Head and neck oncology – 2010, part II

Nowotwory głowy i szyi – 2010, część II

Eugene N. Myers, MD, FACS, FRCS Edin (Hon)

SUMMARY
Part II this article reviewed the current state of the art in head and neck oncology. These include very important and stimulating new areas of interest including the marked acceptance of chemoradiation in favor of surgery in patients with cancer of the head and neck. The concept of HPV as a cause of cancer of the oropharynx is relatively new and very important in the epidemiology of these tumors. New modalities such as PET CT scanning and robotic surgery are discussed and appear to be very important in management of cancer of the head and neck. Endoscopic endonasal skull base surgery is another new high technology contribution to the field of head and neck surgery as is the use of endoscopic assisted thyroid surgery. These and other new concepts are discussed in this manuscript.

Key words: PET CT scanning, robotic surgery, endoscopic endonasal skull base surgery, endoscopic assisted thyroidectomy, nonsurgical treatment of cancer of the head and neck, microvascular free tissue transfer, selective neck dissection, sentinel node biopsy

CRANIAL BASE SURGERY

The combined cranial facial approach to the paranasal sinuses was reported by Smith, Klopp and Williams in 1954 [46]. Ketcham et al [47] in 1963 further refined the technique and called it “Combined Intracranial Facial Approach to the Paranasal Sinuses.” This combined approach allowed a more accurate determination of the true extent of disease and facilitated en bloc resection of the paranasal sinuses in continuity with the cribriform plate area of the anterior cranial fossa and the medial wall of the orbit. By the 1980s most head and neck surgical units had embraced this approach for tumors of the cranial base. This operation produced good oncologic results, but often at the expense of a relatively unpleasing cosmetic result due to the open facial approach. Reconstruction during the early days was suboptimal and resulted in some major problems. There were also major difficulties with managing postoperative cerebrospinal fluid leak and meningitis.

The introduction of endoscopic technology has had a major positive impact on the management of tumors of the sinonasal tract. Benign tumors such as the inverted papilloma and angiofibroma are ideally suited for endoscopic removal. Published series have demonstrated that endoscopic excision of properly selected tumors are associated with improved local tumor control and decreased morbidity compared with the standard open approach. The application of endonasal endoscopic techniques to the management of malignant sinonasal tumors has been somewhat controversial. Snyderman, et al. [48] state that the primary goal of oncologic surgery is complete excision of the neoplasm. Although different instrumentation is used with endoscopic surgery, the surgical strategy is similar to the open procedure. En bloc resection of the entire tumor is not necessary, but en bloc excision of the area of tumor invasion is the essential part of the procedure. This is best exemplified by the treatment of olfactory neuroblastoma where a bulky tumor may have only a small area of attachment to the cribriform plate. It is frequently necessary to debulk these tumors to gain access to the area of invasion.

Contrary to the usual principals in surgical oncology of not violating the tumor, this technique violates the tumor but does not violate normal tissue planes since most of the tumor is residing in the airfilled cavity. Currently there is no evidence that debulking the tumor increases the risk of local recurrence. There are, in fact, multiple examples of other neoplasms that are removed in a piece meal fashion without compromising results such as laser resection of pharyngeal and laryngeal squamous carcinomas and microscopic control of excision of skin cancers (Mohs technique). The authors state that even using open techniques, en bloc excision is not possible because of fragmentation of the specimen as well as proximity to vital structures. In such cases, the endonasal approach may actually decrease the risk of tumor seeding, but ultimately it is the final resection.
margin that is important, not so much the method of tumor removal.

Radiation therapy is an important adjunct to this approach, particularly in high grade malignancies when they involve critical structures, such as the brain, optic nerve, carotid artery or cavernous sinus when complete resection is not feasible. In such cases, chemoradiation is considered as the first therapy with surgical salvage for residual tumor following treatment of tumors such as nasopharyngeal carcinoma.

Endoscopic debulking of tumors may also be considered for palliation of symptoms such as: pain, epistaxis, nasal obstruction, visual loss, and cranial neuropathies secondary to compression. In their series of patients, the authors had a very low rate of complications such as wound infection and central nervous system related complications. Serious spinal fluid leak, which has been the most frequent major complication, has been minimal (less than 5%) since reconstructive techniques have evolved over the last decade, particularly the local nasal septal mucosal flap. Infectious complications are rare despite the contamination of the surgical field with nasal flora. With the perfection of hemostatic techniques, the overall improvement in instrumentation and with the development of vascularized flaps for reconstruction of dural defects, the benefits of enhanced endoscopic visualization and increased access and collaborative teamwork certainly have facilitated more effective and less morbid effects on the patient.

Hanna et al [49], had a somewhat different approach to cranial base surgery and in their article entitled “Endoscopic Resection of Sinonasal Cancers with and without Craniotomy” they describe a series of 120 patients, 93 of whom underwent the endonasal endoscopic approach (EEA) and 27 underwent a cranial endoscopic approach (CEA) in which the surgical resection involved the addition of a frontal or subfrontal craniotomy to the transnasal endoscopic approach. Approximately two-thirds of the patients treated with EEA had a lower disease stage (T1 to T2) while 95% of the patients treated with CEA had a higher disease state (T3, T4). The most common tumor types were olfactory neuroblastoma, sarcoma, adenocarcinoma, and squamous cell carcinoma. Microscopically positive margins were reported in 15% of the patients. Out of 120 patients, 15% were treated with surgery alone, 37% received postoperative radiation therapy, and 13% were treated with surgery, radiation therapy, and chemotherapy. The overall surgical complication rate was 11% for the whole group. The disease control was 85% and the five- and 10-year specific disease specific survival rates were 87 and 80%, respectively. The authors state that endoscopic approaches to the cranial base and sinonasal regions offer several advantages, such as: excellent visualization, reduction of the need for craniofacial soft tissue dissection, scalp disassembly, and brain retraction for tumor access and resection. The authors series of 120 patients is the largest series reported in the United States to date exclusively dealing with malignant tumors treated with endoscopic assisted resection. These advantages are the impetus for the increasing adoption of endonasal approaches for surgical management of sinonasal skull base tumors.

A previous large series reported from Italy by Nicolai, et al [50] recorded 134 patients treated with EEA and 50 patients treated with CEA. Nicolai’s five-year disease specific survival rate was 82%. Endoscopic resection of sinonasal cancer should be performed by surgeons who have extensive experience in two areas: endoscopic technique and surgical oncology.

**SALIVARY GLANDS**

There are several studies recently which describe progress in the management of tumors of the salivary glands. One is a report by Chen and Chang [51] from Taiwan who have evaluated the results of minimally invasive endoscopic assisted parotidectomy. The authors performed 14 resections of diseased parotid glands using the technique of endoscopic parotidectomy. The indications included chronic sialadenitis and benign neoplasms carried out under general anesthesia through a small incision made in the preauricular skin crease. The authors states that due to the magnification through the endoscope the branches of the facial nerve can be identified easily and the tumor could be dissected out and removed through the surgical wound. Their complications were minimal with only two patients having a transient House Grade II facial paresis and in no case was there permanent facial paralysis. The harmonic scalpel was used for the cutting tissue which also provided hemostasis. It was concluded that the advantages of minimally invasive endoscopic assisted parotidectomy included a superior visualization, magnification of the key structures and hemostasis and the concealment of the scar.

Douglas et al [52] described gamma knife stereotactic radiosurgery for salivary gland neoplasms with invasion of the base of the skull following neutron radiotherapy. Their aim was to examine the outcome of these patients with extensive high grade tumors. Their group of 34 patients with skull base involvement were treated from 2001 to 2005 at the University of Washington Cancer Center. The authors concluded that patients with primary salivary gland neoplasms involving the base of the skull treated with neutron radiotherapy alone are at a high risk of local recurrence. Gamma knife boost improved local control and had little additional toxicity. These preliminary results suggest that all patients with salivary neoplasms with invasion of the base of the skull should be considered for gamma knife boost after primary treatment with neutron radiotherapy.

Dr. Laramore et al [52] at the University of Washington have been enthusiastic proponents of treatment with
primary neutron radiotherapy over more than twenty years. In their analysis of the treatment of these tumors, they found that the most significant negative prognostic factor identified was invasion of the base of the skull. Patients not having invasion of the base of the skull had a 5 year local control rate of 70% whereas those having invasion of the base of the skull had a 5 year local control rate of only 19%. The analysis of their treatment planning disclosed that areas of the tumors invading above the lower portion of the temporal lobes had been relatively underdosed with neutron beams leading to this unacceptable low local control rate. The authors postulated that the additional of a single stereotactic boost using gamma knife technology provided an additional dose and as a result improved local control. In 2001 they began giving the boost to all patients with salivary gland malignancies and invasion of the skull base with a gamma knife boost. There was no increase in the complication rate accompanying this increase in local control.

Gopalakrishna Lyer et al [53] from the Sydney Head and Neck Cancer of Australia presented their outcomes for parotidectomy for metastatic squamous cell carcinoma with microscopic residual disease and implications for facial nerve preservation. The authors had a cohort of 15 patients who underwent nerve-sparing surgery with involved margins adjacent to the facial nerve were treated with adjuvant radiation therapy. A comparison of this group to patients with clear margins, showed no difference in local recurrence or survival. This study suggested that patients with metastatic squamous cell to the lymph nodes in the parotid gland with microscopic residual disease involving the facial nerve and normal function can be successfully treated with a facial nerve-sparing approach and appropriate doses of postoperative adjunctive radiation therapy.

Loh et al [54] in Toronto reported a study which identified prognostic factors associated with cancer arising in the minor salivary glands. This was a retrospective study of 171 patients. The authors found that the 5 year and 10 year overall survival in treating minor salivary malignancies was 73.8% and 58.1%, respectively. The three most common pathological types of minor salivary gland malignancies were adenoid cystic mucoepidermoid and adenocarcinoma. Multivariate analysis did not show any difference in survival between the three groups of patients. Patients with adenoid cystic carcinoma developed a higher degree of local recurrence and distant metastasis compared with patients with the other pathological entities. Grade of disease was a significant variable with high grade cancers having a significantly poorer survival. Men seemed to have a worse prognosis than women. Tumors occurring in the nasal cavity were associated with a poor disease free survival and had a greater tendency for local recurrence. Although often quoted as a significant factor, the stage of disease was not borne out as significant in their multivariate analysis. The inability to obtain clear margins lead to a higher recurrence rate. In their series, 50% of those with local recurrence having a positive margin required adjuvant therapy. However, despite this factor, survival was not different from those with clear surgical margins suggesting that adjunctive treatment with radiation therapy improves survival up to the same levels of patients with clear surgical margins. This was especially true in large sinonasal cancers in which complete surgical extirpation may not always be possible. The authors concluded that the 5 and 10 year overall disease free survival from minor salivary gland cancer is good, recurrences are usually local and distant and their data indicate that surgery is the main treatment modality either alone or in combination with radiation therapy.

### THYROID/PARATHYROID

One of the most remarkable trends in thyroid surgery has been to outpatient surgery. Hopkins and Steward [55] looked at the issue of outpatient surgery and the numerous advances which made it possible. Outpatient thyroid surgery is increasingly performed and that the length of stay has progressively been shortened from several nights to less than 6 hours. This was driven by a combination of patient preference and a movement to decrease costs.

However, the risks associated with outpatient thyroid surgery must be thoroughly addressed to determine

<table>
<thead>
<tr>
<th>Table 1. Minimally Invasive Thyroidectomy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td><strong>Contraindications</strong></td>
</tr>
<tr>
<td>Size of thyroid nodule &lt; 4 cm</td>
<td>History of thyroids</td>
</tr>
<tr>
<td>Thyroid volume of &lt; 30 cc, small to med goiters</td>
<td>Large goiters</td>
</tr>
<tr>
<td>Thyroid cancer size of &lt; 2 cm</td>
<td>Aggressive, high risk, poorly differentiated thyroid cancers, i.e., anaplastic, MTC</td>
</tr>
<tr>
<td>Low Risk, well differentiated thyroid cancers</td>
<td>History of previous head/neck surgery</td>
</tr>
<tr>
<td>Follicular neoplasm &lt; 4 cm</td>
<td>History of previous neck surgery</td>
</tr>
<tr>
<td>Experienced thyroid surgeon</td>
<td>Presence of palpable lymphadenopathy</td>
</tr>
</tbody>
</table>
feasibility. The most common complications of thyroid surgery include hypocalcemia, hematoma, injury to the recurrent or superior laryngeal nerve, wound infection, poor wound healing, pain, and a conspicuous scar. In order to decrease the risks, new criteria are being established for outpatient thyroid surgery which include: nodules smaller than 30 to 50 mm, less than 15 to 20 milliliters of thyroid volume, no sign of thyroiditis, no previous neck surgery or radiation, a non-obese patient, cancers less than 2 cm, and no local invasive thyroid malignancy. (Table I) [56].

The preoperative predictors of hypocalcemia include preoperative vitamin D3 level, calcium levels, intraoperative and immediate parathyroid hormone (PTH) level. Postoperative PTH has been shown to be a fast and reliable predictor of hypocalcemia. A recent analysis confirmed that PTH drawn 1 to 6 hours postoperatively can very accurately predict hypocalcemia [57].

Other advances in thyroid surgery which have led to outpatient surgery include minimally invasive video-assisted endoscopic assisted thyroid surgery and the use of ultrasonic technology such as the harmonic scalpel. Nerve monitoring is frequently used in thyroid surgery and may be beneficial in the outpatient setting. By using postoperative PTH testing, technologies (harmonic scalpel) to decrease bleeding, low risk patient selection, and providing proper patient education the safety of outpatient thyroid surgery has improved and it has become feasible as long as caution is used.

The surgical approaches currently used may be classified [58]:

1. Minimally invasive – mini-incision
2. Encoscopic video assisted
3. Completely closed endoscopic
   • Supraclavicular approach
   • Axillary approach
   • Anterior chest approach
   • Breast approach

Recurrent laryngeal nerve paralysis is one of the most concerning complications after thyroid surgery. Reported rates of recurrent laryngeal nerve (RLN) injury range from 1 to 8% and may result in symptoms ranging from dysphonia to severe airway compromise. Injury may result as a result of stretch, pressure, crush, electrocautery, suction trauma, and ischemia, or severing or excision of a portion of the nerve [59]. Two studies involving more than 1,000 and 27,000 nerves at risk revealed that visual identification of the nerve decreased the rates of permanent RLN palsies when compared with cases with no visual identification [60, 61]. The possibility of predicting vocal cord function after thyroidectomy may be important to the surgeon before he or she completes a total thyroidectomy if the nerve is damaged during the surgery. This may also affect the decision for same day discharge as a concern about respiratory compromise and to reassure patients of voice changes after surgery that these are likely due to vocal fold edema or poor effort.

In a study by Donnellan et al [59] an analysis of the Xomed NIM II system was done and the authors data suggest that the NIM II may provide information that can be important to postoperative vocal cord function. However, the authors are quick to point out that “no neuromonitoring system can substitute for careful dissection and visual nerve identification during thyroid surgery”. This becomes extremely important with the findings of Cernea et al [62] who analyzed the frequency of extralaryngeal branching of the recurrent laryngeal nerve in a consecutive series of patients undergoing thyroidectomy. Extralaryngeal branching was found in 64.53% of RLN in the series of 1390 RLNs. In patients with intraoperative laryngeal nerve monitoring, electrophysiologic activity was observed in branches, particularly the anteriorly situated ones. Recognition of this frequent anatomical configuration and meticulous preservation of all branches are of paramount importance to decreased postoperative morbidity associated with thyroidectomy.

Davidson et al [63] used an operating microscope in performing thyroid surgery. This allowed the surgeon an upright posture while performing thyroid surgery thereby reducing the potential for neck and back injury for the surgeon while also providing superior magnification of the visual field.

The issue of central compartment dissection in patients with papillary thyroid carcinoma has become a focal point of study in recent years. Zuniga and Sanabria [64] in 2009 studied the issue of prophylactic central neck dissection in N0 papillary thyroid carcinoma. They studied a total of 266 patients with a mean followup time of 6.9 years. Five-year neck disease free survival was 86.8% in patients who underwent central neck dissection versus 85.6% in a group that did not undergo central neck dissection. Despite the fact that in those patients who had the central neck dissection, 112 out of 136 patients had positive metastatic lymph nodes (82.3%). In the multivariated analysis, factors related to central neck dissection were macroscopic extrathyroidal extension and multifocality. They concluded that prophylactic central neck dissection did not show an advantage in the rate of neck recurrence.

Ondik, et al [65] studied the opposite position, that is the secondary central compartment surgery for thyroid cancer. They stated that reoperative thyroid surgery in the form of secondary central compartment surgery and/or lateral neck dissections is increasing. This may be the result of two phenomena. The first is the incidence of papillary thyroid carcinoma increasing and the second is improved diagnostic techniques which are changing the management of recurrent thyroid cancer particularly: sensitive thyroglobulin assays, high resolution ultrasound techniques, and integrated PET scanning which are detecting small recurrent thyroid cancers and...
promoting surgical intervention in the form of central compartment surgery and lateral neck dissections. The authors report the feasibility of this surgery, however at the cost of a permanent recurrent nerve injury of 6.4%, while the transient and permanent hypoparathyroidism was 11.9 and 9.5% respectively. This was the case for primary central compartment dissection, although as mentioned above, this was not shown to alter the outcome.

Rosenbaum and McHenry [66] studied a series of 110 patients who underwent initial thyroidectomy. Therapeutic central neck dissection was performed in 20% of these patients. One patient developed a recurrence in the lateral neck. Eighty-eight patients had no abnormal lymph nodes and did not undergo central neck dissection. Two of these patients subsequently developed a recurrence in the central component. Permanent hypoparathyroidism occurred in one patient who underwent central neck dissection. The authors conclude that after a total thyroidectomy and central neck dissection, recurrence in the central neck is uncommon, but hypocalcemia is more common raising the question about the use of routine central neck dissection in patients with papillary thyroid carcinoma.

Similar issues have been raised in patients undergoing minimally invasive parathyroidectomy Smith et al [67] reviewed minimally invasive parathyroidectomy in patients undergoing initial surgical management of primary hyperparathyroidism with preoperative localizing sestamibi scanning (MIBI) and concordant ultrasonography (US) to determine if intraoperative parathyroid hormone is necessary in these patients. Minimally invasive parathyroidectomy has become an acceptable therapeutic option in treating patients with hyperparathyroidism. Preoperative sestamibi scanning, high resolution ultrasound with Doppler flow and intraoperative PTH monitoring have refined this technique. Intraoperative PTH monitoring may be eliminated in minimally invasive parathyroid surgery in a carefully selected group of patients who have preoperative localizing sestamibi scanning (MIBI) with concordant ultrasound as a potentially valid increase in operating room efficiency and decrease in cost while performing minimally invasive parathyroidectomy.

**ROBOTICS**

O’Malley and Weinstein in 2007 [68] described the development of a novel approach called transoral robotic surgery (TORS) using the da Vinci surgical robot which provides safe access to the oral cavity, oral pharynx, and supraglottis. They also tested their hypothesis that robotic surgical technology could be applied to the anterior and midline skull base. The approach also allowed excellent visualization and access to the parapharyngeal space and to the infratemporal fossa. They developed a novel surgical approach called a combined C-TORS which enabled them to overcome the instrument angulation and access limitations of TORS. They subsequently performed successful surgical dissection of the sphenoid sinus, clivus, sella and anterior fossa [68].

Weinstein et al [69] applied robotic surgery and the TORS technique to cancer of the supraglottis and used a canine model to define the parameters of the procedure. They felt that the transoral laser supraglottic laryngectomy was superior to the open approach and felt that the TORS technique had the potential to be even more effective. The authors concluded that the TORS program may help to shift the paradigm back to primary surgery with or without radiation for the management of cancer of the supraglottic larynx.

Weinstein et al [70] quote their experience in 225 cases performed using the TORS technique at the University of Pennsylvania. They report that this technique is feasible since it provides access to almost any lesion in the oropharynx as well as many lesions in the supraglottis and hypopharynx. Total operative time paralleled the exposure time for standard transoral resections. The operation was found to be safe and no patient operated on using this technique required a blood transfusion. Most patients were discharged from the hospital on the 5th to 7th postoperative day. Minor postoperative complications were encountered. The functional outcome was excellent and 96% of their patients were swallowing without the use of a gastrostomy tube. The encouraging swallowing function afforded by TORS may ultimately show an advantage when compared to primary chemoradiation for head and neck cancer since in a literature review of patients treated with primary chemoradiation gastrostomy tube dependence was present in 17 to 30% of the patients followed up for one year [71].

The authors quote an important paper by Machtay [72] that “negative surgical margins always resulted in local control” and negative margins were achieved in 27 patients in their current TORS radical tonsillectomy series. They also state that other groups including Moore et al [73] and Genden et al [74] all achieved negative surgical margins.

The authors concluded that the financial cost considerations which included the initial cost of approximately $1.5 million coupled with an approximately $100,000 yearly maintenance fee and $200 of disposable instruments per case is a significant financial investment, however to date the Intuitive Surgical Company which manufactures this instrument has sold units in over 1032 academic and community hospital sites worldwide [70]. A direct cost analysis comparing different treatment modalities is necessary to draw further conclusions, but the authors feel that this is a cost effective way of treating these cancers. Of note is that they also find that teachability, which is a very important issue once a new technique is introduced, was at a very high level.
THYROID ROBOTICS

Kang et al [75] in 2009 reported the operative outcomes of 338 consecutive patients undergoing robotic surgery of the thyroid using a gasless, transaxillary approach with the da Vinci S system. This series was a follow up of their initial series of 100 patients with papillary thyroid carcinoma all operated on by this technique [76]. All patients received prophylactic ipsilateral central compartment neck dissection. Metastasis was identified in 31 patients. There was one case of transient hypocalcemia and two cases of transient hoarseness. Eligibility for this surgery included: (1) follicular proliferation with a tumor size of less than 5 cm and (2) well-differentiated thyroid carcinoma with a tumor size of less than 2 cm [75]. Contraindications were: (1) patients with a history of previous neck operation; (2) severe Grave’s disease; (3) a malignancy with definite extrathyroidal tumor invasion, multiple lateral neck node metastases or perinodal infiltration of metastatic lymph nodes or distant metastasis and (4) lesion located in the posterior capsule area of the thyroid. Two hundred eighty one patients (84.6%) had stage I disease. There were 43 cases of transient hypocalcemia, thirteen cases of transient hoarseness, three cases of permanent RLN injury. Transient recurrent nerve paralysis and hypocalcemia resolved within 2 to 3 months. The use of this technique results in excellent cosmesis, allows for radical central compartment neck dissection to be performed and there was no permanent hypocalcemia.

MICROVASCULAR FREE TISSUE TRANSFER

Microvascular free flap reconstruction following resection of cancer of the head and neck first gained popularity in the United States in the 1980s [77]. Since that time numerous studies have demonstrated the reliability and low morbidity of the use of these flaps in various settings. In theory, microvascular reconstruction should contribute to improved oncologic outcome since its availability results in more aggressive oncologic ablation and facilitates timely administration of adjuvant therapy. Hanasono et al [77] sought to prove this in cancer of the oral cavity and reviewed a series of 484 patients who underwent resection of cancer of the oral cavity at the University of Texas MD Anderson Cancer Center over a 25 year period from January 1, 1980 to December 31, 2004. The authors state that cancers treated after the introduction of free flaps included a significantly higher proportion of T4 lesions compared to T3 lesions and significantly more advanced N stage. Although the cancers were more advanced, survival and recurrence rates were maintained and the rate of positive pathologic margins decreased significantly. In addition, fistula and tracheostomy dependence rates decreased and rates of intelligible speech increased.

The authors concluded that reconstructive microsurgery contributes to improved oncologic outcomes in addition to better function and lower morbidity in the treatment of cancer of the oral cavity.

Chepeha et al [78] described the superior constrictor velopharyngoplasty, base of tongue mounding and primary hypopharyngeal closure in combination with template-based revascularized free tissue transfer in the reconstruction of large defects of the palate. After this surgery, the patients were able to speak normally or required only occasional repetition in speaking in public. These results were independent of the size of the palatal defect. This procedure includes reconstruction of the palatal sphincter and resulted in a substantial reduction of the size of the native oropharynx. Data on swallowing indicated that rehabilitation was not as effective as with speech. Swallowing results were similar to previous techniques which in the larger defects could not be optimized with this technique.

Dirven et al [79] analyzed a series of 144 patients treated for T3 and T4 squamous cell carcinoma of the larynx and hypopharynx with definitive radiotherapy followed by salvage surgery. Radiotherapy dose and addition of concurrent chemotherapy proved to be an important determinant of pharyngocutaneous fistula. It appears that the occurrence of fistula increases with concurrent treatment and that reconstruction with highly vascularized tissue may decrease both the fistula rate and the duration of healing. Even if a tension free primary closure is achieved in these high risk patients, the authors feel that consideration should be given to further augment the closure with either regional or free flaps to minimize the rate and a duration of the fistula. There is an increasing interest in the use of free or regional tissue transfer to minimize complications particularly in patients who have failed concurrent chemoradiation.

Nkenke et al [80] studied a series of patients in order to determine whether an immediate postoperative period of deep sedation, artificial respiration, and monitoring in an intensive care unit lead to fewer complications and a reduced failure rate of microvascular flaps compared with patients who were allowed to breathe spontaneously without sedation or admission to the ICU. Their conclusions were that admission to an ICU does not reduce complications after microvascular reconstruction and therefore should only be considered for selected cases or for indications other than monitoring for improvement in the circulation of microvascular free flaps.

Hildago et al [81] stated that in the past decade refinements in technique for flap inset of existing flaps were reported. The author gives us several examples such as the mandible reconstruction and emphasizes that the basic objectives in reconstruction include: the restoration of continuity, widening of intraoral deficits and replacement of external skin and soft tissue defects. Defects such as these can only be restored effectively
with osseocutaneous free tissue transfer, the sources of which include the fibula, iliac crest, and scapula. The fibula has become the flap of choice for the majority of mandibular reconstructions because it provides up to 30 cm of excellent quality bone that will tolerate multiple osteotomies without being devascularized. Good quality skin and recipient vessels bind with integrated implants for dental restoration and functional results can be outstanding. In the mid and upper face a variety of flaps can provide differing amounts of soft tissue skin surface area and bone. Reconstruction includes the external skin defect, reconstruction of the palate, restoring the oral and nasal passages, and if necessary to cover the cranial base. Tissue and bone can be restored. Compared to mandibular reconstructions, many of the aesthetic results as well as functional results are unsatisfactory. These inadequacies, include poor external skin color and texture, restoration, that compromises the aesthetic results, inadequate reconstruction of functional deficits that include loss of sensation and motor function. These deficits may be magnified when resection include critical midfacial structure such as the lips, muscles of facial expression, nose, eyelids and globe.

Intraoral reconstruction, pharyngoesophageal reconstruction, and laryngeal reconstruction have all been greatly enhanced with free tissue transfers. The defects of the tongue can be resurfaced and closed with a variety of flaps including the radial forearm flap, anterolateral thigh flap and rectus abdominus flap. The choice of flap depends on the size of the defect and the surface area that needs to be covered. The continuity of the cervical esophagus can also be restored with flaps such as the radial forearm flap, lateral thigh flap and jejunum. Structures such as the tongue and vocal cords has so far defied functional reconstruction.

Cordeiro [82] describes the frontiers of reconstruction which are allotransplantation and tissue engineering. Allotransplantation, especially composite tissue allografts, has been controversial and despite the development of immunosuppressive agents over the past four decades long term survival is partial. The composite tissue allografts have been more controversial and less developed until recently because of the idea that these types of tissue transplants are not essential for survival of the patient. These consist of varying combinations skin, bone, soft tissue, muscles, tendons, and nerves. The acceptance has been increased by the fact that techniques of immunosuppression have become more specific and with many fewer side effects. There are multiple centers around the world including our own that transplant hands and arms and there are now reports of successful partial facial transplantation. Technical details following transplantation are essentially the same as those employed in autotransplantation free flaps. However, the applicability of allotransplantation to the head and neck particularly for cancer patients ultimately depends not upon the technical aspects of the surgery, but the extent to which immunosuppression may be developed. The ideal immunosuppressive agents will target the tissue and organ that is transplanted and allow acceptance of the transplanted part without having any other effects on the recipient’s tissue. Therefore the ability of the recipient to combat residual cancer or any potential metastatic sites would remain intact. This form of targeted immunosuppression would have to have no negative effects on the outcomes of the cancer. Current limitations of applying immunosuppression in the cancer patient can be overcome by the development of agents which will revolutionize microsurgical reconstruction because it will allow transfer of previously unreconstructable specialized tissue using well described microsurgical techniques which would maximize the aesthetic and functional results in head and neck reconstruction.

Tissue engineering is one of the areas of biotechnology that is most rapidly expanding and that could potentially have many diverse applications in head and neck reconstruction. This consists of completely ex vivo engineered three dimensional constructs consisting of extracellular matrix in combination with living cells. Thus far, constructs of cartilage and bone created from stem cells placed into molds, and extracellular matrices have allowed creation of three dimensional shapes, such as ear frameworks and tracheal cartilage rings. These structures have generally not, however, maintained structural stability. Thus, the problem of transferring these types of constructs from the ex vivo site or from a non-anatomical site technique may still fall into the domain of the microsurgeon. Establishing blood supply to these constructs remains an unsolved problem.

FOLLOWUP and SURVEILLANCE AFTER TREATMENT FOR CANCER OF THE HEAD and NECK

There is a widely held observation that the cure rate for squamous cell carcinoma of the head and neck has not changed appreciably in the last 50 years despite the fact that there have been improved types of treatment, particularly chemoradiation in an attempt at organ preservation, selective neck dissections, and microvascular reconstruction, all of which have promoted long-term disease-free survival but has not improved the cure rate. Recurrence is a problem which is present in as much as 50% of head and neck cancer patients with advanced disease and bodes a poor prognosis [83]. The lack of improvement in the cure rate is related not only to lack of local-regional control but also second primary cancers which are often diagnosed in advanced stages in which the therapeutic modalities have often been exhausted in the treatment of the primary cancer. The static mortality rate for these cancers over the years is attributed in part to our inability to effectively prevent and treat recur-
rences and prevent second primary cancers. Even more disconcerting are recent studies showing that survival for patients with cancer of the larynx has decreased over this period [84].

Systematic surveillance is advocated to detect asymptomatic recurrent disease since it is assumed that identification of preclinical disease allows for more effective salvage surgery, therefore decreasing cancer specific mortality. However, evidence supporting this assumption is lacking which helps to perpetuate wide variations in surveillance practices. This observation led to a collaborative study between the American Head and Neck Society and the National Comprehensive Cancer Network on advanced consensus surveillance which produced the Advanced Consensus Surveillance Guidelines in 2001 [85]. Despite this publication an optimal surveillance strategy has still not evolved.

Clinicians now question whether scheduled appointments or surveillance based on the symptoms is the better post treatment strategy. Francis et al [83] designed a population-based retrospective cohort study to test the impact of surveillance intensity on both recurrence and survival. This study analyzed a cohort of 3,169 patients with cancer of the larynx. The results of this study indicated that approximately 50% of the patients had no visits in the nine month preceding their diagnosis of recurrent disease, 40% were seen less than recommended, and 10% were seen equal to or more than recommended. No relationship was observed between surveillance intensity and one-year survival with the exception of a survival advantage apparent in patients with recurrent glottic cancer.

Cancer of the oral cavity and oropharynx is considered to be a bad prognostic entity in terms of survival rate. Failure at the primary site will ultimately occur in approximately 20% of these patients. Prospective studies have also demonstrated that second primary cancers develop at a rate of 4% to 7% annually in patients who have had one primary squamous cell carcinoma in the head and neck. Local recurrence and second primary cancers are the leading cause of death among patients who have undergone treatment for early stage oral cancers [86].

Braakhuis et al [87] have proposed a new molecular classification for various types of lesions: (1) true second primary cancer which is genetically different from the original primary; (2) local recurrence in which all molecular aberrations are similar; (3) second field cancer derived from the same genetically altered field as the primary tumor, but divergent in later stage; (4) metastasis. Despite its usefulness for categorization, this new molecular information is not routinely performed in the majority of centers.

Gonzalez-Garcia et al [88] studied a cohort of 522 patients with squamous cell carcinoma of the oral cavity and oropharynx from 1979 to 2006. Only patients treated surgically were considered for evaluation. These patients were treated by surgery with or without adjunctive post-operative radiation therapy. The standard criteria for second primary cancers is: (1) the appearance of a new tumor of different histological type. (2) tumor of identical histological type occurring more than three years after treatment of the primary tumor; (3) second primary tumor separated from the initial primary tumor by more than 2 cm of clinically normal epithelium.

There is a considerable risk of second primary cancers which remains for years after the original diagnosis. The mortality and morbidity from the second primary cancer and local recurrence after successful treatment of the primary tumor remains one of the most challenging problems that we encounter in head and neck surgery. The survival rate for patients who had a documented second primary cancer was 20 to 32% lower than patients diagnosed with oral cavity cancer only. In this study, the authors observed that most of the patients were at higher risk for the appearance of recurrence during the first three years following initial diagnosis. Several factors have been proposed as determinants for survival in patients who have been diagnosed with a local recurrence or a second primary cancer: (1) exhaustion of previous therapeutic modalities such as maximal dose radiation therapy; (2) health impact of previous treatment for the primary cancer; (3) overall health status of the patient; (4) TNM classification of the second primary cancer or local recurrence. Risk factors for the appearance of local recurrence included tumor cT3, T4, pT3, T4, advanced TNM stages III and IV, surgical margins less than 1 cm, bone involvement and administration of post operative radiation therapy. These were not factors related to second primary cancers.

Bhattacharyya [89] in reviewing a series of 44,862 patients with primary cancer of the head and neck observed that a higher incidence of second primary cancers was associated with increased age and location of the primary cancer in the larynx, hypopharynx, oropharynx, nasopharynx, and major salivary glands, but did not find any association with respect to the location of the primary cancer within the oral cavity. This was similar to the findings of Gonzales-Garcia et al [88].

The relationship between postoperative radiation therapy as a criterion was somewhat controversial and the authors [88] were uncertain whether this effect was attributable to the more advanced stage of the disease of patients who were given adjunctive radiation therapy or to DNA damage of adjacent oral epithelium. Surgical margins of less than 1 cm were predictive for local recurrence, but not for second primary cancers. Bone involvement was a risk factor for local recurrence, but not for second primary cancers. In this series, 34.8% of patients with second primary cancers with no local recurrence were alive at the end of the followup period when isolated second surgery was performed, whereas 41% died of the disease despite the second surgical resection. In contrast, when isolated radiation therapy...
or chemotherapy was performed, there were no patients free of disease at the end of the follow up which certainly is a strong indication for primary surgery in these circumstances. This may be related to more advanced stage of the disease in patients treated with combined therapy rather than better survival rate with surgery alone. Most of the patients had received a maximum radiation dosage during the adjuvant treatment following surgical resection of the primary tumor which means that this may no longer be available to the patient with second primary tumor or recurrence. The authors conclude that identification of preoperative and postoperative clinical pathological features may predict a higher risk for the appearance of local recurrence of second primary cancers and should potentially be of interest in determining which patients could benefit from a closer follow up. In a multivariant analysis considering all clinical and pathological features, only bone involvement and postoperative radiation therapy were accurate predictors for the development of local recurrence. Because of the poor survival rate of the affected patients, the authors strongly believe that aggressive surgical treatment following the appearance of a second primary or local recurrence should be performed, balancing this with a potential complication of the second treatment modality in head and neck cancer.

The investigation of the issue of second primary tumors was further elaborated on in an article entitled “Prediction of Simultaneous Esophageal Lesions in Head and Neck Squamous Carcinoma, by Chow et al [90]. As a result of exposure to carcinogenic substances such as tobacco and alcohol, squamous cell carcinoma of the head and neck can coexist with a second primary cancer of the aerodigestive tract. The concommitant second primary cancers may be located in the head and neck, esophagus or lung. To detect the second primary cancer, triple endoscopy (laryngoscopy, bronchoscopy, and esophagoscopy) is usually performed for patients with head and neck squamous cell carcinoma, although intensive endoscopic surveillance has not yet been verified as being effective [91, 92]. The appearance of a simultaneous esophageal cancer, although uncommon, is very important because its presence will alter the management plan. It is also troublesome if esophageal cancer is found during the early follow up period, since the patient may require a second surgery which is increasingly difficult due to prior surgery and radiation therapy for primary in the head and neck. Salvage of the simultaneous lesion occurred in 10% of their patients with squamous cell carcinoma of the head and neck which is not a manageable figure. Esophageal cancer only rarely coexists with squamous cell carcinoma of the oral cavity. The authors question the role of routine triple endoscopy for all squamous cell carcinoma and reserve it for patients with squamous cell carcinoma of the oropharynx, larynx and hypopharynx [90].

Imaging studies such as CT, MR, or PET scanning are sensitive modalities used to identify lung and esophageal cancers. The authors advocate the use of chromol endoscopy, using Lugol iodine solution, which can be helpful in detecting early lesions. The screening for synchronous pulmonary cancer, in patients presenting as squamous cell carcinoma of the head and neck, is important because detection may alter subsequent management. Ghosh et al [93] found 60% of the 1882 patients in their cohort had clinical and/or radiological evidence of cervical lymph node metastasis. Other studies have shown that synchronous metastasis are found in 1.5 to 16.8% of patients presenting with squamous cell carcinoma of the head and neck. The most common site being the lung which accounts for 68.5% of all synchronous tumors [94, 95]. In addition to synchronous distant metastasis, second primary cancers have been reported in the lower respiratory tract in 2% of patients [96]. As a consequence, screening for synchronous second primary cancers in the lung in patients presenting with primary or recurrent squamous cell carcinoma of the head and neck is important because the presence of such cancers is likely to alter the prognosis and therefore the detection will alter the subsequent clinical management.

Ghosh et al [93] state that the overall incidence of synchronous pulmonary cancers detected at the time of presentation is 3.6%; 1.4% were primary bronchogenic carcinoma; and 2.1% were metastasis. In the year following diagnosis, a further 14 patients developed detectable pulmonary cancers. They considered that cancers detected at the time of the initial screening to be true synchronous cancer. The use of dedicated thoracic CT scan has proven to be much more sensitive than routine chest radiographs in detecting pulmonary cancers, with a sensitivity of 90%. The lesions which were missed in initial presentation by thoracic CT were predominantly pulmonary metastasis. The authors concluded that the incidence of synchronous bronchogenic cancers is not related to the upper aero digestive tumor load whereas the presence of synchronous pulmonary metastasis appears to be related to the presenting tumor load in the head and neck. In our Department, we have always considered that synchronous second primary cancer in the lung or esophagus should be managed first because the results often lead to modification of the treatment of cancer of the head and neck. Unfortunately screening for lung cancer in high risk populations does not confer a survival advantage.

**CONCLUSIONS**

Rapid advances in the field of technology and drug development have led to improvement of patient care in the last decade. Innovations and developments described above lead me to believe that in the future we will see not only improvement in the quality of but improvement in the survival statistics in patients with cancer of the head and neck.


