideal head and neck surgeon should understand the oncological principles of head and neck cancers, be able to offer patients the best surgical and reconstructive solutions for their pathology and be familiar with both open and endoscopic approaches. Head and neck surgeons must also be conversant with contemporary medical and radiation oncology treatment regimens that can be offered as an alternative to surgery or as a postoperative adjuvant treatment. Due to the complexity of this treatment, head and neck surgeons should lead a multidisciplinary team of clinicians and surgeons familiar with these techniques.

QUALITY OF LIFE

The importance of quality of life of patients with cancer is now being more and more acknowledged. Quality of life is assessed in an effort to improve treatment modalities, promote restoration of patient's daily functions, and accelerate his or her return to normal life. Estimating the influence of surgical procedures on quality of life can serve as a means by which the most appropriate surgical approach can be selected for a given patient. Detailed understanding of the different aspects of quality of life may help surgeons improve assessment and management of patients, identify specific impediments as early as possible during follow-up, and direct specific medical interventions to patients with increased risk and poor outcome [28]. Disease-specific instruments with multiple domains of quality of life should be used to reliably assess the effect of surgery on the well-being of the patient [29].

CONCLUSIONS

Early identification and treatment of the primary tumor and nodal metastases, a multidisciplinary team approach and use of adjuvant radiation or chemo-radiation therapy have

contributed to increased survival of patients with HNCs. Contemporary surgical techniques, organ preservation means and reconstruction methods are essential to enhance the quality of life of patients after surgical ablation of HNC while allowing complete extirpation of the tumor.

Correspondence:
Dr. Z. Gil
Co-Director, Skull Base Surgery Service, Director, Laboratory for Applied Cancer Research, Dept. of Otolaryngology Head and Neck Surgery, Tel Aviv Sourasky Medical Center, 6 Weizmann St., Tel Aviv 64239, Israel
Phone: (972-3) 697-3544
Fax: (972-3) 697-3543
email: ziv@baseofskull.org

References

1. Nagler RM, Reznick AZ. Cigarette smoke effects on salivary antioxidants and oral cancer – novel concepts. *IMAJ* 2004; 6(11): 691-4.
2. Yao M, Epstein JB, Modi BJ, Pytynia KB, Mundt AJ, Feldman LE. Current surgical treatment of squamous cell carcinoma of the head and neck. *Oral Oncol* 2007; 43(3): 213-23.
3. Holt E. Controversies in the surveillance of patients with well differentiated thyroid cancer. *Curr Opin Oncol* 2007; 19(1): 6-10.
4. Gil Z, Even-Sapir E, Margalit N, Fliss DM. Integrated PET/CT system for staging and surveillance of skull base tumors. *Head Neck* 2007; 29(6): 537-45.
5. Pfister DG, Laurie SA, Weinstein GS, et al. American Society of Clinical Oncology clinical practice guideline for the use of larynx-preservation strategies in the treatment of laryngeal cancer. *J Clin Oncol* 2006; 24(22): 3693-704.
6. Shah JP, Gil Z. Current concepts in management of oral cancer – Surgery. *Oral Oncol* 2008; Epub ahead of print, PMID: 18674952.
7. Gil Z, Patel SG. Surgery for thyroid cancer. *Surg Oncol Clin North Am* 2008;17(1):93-120, viii.
8. Bogdanov-Berezovsky A, Rosenberg L, Cagniano E, Silberstein E. The role of frozen section histological analysis in the treatment of head and neck skin basal and squamous cell carcinomas. *IMAJ* 2008; 10(5): 344-5.
9. Fliss DM, Abergel A, Cavel O, Margalit N, Gil Z. Combined subcranial approaches for excision of complex anterior skull base tumors. *Arch Otolaryngol Head Neck Surg* 2007; 133(9): 888-96.
10. Pentenero M, Gandolfo S, Carrozzo M. Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. *Head Neck* 2005;2 7(12): 1080-91.
11. Paleri V, Rees G, Arullendran P, Shoaib T, Krishman S. Sentinel node biopsy in squamous cell cancer of the oral cavity and oral pharynx: a diagnostic meta-analysis. *Head Neck* 2005; 27(9): 739-47.
12. Schiff BA, Roberts DB, El-Naggar A, Garden AS, Myers JN. Selective vs modified radical neck dissection and postoperative radiotherapy vs observation in the treatment of squamous cell carcinoma of the oral tongue. *Arch Otolaryngol Head Neck Surg* 2005; 131(10): 874-8.
13. Lefebvre JL. Laryngeal preservation in head and neck cancer: multidisciplinary approach. *Lancet Oncol* 2006; 7(9): 747-55.
14. Piazza C, Peretti G, Cattaneo A, Garrubba F, De Zinis LO, Nicolai P. Salvage surgery after radiotherapy for laryngeal cancer: from endoscopic resections to open-neck partial and total laryngectomies. *Arch Otolaryngol Head Neck Surg* 2007; 133(10): 1037-43.
15. Martin A, Jackel MC, Christiansen H, Mahmoodzada M, Kron M, Steiner W. Organ preserving transoral laser microsurgery for cancer of the hypopharynx. *Laryngoscope* 2008; 118(3): 398-402.
16. Mehta RP, Cueva RA, Brown JD, et al. What's new in skull base medicine and surgery? Skull Base Committee Report. *Otolaryngol Head Neck Surg* 2006; 135(4): 620-30.
17. Snyderman C, Carrau R, Kassam A. Who is the skull base surgeon of the future? *Skull Base* 2007; 17(6): 353-5.
18. Gil Z, Abergel A, Leider-Trejo L, et al. A comprehensive algorithm for anterior skull base reconstruction after oncological resections. *Skull Base* 2007; 17(1): 25-37.
19. Ad-el D, Casapi N, Regev E, et al. Reconstruction of the mandible by fibula free flap. *IMAJ* 2002; 4(8): 600-2.
20. Gil Z, Shaham A, Vasilyev T, et al. Novel laser tissue-soldering technique for dural reconstruction. *J Neurosurg* 2005; 103(1): 87-91.
21. Spiro RH, Huvos AG, Wong GY, Spiro JD, Gnecco CA, Strong EW. Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. *Am J Surg* 1986; 152(4): 345-50.
22. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004; 350(19): 1945-52.
23. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med* 2004; 350(19): 1937-44.
24. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck* 2005; 27(10): 843-50.
25. Shah JP. Surgical approaches to the oral cavity primary and neck. *Int J Radiat Oncol Biol Phys* 2007; 69(2 Suppl): S15-18.
26. Shingaki S, Takada M, Sasai K, et al. Impact of lymph node metastasis on the pattern of failure and survival in oral carcinomas. *Am J Surg* 2003; 185(3): 278-84.
27. Gil Z, Patel SG, Singh B, et al. Analysis of prognostic factors in 146 patients with anterior skull base sarcoma: an international collaborative study. *Cancer* 2007; 110(5): 1033-41.
28. Gil Z, Abergel A, Spektor S, et al. Quality of life following surgery for anterior skull base tumors. *Arch Otolaryngol Head Neck Surg* 2003; 129(12): 1303-9.
29. Gil Z, Abergel A, Spektor S, Shabtai E, Khafif A, Fliss DM. Development of a cancer-specific anterior skull base quality-of-life questionnaire. *J Neurosurg* 2004; 100(5): 813-19.

Capsule

Immune cell origins

In the immune system, dendritic cells, monocytes and macrophages are critical for the inflammatory response to pathogens. Although these cell types arise from a common hematopoietic precursor, they are functionally diverse and the developmental relationships between these subsets and where they develop have not been fully delineated *in vivo*. Liu and team elucidate the precursor-progeny relationship between mouse conventional dendritic cells, plasmacytoid dendritic cells, and monocytes. Conventional dendritic cells arise in the bone marrow and travel to the peripheral lymphoid organs, where further differentiation and expansion occurs.

Science 2009;324:392

Eitan Israeli