INTRODUCTION AND HISTORICAL PERSPECTIVE

The desire to target therapies to specific cancers is not new, although the use of the word has taken on greater prominence in recent years. The aim of targeting is to find the so-called silver bullet. The concept arises from folklore, in which a silver bullet was the only defense effective against many mystical foes. In modern terms, for cancer therapy, targeting refers to an effort to create therapies that specifically interact with diseased cells while leaving other tissues of the host untouched. In theory and in practice, targeted therapies either increase efficacy or decrease toxicity related to treatment. The most effective agents do both, but patients and doctors may be willing to tolerate increased toxicity for highly effective treatments or sacrifice efficacy for decreased toxicity. Such trade-offs must be carefully evaluated and tailored to individual patients and disease processes in an informed fashion.

A Medline search for targeted therapy or targeted drug delivery reveals the degree of interest and discovery in this field. Two articles from 1902 to 1978 are available, with the first mention attributed to the use of propranolol for essential hypertension by Lauro and colleagues. In the 1980s, 53 articles were published on targeted approaches, which expanded in the 1990s to 261. Since that time significant expansion of the use of this term has occurred with 1429 articles for targeted approaches from 2000 to 2006 and 8338 in the subsequent 6 years to 2012. Specific to cancer, this increase in enthusiasm for targeting is attributable to several factors, including expanding knowledge of the cancer process from a basic scientific perspective, increased throughput on patient-specific markers, advances in biomedical instrumentation, and technological advances that...
allow interaction with cancer cells in a more selective fashion.

Advances in understanding of the cellular and molecular changes leading to malignancy have assisted this revolution. In the 1950s, Foulds 6 conceptually elaborated the proposed mechanisms of tumor progression. These concepts were followed shortly by documentation of cyogenetic chromosomal changes in the 1960s. Molecular techniques evolved, as did cancer theory, resulting in the belief that tumorigenesis started from abnormalities in a single altered cell. A multistep model with acquisition of various cellular abnormalities was eventually proposed. 4 Even without each step currently stipulated, global understanding of both the cancer cell and the importance of the surrounding milieu continues to expand. With these advances, there is recognition that, in addition to cancer transforming markers available for interaction with targeted approaches, nontransforming markers that are overexpressed for a variety of reasons may also be targeted to offer some selective advantages in cancer treatment. Considering the readership and task, this article focuses on targeted therapies for head and neck cancer in surgery, radiation, and chemotherapy as multimodality treatment of head and neck cancer.

TARGETED SURGERY

In using the definition of targeting as defined earlier, advances of this type are not new. A well-known historical example introduces a discussion that focuses on current investigational strategies and future targeting strategies for head and neck cancer.

In the early 1900s, Crile 5,6 reported the first large series of patients undergoing radical en block neck dissections with a higher success rate than patients undergoing procedures that were less than en bloc. Prominent surgeons promoted radical neck dissection as the standard for treatment of this disease. It was not until the 1960s that modifications by Suarez, Boccia and others led to the modified radical neck dissection. In the 1950s, Fouls introduced the concept of sentinel lymph node biopsy (SLNB), which in recent years has dramatically changed the treatment of some cancers. In the sentinel node approach, removal of major sets of lymph nodes is completed only in cases of advanced disease or when the sentinel lymph node, harvested in a minimally invasive fashion, is found to be positive for cancer.

The sentinel node refers to the first or a small set of initial nodes draining a cancer within the body. This node is assumed to be the gatekeeper (sentinel), such that its tumor status indicates the probability of other, more distant, nodal involvement. If cancer has not spread to the sentinel node, then the likelihood of other nodal involvement is presumed to be low. The reliability of this technique has been proved in melanoma, including melanoma of the head and neck, as well as breast cancers, and remains under study in several other cancers (including SCC of the head and neck).

Sentinel node mapping generally is performed using 2 modalities. First, preoperative planar lymphoscintigraphy uses a low-activity radionuclide injected at the site of the tumor, followed by serial scintigraphic imaging until the sentinel node is identified, which is followed by intraoperative \( \gamma \) probe/Geiger meter detection to identify radioactive, or hot, nodes. Second, the injection of a visual blue dye at the site of cancer just before operation, which leads to blue dye visualization in the draining lymph nodes at the time of neck exploration. Nodes are generally reported as hot, blue, or hot and blue, indicating the presence or absence of radioactivity and blue dye uptake (Fig. 1). The sentinel node(s) harvested can then be carefully examined not only histopathologically.
but with immunohistochemistry and molecular examination for micrometastasis and conventional metastasis of cancer.

Sentinel node biopsy for SCC of the head and neck continues to be a controversial topic but several studies have been undertaken to validate the use of sentinel node biopsy for this purpose. In 2010, a prospective multi-institutional trial for SLNB was reported involving 25 institutions over a 3-year period with the accrual of 140 patients with T1/T2 primaries and clinically N0 necks. The patient population included 95 cancers of the tongue, 26 of the floor of mouth, and 19 other oral cancers. Exclusion criteria included lesions less than 6 mm and lesions with minimal invasion (although a criterion for minimal invasion was not defined in the report). In the protocol, all patients underwent sentinel node biopsy followed by a formal neck dissection for the purpose of defining the negative-predictive value (NPV) of SLNB. Of the 106 SLNBs that were negative on hematoxylin and eosin staining, 100 patients were without additional nodal disease (NPV 94%). NPV was increased to 96% with additional sectioning and immunohistochemistry. For patients found to have positive nodal disease in the neck on formal dissection, the true-positive rate or sensitivity overall of the sentinel node was 90.2%, indicating that, in approximately 10% of cases, the sentinel node was negative but the neck overall was positive. The breakdown of these falsely negative nodes revealed a sensitivity of 85% for T2 and 100% for T1 lesions. The sentinel node performed better on tongue lesions than lesions of the floor of the mouth. Surgeons designated prospectively as experienced also had a false-negative rate of 0.

Overall, the current literature suggests that the predictive value of a negative SLNB is 90% to 100%, that serial step sectioning with immunohistochemistry is critical to achieve this outcome, and that SLNB may assist in upstaging patients who might not generally undergo formal neck dissection (including the ability to identify abnormal drainage patterns that may alter the surgical plan). Concerns remain about the false-negative rate potentially related to the possibility of skip metastasis, the learning curve associated with this technique, and a lack of level I evidence to support its use. Technological advances in this area include studies of novel tracers and improving the throughput of results that would obviate 2 separate surgical interventions in patients found to have a positive sentinel node.

**Margin Control**

Clean surgical margins remain the goal of cancer resection surgery. Surgical margins positive for
cancer are an indication for the addition of chemotherapy to postoperative radiation because of the significant increase in persistent disease. In addition, some evidence suggests that margins with mild to moderate dysplasia likewise increase the risk of recurrence.\textsuperscript{13} Much has been written and reported about what constitutes a clean margin; that discussion is beyond the scope of this article. Regardless, attempts to fine-tune the ability to define the margin constitute targeting; this is an example of targeting in which additional toxicity is generally accepted in the form of larger resections with the goal of increased efficacy in long-term tumor control.

Toluidine blue staining has been investigated as a technique for diagnosis of oral SCCs and epithelial dysplasia for many years with variable reported outcomes. In addition, toluidine blue has been reported as a tool for obtaining clean surgical margins, and recently as a replacement for frozen section analysis in locations where frozen section is not feasible. Junaid and colleagues\textsuperscript{14} reported a comparative analysis of toluidine blue and frozen section in 56 consecutive patients with 280 tumor margins. Eleven margins stained positive for toluidine blue, and, of those margins, 3 were positive on frozen or final pathology. There were no false-negatives, indicating that toluidine blue may overpredict the needed resection but did not underpredict in any of the cases in the study. In this application, toluidine blue had a sensitivity of 100\% with a specificity of 97\% owing to the small number of false-positives in which toluidine blue overpredicted the needed margin. The routine use of toluidine blue for surgical margins is not standard but is an indication of the possibilities that exist in the quest for better margin control.

Kurita and colleagues\textsuperscript{15} reported the use of tissue staining with indigo carmine and Congo red with assessment of the deep surgical margin in comparison with hematoxylin and eosin staining as the gold standard. The extent of carcinoma could be accurately visualized in 80\% of the specimens, with no significant difference between the tumor-stained margin and the histopathologic margin. Staining in this way may decrease the randomness in choosing locations for frozen section analysis and thereby decrease the risk of false-negative results.

Fluorescence visualization has been examined as an adjunct to visual examination in the operating room to determine surgical margins. In their protocol, Poh and colleagues\textsuperscript{16} first examined 20 oral cavity lesions planned for resection under white light marking the anticipated surgical margin, which was followed by autofluorescence examination and an additional marking of margins. Following excision around both margins, the fluorescent visualization loss (FVL)–guided region was examined for histologic and genetic changes. In 19 of the 20 specimens, FVL changes extended beyond the clinically visible lesions. Thirty-two of the 36 biopsies in these areas revealed changes from mild/moderate dysplasia to SCC. Molecular analysis of biopsies with low-grade or no dysplasia revealed loss of heterozygosity markers 3p and/or 9p, which have been associated with tumor recurrence. Although this study only provides proof of principle, a well-designed, randomized, multicenter, double-blind, controlled surgical trial evaluating the use of the addition of fluorescence visualization in surgical margin control is underway. The study anticipates the recruitment of 160 cases of severe dysplasia or carcinoma in situ and 240 invasive cancers. The study end point is local recurrence following resection with patients followed for up to 5 years. The results of this study will give a high level of evidence either in favor or against the use of this technique to more adequately address surgical margins.

Genetic analysis applications have also been studied as a form of margin control. For example, Heah and colleagues\textsuperscript{17} studied immunohistochemistry and fluorescent in situ hybridization of the tumor suppressor TP53 gene in the margins of 26 oral SCCs, showing that 96\% of excisions contained genetic alterations at the excision margins. Other genetic analyses have included chromosomal changes with multiplex ligation-dependent probe amplification, loss of heterozygosity with microsatellite polymerase chain reaction, and DNA index alterations using DNA image analysis.\textsuperscript{18} Shaw and colleagues investigated quantitative methylation at resection margins and lymph nodes using pyrosequencing methylation assays (PMA) of CpG islands within the gene promoter of p16 and CYGB genes. PMA upgraded 13 of the 20 surgical margins, 6 of which eventually recurred. Although the study population and adjuvant treatments made firm conclusions difficult, this provides another potential avenue for molecular marker margin control.

**Transoral Robotic Surgery**

The introduction of robotic-assisted surgery has transformed minimally invasive surgery in a variety of surgical disciplines. Several advantages to this approach have been proposed in head and neck SCC. These advantages include the decreased need for access surgery with large incisions and the ability to surgically treat diseases in a minimal surgical fashion that were previously amenable to treatment only with chemotherapy and radiation.
therapy organ preservation protocols because of associated surgical morbidity.

Robotic surgery was first introduced in the mid 1980s. Multiple advances since that time have led to the current da Vinci Surgical System (Intuitive Systems, Sunnyvale CA), which is the most common robotic system in use today. Robotic surgery uses optics and instrumentation with varying degrees of rotation such that access can be achieved to the base of tongue and entire pharyngeal region as well as access to portions of the larynx. A single-institution report on the use of transoral robotic surgery (TORS) in 54 patients with laryngopharyngeal SCC with 11.8 months’ follow-up was retrospectively evaluated. There were no major intraoperative complications and no aborting of any procedure because of an inability to remove the cancer. A 7% positive margin rate was noted. All patients tolerated an oral diet on the day of surgery and no airway compromise was noted. The investigators concluded that TORS spared patients radiation therapy or combined chemotherapy and radiation in 50% of stage I/II tumors. In addition, chemotherapy was spared in 34% of stage III/IV tumors. These results indicate a significant decrease in overall morbidity for patients treated for their disease with TORS.19

A multicenter study evaluating the feasibility, safety, and surgical margins of TORS reviewed early results from 3 institutions that had undertaken prospective clinical trials using TORS. Of 177 total patients, 78% had oropharynx tumors and 26% tumors of the larynx. Nineteen percent of the tumors were malignant, with 95% of these being SCC. Most were early lesions (T1 32.7%, T2 48.4%, T3 13.7%, and T4 5.2%). The average follow-up was almost 1 year. The rate of positive surgical margins was 4.3%. There were 34 serious adverse events requiring hospitalization but none of these were deemed to be directly related to the use of TORS.20

Additional detailed information is available in an article specifically dedicated to TORS by Eric and colleagues in this issue. In summary, TORS is an important advance in the care of patients, especially those with early laryngopharyngeal and oropharyngeal cancer in which significant decreases in morbidity of treatment can be achieved. At present, long-term functional data and data for oncologic safety are lacking, but what has accumulated to date is encouraging.

TARGETED RADIATION

The complex anatomy and multitude of adjacent critical structures creates complexities for radiation therapy for the head and neck. For example, the spinal cord, brainstem, and optic system are barriers in terms of dose. In addition, quality-of-life issues arise when high doses of radiation lead to changes in taste, hearing, speech, and oral/pharyngeal function related to swallowing. Although several strategies exist to target radiation delivered specifically to the tumor bed while protecting outlying structures, this article discusses only intensity-modulated radiotherapy (IMRT) as an example of advances in targeted radiation therapy. IMRT is an example of targeting in which there is the possibility of increased efficacy through higher radiation doses to tumor beds. In addition, similar efficacy with decreasing toxicity because of decreased radiation to adjacent structures has been extensively documented.

IMRT is a high-precision radiotherapy developed in recent years that uses computer-controlled linear accelerators to modulate the intensity of each beam of radiation (Fig. 2). In addition, it uses multiple ports of entry that conform the radiation three-dimensionally to the tumor bed. The combination of these approaches leads to maximal radiation in the specific desired location while minimizing radiation to surrounding tissues. This targeted approach to radiation allows higher doses to be directed to the tumor with significant decreased morbidity to surrounding structures. Treatment planning of these regimens uses images in isolation or combination from computed tomography, magnetic resonance imaging, and positron emission tomography to create three-dimensional plans for radiation delivery by noting the tumor bed as a desired site for high-intensity radiation and marking sites with desired sparing so that computer plans can be generated. Given the preciseness of the plan, patients are often fitted with a radiation mask that immobilizes the sites of interest during treatment, because even slight movements create deviation from the computer-generated plan and thereby deliver radiation to an undesired location.

A recent systematic review by O’Sullivan and colleagues21 highlights some of the advantages of IMRT compared with standard external beam radiation therapy, specifically as it relates to decreased toxicity. The review included 14 studies in total, with 3 randomized controlled trials providing the highest levels of evidence. The reviewed data led to 4 specific recommendations, 3 of which suggested a benefit of IMRT compared with standard external beam radiation therapy. IMRT was recommended to decrease xerostomia, blindness, and osteoradionecrosis (ORN) as side effects of treatment. There was not strong
evidence in the studies reviewed for treatment benefit, and therefore the guidelines concluded that IMRT is, at worst, not inferior to standard radiation therapy. Taken as a whole, IMRT offers clinically relevant and statistically significant reductions in adverse event rates with associated increases in quality of life. The author’s experience mirrors these findings, particularly as it relates to xerostomia and a decreased, but not zero, rate of ORN. These data and experience give rise to questions for which additional data are not available to provide definitive answers. As an example, what is the success rate of implants in native mandible and free flaps for patients receiving IMRT versus standard external beam radiation? At our institution we have experienced greater numbers of implant failures in patients who have sought their radiation from centers that do not have expertise in IMRT. In the limited number of cases in which implant failure ultimately led to ORN and loss of bone segments, failure occurred in patients who did not receive IMRT. In light of the data and experience, all patients at our primary institution receiving adjunctive radiation therapy in addition to surgery receive IMRT. We offer strong encouragement to patients who require radiation treatment elsewhere to pursue only locations where IMRT can be delivered and where expertise in IMRT specifically for the head and neck is available.

**TARGETED CHEMOTHERAPY**

Advances in surgery and radiation presently provide, and have great additional potential for, augmented targeting through combination with targeted chemotherapeutic strategies. Until recently, chemotherapy was limited to cytotoxic agents specifically designed against cell replication, thus taking advantage of constant tumor growth. These drugs were generally nonspecific; for example, common chemotherapeutic agents like cisplatin (inducing DNA damage), fluorouracil (focused on DNA replication), and taxanes
Epidermal Growth Factor Receptor

Epidermal growth factor receptor (EGFR) was discovered in the 1950s and is a member of the HER/erbB family of receptor tyrosine kinases. On binding one of its ligands (e.g., epidermal growth factor receptor (EGFR) or transforming growth factor (TGF)-β), the EGFR forms homodimers, or heterodimers with the other family members, leading to the activation of the intrinsic receptor tyrosine kinase enzyme activity. Mutations or high expression levels of EGFR have been identified in many cancer types, including lung, colon, breast, and head and neck. In these diseased tissues, the autophosphorylation of EGFR leads to the activation of downstream signaling pathways and nuclear expression of multiple molecules that eventually lead to cell proliferation, angiogenesis, tumor invasion, and metastasis. More than 90% of head and neck cancers show overexpression of EGFR, making this abnormality very common and an excellent candidate for targeting. Several EGFR inhibitors have been tested in the clinic, with additional preclinical candidates under study. The landmark phase III trial by Bonner and colleagues using cetuximab (Erbitux; ImClone Systems, Bristol-Myers Squibb and Merck, New York, NY), a monoclonal antibody to EGFR, was the first to offer evidence of increased efficacy for radiation therapy when combined with a targeted chemotherapeutic. Patients with locally advanced disease were randomized to receive radiation therapy in conjunction with cetuximab versus radiation therapy alone as control. Both progression-free and overall survival were improved with the addition of the targeted chemotherapeutic. The success of the trial by Bonner and colleagues has prompted several additional studies using cetuximab with radiation or cetuximab in addition to chemoradiation with fluorouracil and platinum-based chemotherapies in which the addition of cetuximab has likewise showed a clinical benefit. However, the studies related to cetuximab have been controversial. For example, some patients in the initial trial received different radiotherapy regimens and the trial had no comparison with standard chemoradiation, which has also been showed to have survival benefit in some patients. In addition, the emergence of human papillomavirus–related cancers and their potential effect on the results of studies for which this was an unaccounted variable have the potential to invalidate any positive results. However, cetuximab remains the flagship of targeted chemotherapy in head and neck SCC and an excellent example of the length of time it takes to achieve clinical use, with more than 50 years from discovery to phase III clinical validation.

The success of cetuximab has led to several other attempts to interact with EGFR at the extracellular domain, including the monoclonal antibodies panitumumab (Vectibix, Amgen, Thousand Oaks, CA; approved in colorectal cancer and under evaluation in head and neck SCC), zalutumumab (HUMax-EGFR, Genmab, Copenhagen, Denmark), and nimotuzumab (BIO-Mab EGFR, Biocon, India; Theracim, YM biosciences, Cuba; Theraloc, Oncosciences, Europe; CIMaher, Cuba), which are currently under study. In addition, the use of small-molecule inhibitors that interact with the intracellular activity of EGFR have been studied in phase II and III trials. Gefitinib (Iressa, AstraZeneca Pharmaceuticals, London, UK) is directed against the intracellular domain of EGFR. A phase II trial using gefitinib showed some benefit to patients with recurrent disease but this result has not been replicated in phase III endeavors. Several similar agents are in phases I to III, with none validated for routine clinical use at the present time.

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) is an example of targeting using the increased need for angiogenesis of tumors compared with normal tissue. There are several VEGFs, each binding to a tyrosine kinase receptor for activity. Increased VEGF expression has been correlated with a decrease in overall and progression-free survival as well as lymph node metastasis. Similar to EGFR, attempts have been made to target both the extracellular receptor through monoclonal antibodies, and intracellular pathways through small-molecule inhibitors. Bevacizumab (Avastin, Genetech/Roche, San Francisco, CA) is approved...
by the US Food and Drug Administration for colorectal and lung cancer and has been studied in patients with head and neck SCC. Several phase I and II trials have been reported with promising results in efficacy and toxicity. For example, in a phase II Radiation Therapy Oncology Group (RTOG) trial, patients who had the addition of bevacizumab to the regimen of chemoradiation had fewer distant metastases than historical controls. In the small-molecule inhibitor realm, cediranib (AZD2171, Recentin, AstraZeneca, London, UK) has been given to patients with non–small cell lung cancer with some demonstrated effect, but studies specific to head and neck SCC have been disappointing.

**Mammalian Target of Rapamycin**

Mammalian target of rapamycin (mTOR) is an example of potential targeting that benefits from a wide range of basic and preclinical translational supportive science leading to its current early clinical phase. mTOR is a highly conserved serine/threonine kinase that plays a role in the PI3K/AKT signaling pathway involved in cell growth, proliferation, and survival. Aberrant regulation of the mTOR pathway has been shown in head and neck SCC as well as several other tumors. Rapa-mycin is a natural macrolide antibiotic and immunosuppressant with demonstrated antitumor effects. Years of research and development have resulted in the development of 3 rapamycin analogues with enhanced pharmacologic properties: temsirolimus, everolimus, and deforolimus. Most trials to date have been based on patients with renal cell carcinoma, in whom promising results have been obtained, leading to enthusiasm for translation to head and neck SCC. At present, several phase II trials evaluating mTOR inhibitors in patients with head and neck SCC are currently recruiting patients.

**Nanotargeted Chemotherapy**

Nanotechnology offers the unique opportunity of developing personalized therapeutics based on targeting and treating specific receptors and abnormalities of a patient’s tumor. As predicted by the National Cancer Institute, it is likely that nanotechnology will enhance all current aspects of cancer prevention, detection, and treatment. Nanotargeted chemotherapy to head and neck SCC is one representative area of research in an ever-growing field of basic science seeking better targeted approaches in chemotherapy. Scientific discovery in tumor pathways, receptors, and microenvironment, as well as the creation and optimization of pharmaceutical approaches, all contribute to this field. The author’s personal experience represents a vast array of research endeavors likely to change the landscape of cancer treatment in the decades to come.

Dendrimers or dendritic polymers are uniform spherical nanostructures ranging from 10 to 200 Å in diameter. Dendrimers possess several advantages compared with other drug delivery vehicles in their small size, globular shape, multiple ligand valence capacity, flexibility, and stability. Dendrimers have served as a platform to which the attachment of several types of biologic materials has been validated. Examples of functional attachments have included iron oxide for targeted imaging, phiphiluxG1D2 apoptosis sensor for monitoring, drugs including methotrexate and taxol chemotherapeutics, and folic acid, RGD peptides, EGF, and antibody fragments for targeting. The structure, connection, and numbers of targeting molecules are pivotal to the ultimate function of these drug delivery devices. Dendrimers for cancer have been validated using folate for targeting and methotrexate for chemotherapy. This example therefore both increases efficacy and decreases toxicity, which is the ultimate goal for optimal targeting. Translating these findings to preclinical models in head and neck SCC has required the ability to ascertain folate receptor activity in several cell lines followed by animal model validation of therapeutic effect. Screening a large number of cell lines in head and neck SCC showed a scalable array of expression that, when put into animal models, showed direct correlation with tumor control (ie, no expression having no benefit from targeting, moderate expression having moderate effect, and high expression having high efficacy of drug). Preclinical validation was achieved using folate receptor–targeted chemotherapy with methotrexate in a mouse xenograft model in which both increased efficacy and decreased toxicity were confirmed compared with free drug. This report represented the first translation of nanotargeted chemotherapy with dendrimer to a clinically relevant preclinical tumor model.

Expanding on this technology, creation of a multitude of devices specific to both the desired target and the desired chemotherapeutic may be possible. For example, a tumor high in EGFR and with high sensitivity to taxol could be treated with
dendrimer bound to EGF and taxol. In other patients with either different targets or sensitivity to alternative agents, the device could be specifically created to treat their particular tumors. Further development in dendrimer chemotherapeutics and tumor screening would combine to enable a tumor-centric regimen for any given patient. In addition, the ability to have dendrimers with imaging-sensing and apoptosis-sensing capabilities raises the possibility of a single therapeutic that not only treats tumor but documents its presence and ultimate eradication.

SUMMARY AND FUTURE DIRECTIONS

Targeting of treatments to head and neck SCC is continually advancing. For the purposes of this article, targeting is discussed under the headings of surgical, radiation, and chemotherapeutic targeting. It is likely that no single technique will ultimately resolve the issues for all patients with head and neck cancer, but that a contribution from each will create the synergism needed for advances in the care of these patients. Surgeons should continue to seek the treatments that target tumor to the maximum extent possible, such that efficacy is consistently maximized and the toxicity of treatments is limited for both survival and quality-of-life improvements. Robust scientific discovery will undoubtedly yield the greatest benefit to patients with cancer.

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