Chapter 11
Translational Research in Head and Neck Oncology

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Abstract Translational research in head and neck oncology has evolved dramatically. Ongoing discoveries in basic mechanisms of cancer biology and technological advances in both diagnostic imaging and radiation delivery have enhanced the ability to improve treatment outcomes. The overarching goal for all translational research should be to enlarge the armamentarium from which clinicians can rationally select the most appropriate options for individual patients in ways that maximize therapeutic benefit and minimize toxicity.

Focusing on this goal will become more critical as the health care system deals with external economic, social, and political pressures and forces that will affect both bench and bedside. As these concerns encroach on the translational process, it is imperative to recognize that the research itself is best equipped to address them – more efficacious treatments, improved patient selection, decreased toxicity.

What also should not be lost in translation is the unpredictable and occasional serendipitous nature of research. Two cornerstones of head and neck cancer therapy, cisplatin [1, 2] and cetuximab, owe their existence to chance and fate. Meanwhile, the compelling story of tumor hypoxia has yet to result in any new additions to the therapeutic arsenal. This chapter will explore the meaning of translational research means, identify potential pitfalls on the horizon, and highlight common themes and new avenues of research using specific examples from both the head and neck and general oncology literature.

Keywords Translational research • Oncology • Targeted therapy • Cetuximab

Introduction

Translational research is not unlike world peace, the meaning of which depends upon whom is asked. But it sounds great, and everyone is for it. Unfortunately, success can be elusive, with many setbacks along the way. Progress requires seeking and forging of new relationships, many times between seemingly unrelated and disparate camps that speak different languages.

The concept of translational research in oncology evokes images of a bridge, spanning and connecting the separate worlds of basic bench research and clinical bedside investigation and treatment. Cellular and molecular discoveries in the laboratory yield clues to underlying mechanisms of disease, identifying novel targets for therapeutic intervention that ultimately improve cancer patient outcomes. The National Cancer Institute expands on this concept, defining translational research as that which "transforms scientific discoveries that arise from laboratory, clinical, or population studies into clinical applications to reduce cancer incidence, morbidity, and mortality" [3].

The discipline of head and neck oncology possesses a strong history of translational research and continues to expand and build upon its foundation of scientific discoveries. Several chapters in this textbook are singularly devoted to epidemiology, genetics, virology, proteomics, predictors and prognosticators, hypoxia, targeted therapies, and functional imaging. Other chapters discuss preclinical models and phase I study methodology. Translational research links these topics together and is ultimately responsible for writing and shaping the current and future chapters on patient management and evidence-based practice.

Roadblocks

One of the ironic aspects of cancer research today is that the sheer avalanche of data and knowledge generated may overwhelm the ability to ask the most appropriate clinical

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questions. When the haystack is filled with needles, finding one gives way to the more challenging task of finding the right one. For example, at least 12 different agents target the epidermal growth factor receptor (EGFR) alone [4]. There are four downstream pathways associated with EGFR, and the number of potential therapeutic strategies to shepherd through from conception to daily practice expands geometrically along each signaling cascade [5]. The danger then becomes one of seeing a promising new treatment get lost in the translation.

The Clinical Research Roundtable at the Institute of Medicine (IOM) in their special communication to JAMA in 2003 highlighted an example of one of the dilemmas in translational research [6]. The IOM, comprised of individuals from the fields of nursing, medicine, basic science, public health, medical informatics, insurance companies, industry, and private foundations, described two translational roadblocks that "impede efforts to apply science to better human health in an expeditious fashion." The first exists when trying to convert basic in vitro and in vivo laboratory discoveries into novel interventions for human studies. The second occurs in the process of applying the results of these human studies and attempting to integrate them into everyday clinical practice and decision-making. The culprits deemed to be responsible for both blocks including insufficient funding, insufficient infrastructure, lack of qualified personnel, lack of career incentives, and a dearth of willing research subjects.

Much of the emphasis and funding in medical research to date has been placed on trying to overcome the first block. Novel therapeutics and new diagnostic modalities generate great excitement and enthusiasm, translating well not only within the medical profession, but also to the general public as well. Many are now concerned, however, that the second translational block constitutes the greatest bottleneck and is most detrimental to the health outcomes of everyday patients. More people, it has been argued, can be better served by focusing on the appropriate delivery of already proven treatment strategies rather than inventing new ones [7]. For example, the expenditure of effort to develop new and incrementally more efficacious statins or antiplatelet drugs contributes less to the overall societal health than using those same resources to ensure delivery of already available drugs to all eligible patients [8].

US health care expenditures in 2007 totaled $2.4 trillion, nearly 17% of the gross domestic product (GDP) [9]. Current projections are for this sum to increase to 20% of GDP by 2017. Historically, approximately 5% of this spending has been related to cancer therapy, although this percentage is also expected to rise with the aging US population and the adoption of newer, more expensive technologies and therapies [10]. How much should be spent and what level of care it should buy will require national debate and political intervention, meaning the probability of a rational solution is low.

The growing awareness of the extent to which new cancer treatments contribute to the escalating costs of health care has resulted in urgent calls to police within the oncology community before outside government agencies are mandated to do so. Such external intervention could set up more translational blocks, likely with less precision and more regulation. A recent report from the NIH reviewed four molecular targeted agents – cetuximab, bevacizumab, erlotinib, sorafenib – pinnacles of the translational research effort and compared their "purported" benefits and estimated costs [11]. They highlighted the recent multinational phase III FLEX (First-Line ErbituX) study comparing platinum-based chemotherapy with or without cetuximab as first-line therapy in EGFR-overexpressing nonsmall cell lung cancer patients with either wet stage IIIB or stage IV disease [12]. Patients randomized to the cetuximab arm received a loading dose of 400 mg/m^2, followed by weekly doses of 250 mg/m^2 concurrent with up to six cycles of chemotherapy and continuing weekly until disease progression or unacceptable toxicity. The primary endpoint was achieved with a statistically significant increase in median survival from 10.1 to 11.3 months with the addition of cetuximab. Ten percent developed grade 3 acne-like skin toxicity.

The cost of adding cetuximab to 18 weeks of chemotherapy (60 kg patient and $11.52 per mg of cetuximab) was $80,352 per patient [11]. Similarly, the addition of the small molecule tyrosine kinase inhibitor erlotinib to gemcitabine in advanced pancreatic cancer increased median survival by 10 days [13] for a cost of $15,752 [11]. Similar examples were presented for the use of bevacizumab in metastatic breast cancer [14] and sorafenib in renal cell carcinoma [15], emphasizing the tension that exists reconciling the costs of these therapies and their limited impacts on overall survival and/or quality of life.

The EXTREME (ErbituX in first-line Treatment of REcurrent or MEtastatic head and neck cancer) trial had a very similar design to the FLEX study in lung cancer. In this trial, 442 patients with previously untreated recurrent or metastatic disease not amenable to local therapy were randomized to platinum and 5FU-based chemotherapy alone versus chemotherapy with weekly cetuximab [16]. Those patients with stable disease on concurrent therapy continued with weekly cetuximab until disease progression or unacceptable toxicity. The addition of cetuximab improved median survival from 7.4 to 10.1 months, along with improvements in progression-free survival and response rates.

This increase represented a significant achievement in the recurrent/metastatic setting, the first intervention shown to improve survival in this population since cisplatin over 30 years ago [17]. However, this 2.7-month improvement in EXTREME may face further scrutiny, given the shot across the bow from the NIH regarding the results of FLEX. A typical patient in the USA with a body surface area of 2 mg/m^2

would have required 9,300 mg of cetuximab in 18 weeks in the experimental arm of the EXTREME trial at a cost of $107,136 based on 2008 data. Weekly treatment for 12 months in the setting of stable disease would have received 26,300 mg, which would have cost $302,976. Neither a privately run nor a publicly administered health care system can sustain this level of expense. A potential doomsday scenario for translational research could result if insurance companies and/or governments decide to offer patients a fraction of that cost to NOT take therapy.

The American Society of Clinical Oncology published the initial deliberations of its Cost of Care Task Force focusing on the perspectives of the different stakeholders in the oncology community – patients, industry, payers, and physicians – and highlighted the need to "define the value of specific cancer interventions" [18]. Some advocate funding restraints on research studies which would place cost limits on experimental interventions depending on their potential survival advantages [11]. In the same vein, some industry stakeholders may decide that certain disease entities, including head and neck cancers, lack the necessary patient numbers and potential market share for allocation of their resources in support of clinical trials.

Common Themes

The story of ICI 46,474, more commonly known as tamoxifen, is an instructive case study. This compound was first developed in the 1970s by Imperial Chemical Industries Ltd. Pharmaceuticals Division (now AstraZeneca) as a postcoital contraceptive [19]. The initial research that established tamoxifen as an antiestrogen capable of controlling hormone-dependent tumors almost did not happen. At the time, the company did not see a financial incentive to market a drug used for a short period of time by a small number of metastatic breast cancer patients, most of who were getting the latest and most promising therapy, cytotoxic chemotherapy combinations. It took the threatened resignation of the Head of Research, serendipity and years of preclinical data before the antitumor activity of tamoxifen was established. Moreover, testing in humans was originally performed in patients with advanced metastatic disease. Although somewhat effective, it was not until tamoxifen was studied in an adjuvant setting that the large benefits in reducing recurrence and improving overall survival were seen in estrogen receptor positive patients [20]. As stated by Dr. Jordan, the man who helped translate tamoxifen into clinical practice, "the key to success was targeting women with the right tumor with the correct duration of treatment at the right stage."

The right woman, the right tumor, at the right stage – many parallels can be drawn from the tamoxifen story to the targeted agents of today. Cetuximab's origins can be traced back to a woman born in the late nineteenth century. What she did for the first eight decades of her life is not known, but at the age of 85, her squamous cell carcinoma of the vulva was harvested and transformed into the immortalized cell line A431 [21]. Eleven years later in 1984, her cell line provided the substrate for the creation of murine monoclonal antibodies against the EGF receptors over-expressed along the cell surface [22]. In 1991, one of these antibodies, mAb 225, was successfully injected and studied in human subjects [23]. By 1995, the chimeric antibody C225, aka cetuximab, was developed to overcome the human antimouse antibody phenomenon that limited the clinical utility of mAb 225 [24].

Head and neck cancer patients with over-expression of EGFR were noted to have a poorer prognosis, providing the rationale for targeted therapy with C225 [25, 26]. Cetuximab has been utilized in a variety of different clinical scenarios since – as a single agent in advanced chemorefractory disease [27], with chemotherapy in the recurrent/metastatic setting [16, 28], with radiation therapy alone in locally advanced but nonmetastatic patients [29], and with concurrent chemoradiation [30]. In refractory patients, single-agent cetuximab showed a median survival of 178 days [27]. The results of EXTREME in previously untreated recurrent/metastatic patients were outlined earlier, showing an increase in median survival from 7.4 to 10.1 months [16]. The phase III pivotal trial from Bonner et al., which compared radiation therapy alone in the definitive setting with or without cetuximab, showed significant improvements in both local control and survival, increasing median survival from 29.3 to 49 months and 3 year overall survival from 45 to 55% [29]. As with tamoxifen, the earlier utilization of cetuximab in the nonmetastatic and treatment-naïve setting demonstrated a more robust improvement in clinical outcomes. Building upon these findings, the RTOG has recently completed enrollment onto a phase III study evaluating whether the addition of cetuximab to definitive chemoradiation can further improve outcome.

The fate of cetuximab and other novel therapeutic agents as they progress through various phases of development highlights several important themes for current and future translational research efforts. As the specificity of these agents toward their molecular targets increases, so too should the process of patient selection in order to optimally use them in various clinical scenarios. The keys to success require several interrelated questions to be addressed: who gets therapy, what agent(s) gets tested, whether to give or not give therapy, scheduling, and sequencing, where is the primary tumor located, and why did things work or not work? Limitations on resources and competition for study patients will prevent all of these questions from being asked. The head and neck oncology community will need to prioritize which ones are most important.

Who Gets Treated

The standard approach for new investigational agents that survive the preclinical gauntlet is to first test them in patients that have failed all known conventional therapies, initially for dose-limiting toxicities and safety and then for efficacy. An exciting and challenging avenue for research is now asking how improvements in outcomes in the recurrent and refractory setting translate in treatment-naïve patients. Are the additional months in median survival outback simply reshuffled upfront? Or are there true qualitative and quantitative improvements in survival, with more cures and less patients going on to require therapy for recurrent or metastatic disease? In head and neck cancer, the EXTREME and Bonner studies suggest the latter.

This has not always been the case. In colorectal cancer, the addition of bevacizumab to irinotecan, bolus fluorouracil, and leucovorin in previously untreated metastatic patients resulted in a statistically significant improvement in survival (median duration 15.6 vs. 20.3 months, HR 0.66, $p<0.001$) [31]. A similar benefit in overall survival was seen in a phase III ECOG study in patients with previously treated metastatic colorectal cancer. In this trial, the addition of bevacizumab to fluorouracil, leucovorin, and oxaliplatin (FOLFOX) improved median survival from 10.8 to 12.9 months compared to FOLFOX alone [32]. However, the survival benefits of adding bevacizumab to standard of care chemotherapy do not appear to automatically translate in the nonmetastatic setting. Preliminary results from NSABP C-08 showed no statistically significant improvement in disease-free survival with the addition of bevacizumab to FOLFOX in resected stage II–III colon cancer patients [33].

Another more ominous example is a phase III SWOG adjuvant lung cancer study. Patients received definitive concurrent thoracic chemoradiation and consolidation docetaxel chemotherapy with or without the addition of gefitinib, a small molecule EGFR tyrosine kinase inhibitor. Patients receiving gefitinib had a significant decrease in median survival (23 vs. 35 months) [34]. These findings further emphasize the importance that promising preclinical and early phase data for targeted agents must be validated in a rigorous phase III setting before they can be incorporated into widespread clinical practice.

Even then, the translation of successful randomized phase III trials in the phase IV practice setting can encounter unexpected hazards. Cetuximab is associated with an approximate 3–4% incidence of grade 3–4 infusion reactions in the USA. However, in certain geographic locations, the rate of severe anaphylactic hypersensitivity-type reactions approaches 20–25% [35]. In an illustrative example of bedside-to-bench reverse translation, these reactions have been linked to preexisting IgE antibodies that cross-react to a galactose-alpha-1,3-galactose moiety that is tagged to the Fab portion of the mouse component of the cetuximab molecule during antibody production [36]. Moreover, preexisting IgE antibodies in the general population were found to be more prevalent in people from Tennessee, Arkansas, and North Carolina (20.8%) as opposed to northern California (6.1%) or Boston (0.6%). The potential increased risk for these severe reactions has limited the enthusiasm for and restricted utilization of cetuximab in pockets of the Southeast USA. It was perhaps serendipitous that C225 was developed in other parts of the country.

Parallels may be drawn to trials examining the addition of concurrent chemotherapy to radiation in nasopharyngeal carcinoma (NPC), a tumor known for significant geographic variability with regards to histology and EBV status. Following the positive results of the Intergroup 0099 trial [37], studies were undertaken throughout Asia to determine whether the significant survival benefit seen in North American patients with a concurrent chemoradiation strategy translated to the endemic form of NPC found more predominantly in that part of the world. Three phase III trials from Taiwan, Singapore, and Hong Kong confirmed a survival benefit with concurrent chemoradiation versus radiation alone [38–40]. However, preliminary results from a fourth study with nonkeratinizing/undifferentiated histology patients from Hong Kong and Canada showed no survival benefit but increased acute and late toxicity with concurrent chemoradiation [41]. Whether regional or demographic differences in efficacy and/or toxicity will be discovered with targeted therapies remains to be seen.

The question of who gets certain therapies is further complicated by the growing awareness of a likely causal association between certain subsets of head and neck cancers and the human papillomavirus (HPV) [42]. These double-stranded DNA viruses have survived millennia in the inhospitable terminally differentiated epithelia of higher level organisms, cleverly restarting their nondividing hosts' replication machinery by inactivating both the p53 and pRb tumor suppressors. The first suggestion of HPV involvement in head and neck cancer came in 1983 based on histopathologic findings seen in a subset of oral squamous cell carcinomas similar to those caused by HPV in the uterine cervix [43]. Detection of high risk HPV16 DNA in tonsil cancer specimens came in 1990 [44]. Multiple retrospective series and a subsequent meta-analysis suggested that patients with HPV-positive oropharyngeal tumors had improved disease-free and overall survival, with a 28% reduced risk of death compared to HPV-negative patients [45]. The prognostic significance of HPV status was demonstrated prospectively in 96 patients from a phase II ECOG study examining an induction chemotherapy regimen followed by chemoradiation [46]. Patients with HPV-positive tumors had higher response rates to chemotherapy and chemoradiation, as well

as a 2-year overall survival of 95% [95% CI = 87–100%] versus 62% [95% CI = 49–74%] for the HPV-negative patients.

The improved outcomes and atypical presentations (younger age, female, lack of prior tobacco and alcohol use) of HPV-positive head and neck cancer patients suggest these tumors may represent a distinct clinical entity [47]. Given the potential for confounding of clinical trial results, future translational studies in head and neck cancer will likely need to stratify patients according to HPV status [48]. RTOG 0619, discussed below, includes stratification of oropharyngeal primary tumors by HPV status. Moreover, the excellent prognosis of HPV-positive patients has further implications regarding the future direction of treatment strategies that incorporate novel translational therapies. The question arises whether intensive concurrent regimens using radiation, chemotherapy, and molecular targeted agents are necessary for optimal tumor control in HPV-positive patients or are they just more toxic. Therefore, strategies for deintensification of therapy in this subset of patients, including radiation dose reduction and/or combining radiation with lower doses of cisplatin chemotherapy or with well-tolerated targeted agents in lieu of chemotherapy, will likely be emphasized in the near future.

What

With more stratification and potential reclassification of HPV-positive patients into a separate disease entity, the already small pie of head and neck cancer eligible to participate in clinical trials could get sliced further, reducing the ability to definitively answer study questions. RTOG 9003, the largest trial in head and neck cancer, needed over 6 years to enroll 1,113 patients [49]. Already, the increasing number of investigational agents has likely outgrown the number of people available for enrollment in clinical trials and the resources available to conduct them. To date, the RTOG has opened four head and neck protocols with targeted agents. Three are closed to accrual, 0234 and 522 with cetuximab, and 0615 with bevacizumab in NPC. The open 0619 study examines the addition of vandetanib, a dual EGFR and VEGFR tyrosine kinase inhibitor, to cisplatin in high-risk postoperative patients with extracapsular extension and/or microscopic positive margins. During the initial conception of 0619, the authors tallied the number of ongoing phase I/II studies in head and neck cancer with targeted agents, noting 32 trials involving cetuximab, gefitinib, erlotinib, panitumumab, celecoxib, bevacizumab, and lapatinib.

The study of one agent at a time is challenging enough, with or without radiation, with or without chemotherapy. Another area of increasing interest involves targeting multiple signaling pathways at once, either with multiagent cocktails or more promiscuous inhibitors such as vandetanib. The rationale for this approach has been the limited clinical utility seen with single targeted agents alone and the redundancy of signaling pathways. Despite the fact that a majority of head and neck tumors have EGFR over-expression, cetuximab with radiation therapy still showed a 50% local recurrence rate in the Bonner trial [29].

This fact is not surprising, given the complexity of the molecular signaling pathways involved in the pathogenesis of head and neck cancers [50]. Preclinical studies have shown significant cross-talk, with both direct and indirect associations between the various signaling cascades, providing alternative routes to bypass inhibition of one pathway [51]. Already, the simultaneous inhibition of the EGFR and VEGF pathways with erlotinib and bevacizumab has been studied in the recurrent/metastatic setting, showing the combination was well tolerated and potentially more efficacious in a subset of patients with molecular evidence of activated pathways [52]. At Duke University, a phase I/II trial examining the use of erlotinib, bevacizumab, and concurrent cisplatin with hyperfractionated radiation therapy in treatment-naïve, locally advanced nonmetastatic patients has recently completed accrual. Median follow-up is 2 years, and the results have been promising, with only 2 of the 28 patients having had a local recurrence. The trial design has also incorporated companion studies with serial functional imaging scans and serum samples collected at time points before, during, and after the completion of therapy. The goal is to help identify potentially predictive and/or prognostic factors that correlate with treatment outcomes, improving the selection of patients for targeted therapies in the future.

However, more is not always better. The Dutch CAIRO2 study in metastatic colorectal cancer found that the addition of cetuximab to capecitabine, oxaliplatin, and bevacizumab lead to a decrease in progression-free survival and quality of life [53]. The search for molecular rationales, including mechanisms of resistance, will require more bench research to help translate these unexpected bedside findings.

When

Clearly, not every patient benefits from the administration of targeted therapies. Even with the potential for more dramatic clinical improvements in the definitive and nonmetastatic setting, it does not appear economically feasible to incorporate one or two (or more) targeted therapies into the treatment regimen of every patient that presents de novo with locally advanced head and neck cancer. Finding biomarkers and molecular assays that can reliably predict who might respond favorably to certain agents and when they should be utilized is a key emphasis of ongoing studies. In colorectal

cancer, patients with EGFR expressing tumors and unresectable metastatic disease were randomized to FOLFIRI chemotherapy with or without cetuximab. Tumor KRAS gene mutation status was also examined. A progression-free survival benefit for cetuximab was limited to those patients with wild-type KRAS [54]. In the previously mentioned phase I/II study examining erlotinib and bevacizumab in recurrent/metastatic head and neck cancer, patients with increased phosphorylation of VEGFR in tumors and EGFR in endothelial cells were more likely to have complete responses [52]. Another study examining cisplatin and erlotinib in recurrent/metastatic head and neck patients found a correlation between improved treatment response and high EGFR gene copy number [55]. More robust and clinically applicable prognostic and/or predictive tools will be identified and validated. In fact, given the current climate, research that results in the more judicious use of novel therapies is mission critical to the viability and support of future translational studies.

The ability to identify responders versus nonresponders to targeted therapy early on in the treatment course would further improve patient selection and efficacy, providing guidance on when changes in therapy should be made. Recent trials with targeted agents have incorporated correlative studies with functional imaging modalities to noninvasively and serially assess the tumor microenvironment and monitor any possible treatment-related changes. Tools such as dynamic contrast-enhanced MRI (DCE-MRI) and PET-based assays attempt to capture novel information based on the underlying tumor biology, yielding potentially prognostic and predictive information to augment the anatomically based TNM staging system. For example, many antiangiogenic targeted agents exert their effects on tumor perfusion and vascular permeability, physiologic processes that can be quantitatively measured with DCE-MRI [56]. In breast cancer, early changes in tumor microvessel functionality as monitored by changes in DCE-MRI signaling predicted final clinical and pathologic response to neoadjuvant chemotherapy [57]. Other DCE-MRI parameters have also correlated with local control, disease-free, and overall survival in multiple tumor sites, including lung, cervix, and head and neck [58–63].

How

The question of how to optimally incorporate novel therapeutic agents in radiation-based treatment regimens is an active area of research. One limitation of the Bonner cetuximab trial that likely impacted widespread accrual and subsequent acceptance into clinical practice was the use of a control arm in the study that utilized radiation therapy alone in locally advanced patients. Based on the meta-analysis of Chemotherapy in Head and Neck Cancer (MACH-NC), which examined updated patient data on 16,485 patients from 87 trials published between 1965 and 2000, the addition of chemotherapy to radiation provided an absolute benefit of 4.5% at 5 years with a hazard ratio of 0.88 [64]. This benefit was more pronounced (6.5% at 5 years, HR 0.81) with the concomitant use of chemotherapy and radiation as compared to induction or adjuvant strategies.

The RTOG is addressing in two phase III trials whether the addition of targeted agents to current standards of care in both locally advanced and high-risk postoperative patients provides further benefit. RTOG 0522 asks whether cetuximab improves outcome when added to concurrent chemoradiation in the definitive setting while RTOG 0619, as described previously, is testing whether vandetanib improves upon combined modality therapy in high-risk postoperative patients. How novel targeted agents are incorporated into subsequent treatment regimens will be a critical area of ongoing research. Potential improvements in efficacy will need to be balanced against any increases seen in acute and late toxicity. In this context, tools to improve patient selection will play increasingly more important roles to optimally match treatment regimens of varying intensities to individual patients in order to optimize their therapeutic ratio.

The addition of targeted agents to concurrent chemoradiation may represent the evolution of a new standard of care for patients with high-risk, poor prognosis disease. In other clinical scenarios, such as HPV-positive patients with better prognoses where chemotherapy may not be necessary or in elderly patients where the addition of chemotherapy may only increase toxicity, targeted agents may ultimately replace concurrent chemotherapy [65]. For example, the use of lapatinib with concurrent chemoradiation is being evaluated in locally advanced head and neck patients [66]. At the same time, others are examining lapatinib with radiation therapy alone in locally advanced patients who cannot tolerate chemoradiation [67].

One hypothesis-generating result from Bonner's pivotal trial arises from the differences in survival seen between those patients who received cetuximab with altered fractionation versus conventional daily treatment schedules. Subset analyses showed that patients treated with concomitant boost regimens had a hazard ratio (HR) of 0.62 while the hyperfractionation group had a HR = 0.74. No difference in survival was seen in those patients who underwent conventional fractionation (HR = 1.01) [29]. This suggests that a trial design that utilized only conventional radiation with cetuximab would have resulted in a negative study.

Determining the optimal radiation fractionation schedules to use with the various targeted agents may present an ongoing challenge. Sobering parallels may be drawn from the now nearly completed search for the ideal schedule to use with decades-old systemic agents. Results from the recently updated MACH-NC suggest that the survival benefit seen with concurrent chemotherapy is similar irrespective of the

radiation fractionation regimen utilized (conventional HR 0.83 [95% CI 0.78–0.88] vs. altered HR 0.73 [95% CI 0.65–0.82] $p=0.14$) [64]. The results of RTOG 0129, which tests conventional versus accelerated fractionation, will help to determine the optimal radiation fractionation scheme to use with platinum-based chemotherapy. To re-emphasize the fact that more does not always mean better, a GORTEC phase III study showed no difference in progression-free survival at 3 years between accelerated versus conventional radiation therapy with concomitant carboplatin and 5-FU [68].

Where

The location of the primary tumor site has been suggested to influence survival. A multivariate analysis of 492 patients showed better prognosis in patients treated for larynx and nasopharyngeal tumors compared to those with oropharynx, oral cavity, and hypopharyngeal primaries [69]. In another series of locally advanced patients treated with intra-arterial cisplatin and radiation (RADPLAT), those with hypopharyngeal primaries were more likely to develop distant metastases (odds ratio 2.8) compared to patients with oral cavity, oropharynx, or laryngeal tumors [70]. In the Bonner trial, 253 of the 424 patients in the study had oropharyngeal tumors. On subgroup analysis, these patients appeared to derive the greatest benefits in locoregional control and survival from the addition of cetuximab [29]. Whether or not this benefit reflects the influence of HPV-associated malignancy in the oropharynx is unknown.

These findings further underscore the complexities facing the successful translation of targeted agents into clinical practice. Future prospective trials will likely need to focus on specific head and neck cancer subsites to avoid potential dilution of successful outcomes by the inclusion of possibly "non-responding" patients. In the case of oropharyngeal tumors, these will need to be further subdivided according to HPV status. At the same time, excessive stratification and selection of patients may severely cripple study power and applicability of results to the general head and neck cancer population.

Why

The need to confirm hypotheses in prospective trials is highlighted by several pitfalls in the translation of the very logical and rational hypoxia story into clinical practice. Since 1912, when Swartz observed less severe skin reactions when a radiation source compressed the surrounding blood flow, careful clinical and laboratory research has subsequently established the significant role hypoxia plays in cancer progression and increased resistance to radiation and chemotherapy [71, 72]. In head and neck cancer, studies directly measuring pretreatment intratumoral oxygenation levels in primary tumors and lymph node metastases using polarographic electrode techniques predicted for response to radiation therapy [73] and was prognostic for disease-free survival [74]. More recent studies have focused on less invasive methods such as hypoxia-related biomarkers and functional imaging studies to correlate tumor hypoxia with treatment-related outcomes [75]. Using tissue samples from RTOG 90-03 patients, expression of lysyl oxidase, a hypoxia-related protein, was shown to be strongly associated with increased metastases, disease progression, and death [76].

This rationale lead to the testing of therapeutic strategies designed to ameliorate or target hypoxia. Anemia, which contributes to tumor hypoxia, is associated with inferior outcomes following both radiotherapy alone and concurrent chemoradiation [77–79]. However, correction of anemia has not improved treatment outcome in prospective trials. In one series of patients treated with sequential chemotherapy followed by chemoradiation, the use of blood transfusions to maintain hemoglobin levels >12 g/dL was associated with worse survival [80]. Two randomized DAHANCA studies that incorporated blood transfusions for low hemoglobin levels showed no benefit [81, 82].

Both erythropoietin [83] and darbepoietin alfa [84] reversed the effects of anemia on radiation response in preclinical models. Moreover, a retrospective study of patients treated with neoadjuvant chemoradiation and surgery for oral cavity/oropharyngeal cancers, the use of recombinant human erythropoietin completely abrogated the negative prognostic impact associated with hemoglobin levels <14.5 g/dL [85]. However, two randomized phase III trials showed no benefit to the addition of erythropoietin in anemic HNC patients undergoing radiation therapy [86, 87]. In fact, the Henke study resulted in poorer disease control and survival in patients randomized to receive erythropoietin [86]. A randomized study in cervix cancer patients was closed prematurely due to concern for increased thromboembolic events with erythropoietin [88]. A Cochrane review including 13,933 cancer patients in 53 trials showed that erythropoiesis-stimulating agents were associated with increases in on-study mortality and worse overall survival [89]. These unexpected clinical findings stimulated laboratory research that demonstrated expression of erythropoietin receptors on tumor cells in a variety of malignancies, including squamous cell carcinomas of the head and neck [90]. Potential erythropoietin-mediated signaling mechanisms responsible for increased cancer cell survival have been implicated [91, 92].

An alternate strategy of specifically targeting hypoxic cancer cells lead to the study of bioreductive agents such as tirapazamine [93]. Preclinical data showed preferential

cytotoxicity to hypoxic tumor cells, and early phase I/II data demonstrated encouraging results when this agent was combined with chemotherapy and/or radiation [94–96]. However, two randomized phase III studies have shown no benefit from the addition of tirapazamine to radiation and chemotherapy. The HEADSTART trial showed no benefit in patients with locally advanced HNC treated to 70 Gy with three cycles of concurrent cisplatin [97]. The TRACE study, which used the same treatment scheme, was terminated early due to excessive mortality in the experimental tirapazamine arm [98]. Unfortunately, no systematic assessment of tumor hypoxia was performed in either of these trials. Studies using electrode and PET-based techniques suggest that approximately one third to one half of HNC patients do not have significant levels of tumor hypoxia [99, 100]. Therefore, it is possible that both of these trials were "biologically underpowered" to address the hypoxia question which was being investigated.

Translational studies using functional imaging modalities that correlate with tumor hypoxia may better identify candidates for hypoxia-targeted therapy [101]. A substudy of TROG-98.02 using 18-F misonidazole-PET to image tumor hypoxia found a significantly higher risk of locoregional failure in hypoxic patients who received concurrent chemotherapy compared to those who also received tirapazamine [100]. The ability to image hypoxia-specific regions with PET and/or functional MRI may further allow for physical targeting and treatment intensification with radiation techniques such as intensity-modulated radiation therapy [102]. However, significant daily fluctuations in tumor hypoxia imaging have been seen in as many as 30% of patients [103]. This suggests widespread clinical application will require further translational research into the dynamic nature of these processes studied by functional imaging modalities – vascular permeability, perfusion, and metabolism.

Conclusion

Successful translational research will help to define new standards of care by improving the therapeutic ratio between treatment efficacy and toxicity. Better prognostic tools and more robust predictive assays will help to improve patient selection, stratifying patients to appropriate intensifications or deintensifications of therapy, and identifying those most likely to benefit from various treatments. In future trials, enriching the study population with those most likely to need and respond to certain therapies will hopefully magnify any potential improvements in outcome, in turn lowering the number of subjects needed to detect statistically significant differences. This is especially critical for head and neck cancer where the eligible patient pool from which to draw is smaller than other disease sites.

New experimental therapies will need to be built on the foundation of prior successes, incorporating themselves into optimized standard of care regimens. Due to increasing economic constraints, leadership and guidance will likely need to come from the large umbrella cooperative groups such as the RTOG and EORTC regarding trial design and priorities. The design of trials should continue to combine treatment interventions with various correlative studies to identify and validate predictors that will help determine who benefits most from specific therapies. Strategic plans within RTOG have been discussed to improve the ability to perform more successful translational studies – tissue banking, seed grants, bioinformatics, and statistical support [104].

The war on cancer has seen decades of translational research create a new generation of targeted weapons with increasing specificity and accuracy. The danger now lies in using these agents to carpet-bomb entire patient populations, failing to commit the same level of resources to identifying the correct human targets.

References

1. Fricker SP. Metal based drugs: from serendipity to design. Dalton Trans. 2007 Nov 21; (43):4903–17.
2. Rosenberg B. Possible mechanisms for the antitumor activity of platinum coordination complexes. Cancer Chemother Rep. 1975;59(3):589–98.
3. National Cancer Institute. http://www.cancer.gov/trwg/TRWG-definition-and-TR-continuum. [cited July 20, 2009]; Available from: http://www.cancer.gov/trwg/TRWG-definition-and-TR-continuum. Accessed 2011.
4. Karamouzis MV, Grandis JR, Argiris A. Therapies directed against epidermal growth factor receptor in aerodigestive carcinomas. JAMA. 2007;298(1):70–82.
5. Egloff AM, Grandis JR. Targeting epidermal growth factor receptor and SRC pathways in head and neck cancer. Semin Oncol. 2008;35(3):286–97.
6. Sung NS, Crowley Jr WF, Genel M, et al. Central challenges facing the national clinical research enterprise. JAMA. 2003;289(10):1278–87.
7. Woolf SH. The meaning of translational research and why it matters. JAMA. 2008;299(2):211–3.
8. Woolf SH, Johnson RE. The break-even point: when medical advances are less important than improving the fidelity with which they are delivered. Ann Fam Med. 2005;3(6):545–52.
9. NCHC. Facts about Healthcare – Health Insurance Costs. [cited July 22, 2009]; Available from: http://nchc.org/facts-resources/fact-sheet-cost. Accessed 2011.
10. Institute NC. Cancer Trends Progress Report – 2007 Update. 2007 [cited August 1, 2009]; Available from: http://progressreport.cancer.gov. Accessed 2011.
11. Fojo T, Grady C. How much is life worth: cetuximab, non-small cell lung cancer, and the $440 billion question. J Natl Cancer Inst. 2009;101(15):1044–8.
12. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet. 2009; 373(9674):1525–31.
13. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National

Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007;25(15):1960–6.
14. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 2007;357(26):2666–76.
15. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356(2):125–34.
16. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008;359(11):1116–27.
17. Wittes RE, Cvitkovic E, Shah J, Gerold FP, Strong EW. CIS-Dichlorodiammineplatinum(II) in the treatment of epidermoid carcinoma of the head and neck. Cancer Treat Rep. 1977;61(3):359–66.
18. Meropol NJ, Schrag D, Smith TJ, et al. American Society of Clinical Oncology Guidance Statement: The Cost of Cancer Care. J Clin Oncol. 2009.
19. Jordan VC. Tamoxifen: catalyst for the change to targeted therapy. Eur J Cancer. 2008;44(1):30–8.
20. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet. 1998;351(9114):1451–67.
21. Giard DJ, Aaronson SA, Todaro GJ, et al. In vitro cultivation of human tumors: establishment of cell lines derived from a series of solid tumors. J Natl Cancer Inst. 1973;51(5):1417–23.
22. Masui H, Kawamoto T, Sato JD, Wolf B, Sato G, Mendelsohn J. Growth inhibition of human tumor cells in athymic mice by anti-epidermal growth factor receptor monoclonal antibodies. Cancer Res. 1984;44(3):1002–7.
23. Divgi CR, Welt S, Kris M, et al. Phase I and imaging trial of indium 111-labeled anti-epidermal growth factor receptor monoclonal antibody 225 in patients with squamous cell lung carcinoma. J Natl Cancer Inst. 1991;83(2):97–104.
24. Goldstein NI, Prewett M, Zuklys K, Rockwell P, Mendelsohn J. Biological efficacy of a chimeric antibody to the epidermal growth factor receptor in a human tumor xenograft model. Clin Cancer Res. 1995;1(11):1311–8.
25. Rubin Grandis J, Melhem MF, Gooding WE, et al. Levels of TGF-alpha and EGFR protein in head and neck squamous cell carcinoma and patient survival. J Natl Cancer Inst. 1998;90(11):824–32.
26. Ang KK, Berkey BA, Tu X, et al. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. Cancer Res. 2002;62(24):7350–6.
27. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol. 2007;25(16):2171–7.
28. Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol. 2005;23(34):8646–54.
29. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006;354(6):567–78.
30. Radiation Therapy Oncology Group. Head and Neck Cancer Protocols. [cited August 1 2009]; Available from http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0522. Accessed 2011.
31. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335–42.
32. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol. 2007;25(12):1539–44.
33. Allegra CJ, Yothers G, O'Connell MJ, et al. Initial safety report of NSABP C-08: a randomized phase III study of modified FOLFOX6 with or without bevacizumab for the adjuvant treatment of patients with stage II or III colon cancer. J Clin Oncol. 2009; 27(20):3385–90.
34. Kelly K, Chansky K, Gaspar LE, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. J Clin Oncol. 2008;26(15):2450–6.
35. O'Neil BH, Allen R, Spigel DR, et al. High incidence of cetuximab-related infusion reactions in Tennessee and North Carolina and the association with atopic history. J Clin Oncol. 2007;25(24):3644–8.
36. Chung CH, Mirakhur B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1, 3-galactose. N Engl J Med. 2008;358(11):1109–17.
37. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol. 1998;16(4):1310–7.
38. Chan AT, Leung SF, Ngan RK, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. J Natl Cancer Inst. 2005;97(7):536–9.
39. Lin JC, Jan JS, Hsu CY, Liang WM, Jiang RS, Wang WY. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. J Clin Oncol. 2003;21(4):631–7.
40. Wee J, Tan EH, Tai BC, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. J Clin Oncol. 2005;23(27):6730–8.
41. Lee AW, Lau WH, Tung SY, et al. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. J Clin Oncol. 2005;23(28):6966–75.
42. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst. 2000;92(9):709–20.
43. Syrjanen K, Syrjanen S, Lamberg M, Pyrhonen S, Nuutinen J. Morphological and immunohistochemical evidence suggesting human papillomavirus (HPV) involvement in oral squamous cell carcinogenesis. Int J Oral Surg. 1983;12(6):418–24.
44. Niedobitek G, Pitteroff S, Herbst H, et al. Detection of human papillomavirus type 16 DNA in carcinomas of the palatine tonsil. J Clin Pathol. 1990;43(11):918–21.
45. Ragin CC, Taioli E. Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: review and meta-analysis. Int J Cancer. 2007;121(8):1813–20.
46. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst. 2008;100(4):261–9.
47. Vidal L, Gillison ML. Human papillomavirus in HNSCC: recognition of a distinct disease type. Hematol Oncol Clin North Am. 2008;22(6):1125–42. vii.
48. Gillison ML. Human papillomavirus and prognosis of oropharyngeal squamous cell carcinoma: implications for clinical research in head and neck cancers. J Clin Oncol. 2006;24(36):5623–5.
49. Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. Int J Radiat Oncol Biol Phys. 2000;48(1):7–16.

50. Molinolo AA, Amornphimoltham P, Squarize CH, Castilho RM, Patel V, Gutkind JS. Dysregulated molecular networks in head and neck carcinogenesis. Oral Oncol. 2009;45(4–5):324–34.
51. Matta A, Ralhan R. Overview of current and future biologically based targeted therapies in head and neck squamous cell carcinoma. Head Neck Oncol. 2009;1(1):6.
52. Cohen EE, Davis DW, Karrison TG, et al. Erlotinib and bevacizumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck: a phase I/II study. Lancet Oncol. 2009;10(3):247–57.
53. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med. 2009; 360(6):563–72.
54. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009;360(14):1408–17.
55. Agulnik M, da Cunha Santos G, Hedley D, et al. Predictive and pharmacodynamic biomarker studies in tumor and skin tissue samples of patients with recurrent or metastatic squamous cell carcinoma of the head and neck treated with erlotinib. J Clin Oncol. 2007;25(16):2184–90.
56. Hylton N. Dynamic contrast-enhanced magnetic resonance imaging as an imaging biomarker. J Clin Oncol. 2006;24(20):3293–8.
57. Ah-See ML, Makris A, Taylor NJ, et al. Early changes in functional dynamic magnetic resonance imaging predict for pathologic response to neoadjuvant chemotherapy in primary breast cancer. Clin Cancer Res. 2008;14(20):6580–9.
58. Baba Y, Yamashita Y, Onomichi M. Dynamic MR imaging and radiotherapy. Magn Reson Med Sci. 2002;1(1):32–7.
59. Hoskin PJ, Saunders MI, Goodchild K, Powell ME, Taylor NJ, Baddeley H. Dynamic contrast enhanced magnetic resonance scanning as a predictor of response to accelerated radiotherapy for advanced head and neck cancer. Br J Radiol. 1999;72(863):1093–8.
60. Loncaster JA, Carrington BM, Sykes JR, et al. Prediction of radiotherapy outcome using dynamic contrast enhanced MRI of carcinoma of the cervix. Int J Radiat Oncol Biol Phys. 2002;54(3):759–67.
61. Ohno Y, Nogami M, Higashino T, et al. Prognostic value of dynamic MR imaging for non-small-cell lung cancer patients after chemoradiotherapy. J Magn Reson Imaging. 2005;21(6):775–83.
62. Tomura N, Omachi K, Sakuma I, et al. Dynamic contrast-enhanced magnetic resonance imaging in radiotherapeutic efficacy in the head and neck tumors. Am J Otolaryngol. 2005;26(3):163–7.
63. Yamashita Y, Baba T, Baba Y, et al. Dynamic contrast-enhanced MR imaging of uterine cervical cancer: pharmacokinetic analysis with histopathologic correlation and its importance in predicting the outcome of radiation therapy. Radiology. 2000;216(3):803–9.
64. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17, 346 patients. Radiother Oncol. 2009;92(1):4–14.
65. Pignon JP, le Maitre A, Bourhis J. Meta-analyses of chemotherapy in head and neck cancer (MACH–NC): an update. Int J Radiat Oncol Biol Phys. 2007;69(2 Suppl):S112–4.
66. Harrington KJ, El-Hariry IA, Holford CS, et al. Phase I study of lapatinib in combination with chemoradiation in patients with locally advanced squamous cell carcinoma of the head and neck. J Clin Oncol. 2009;27(7):1100–7.
67. Le QT, Raben D. Integrating biologically targeted therapy in head and neck squamous cell carcinomas. Semin Radiat Oncol. 2009;19(1):53–62.
68. Bourhis J, Sire C, Lapeyre M, et al. Accelerated versus conventional radiotherapy with concomitant chemotherapy in locally advanced head and neck carcinomas: results of a phase III randomized trial. Int J Radiat Oncol Biol Phys. 2008;72(1):S31–2.
69. Cerezo L, Millan I, Torre A, Aragon G, Otero J. Prognostic factors for survival and tumor control in cervical lymph node metastases from head and neck cancer. A multivariate study of 492 cases. Cancer. 1992;69(5):1224–34.
70. Doweck I, Robbins KT, Vieira F. Analysis of risk factors predictive of distant failure after targeted chemoradiation for advanced head and neck cancer. Arch Otolaryngol Head Neck Surg. 2001; 127(11):1315–8.
71. Bernier J, Hall EJ, Giaccia A. Radiation oncology: a century of achievements. Nat Rev Cancer. 2004;4(9):737–47.
72. Vaupel P, Mayer A. Hypoxia in cancer: significance and impact on clinical outcome. Cancer Metastasis Rev. 2007;26(2):225–39.
73. Nordsmark M, Overgaard M, Overgaard J. Pretreatment oxygenation predicts radiation response in advanced squamous cell carcinoma of the head and neck. Radiother Oncol. 1996;41(1):31–9.
74. Brizel DM, Sibley GS, Prosnitz LR, Scher RL, Dewhirst MW. Tumor hypoxia adversely affects the prognosis of carcinoma of the head and neck. Int J Radiat Oncol Biol Phys. 1997;38(2):285–9.
75. Le QT, Kong C, Lavori PW, et al. Expression and prognostic significance of a panel of tissue hypoxia markers in head-and-neck squamous cell carcinomas. Int J Radiat Oncol Biol Phys. 2007;69(1):167–75.
76. Le QT, Harris J, Magliocco AM, et al. Validation of lysyl oxidase as a prognostic marker for metastasis and survival in head and neck squamous cell carcinoma: Radiation Therapy Oncology Group Trial 90-03. J Clin Oncol. 2009;27(26):4281–6.
77. Prosnitz RG, Yao B, Farrell CL, Clough R, Brizel DM. Pretreatment anemia is correlated with the reduced effectiveness of radiation and concurrent chemotherapy in advanced head and neck cancer. Int J Radiat Oncol Biol Phys. 2005;61(4):1087–95.
78. Fortin A, Wang CS, Vigneault E. Effect of pretreatment anemia on treatment outcome of concurrent radiochemotherapy in patients with head and neck cancer. Int J Radiat Oncol Biol Phys. 2008; 72(1):255–60.
79. Rades D, Stoehr M, Kazic N, et al. Locally advanced stage IV squamous cell carcinoma of the head and neck: impact of pre-radiotherapy hemoglobin level and interruptions during radiotherapy. Int J Radiat Oncol Biol Phys. 2008;70(4):1108–14.
80. Bhide SA, Ahmed M, Rengarajan V, et al. Anemia during sequential induction chemotherapy and chemoradiation for head and neck cancer: the impact of blood transfusion on treatment outcome. Int J Radiat Oncol Biol Phys. 2009;73(2):391–8.
81. Overgaard J, Hansen HS, Overgaard M, et al. A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish Head and Neck Cancer Study (DAHANCA) Protocol 5-85. Radiother Oncol. 1998;46(2): 135–46.
82. Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet. 2003;362(9388):933–40.
83. Stuben G, Pottgen C, Knuhmann K, et al. Erythropoietin restores the anemia-induced reduction in radiosensitivity of experimental human tumors in nude mice. Int J Radiat Oncol Biol Phys. 2003;55(5):1358–62.
84. Ning S, Hartley C, Molineux G, Knox SJ. Darbepoietin alfa potentiates the efficacy of radiation therapy in mice with corrected or uncorrected anemia. Cancer Res. 2005;65(1):284–90.
85. Glaser CM, Millesi W, Kornek GV, et al. Impact of hemoglobin level and use of recombinant erythropoietin on efficacy of preoperative chemoradiation therapy for squamous cell carcinoma of the oral cavity and oropharynx. Int J Radiat Oncol Biol Phys. 2001;50(3):705–15.
86. Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. Lancet. 2003;362(9392):1255–60.

87. Machtay M, Pajak TF, Suntharalingam M, et al. Radiotherapy with or without erythropoietin for anemic patients with head and neck cancer: a randomized trial of the Radiation Therapy Oncology Group (RTOG 99-03). Int J Radiat Oncol Biol Phys. 2007; 69(4):1008–17.
88. Thomas G, Ali S, Hoebers FJ, et al. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. Gynecol Oncol. 2008;108(2):317–25.
89. Bohlius J, Schmidlin K, Brillant C, et al. Erythropoietin or Darbepoetin for patients with cancer – meta-analysis based on individual patient data. Cochrane Database Syst Rev. 2009;(3):CD007303.
90. Arcasoy MO, Amin K, Chou SC, Haroon ZA, Varia M, Raleigh JA. Erythropoietin and erythropoietin receptor expression in head and neck cancer: relationship to tumor hypoxia. Clin Cancer Res. 2005;11(1):20–7.
91. Pajonk F, Weil A, Sommer A, Suwinski R, Henke M. The erythropoietin-receptor pathway modulates survival of cancer cells. Oncogene. 2004;23(55):8987–91.
92. Winter SC, Shah KA, Campo L, et al. Relation of erythropoietin and erythropoietin receptor expression to hypoxia and anemia in head and neck squamous cell carcinoma. Clin Cancer Res. 2005;11(21):7614–20.
93. Zeman EM, Brown JM, Lemmon MJ, Hirst VK, Lee WW. SR-4233: a new bioreductive agent with high selective toxicity for hypoxic mammalian cells. Int J Radiat Oncol Biol Phys. 1986;12(7):1239–42.
94. Rischin D, Peters L, Hicks R, et al. Phase I trial of concurrent tirapazamine, cisplatin, and radiotherapy in patients with advanced head and neck cancer. J Clin Oncol. 2001;19(2):535–42.
95. Le QT, Taira A, Budenz S, et al. Mature results from a randomized Phase II trial of cisplatin plus 5-fluorouracil and radiotherapy with or without tirapazamine in patients with resectable Stage IV head and neck squamous cell carcinomas. Cancer. 2006;106(9):1940–9.
96. Lunt SJ, Telfer BA, Fitzmaurice RJ, Stratford IJ, Williams KJ. Tirapazamine administered as a neoadjuvant to radiotherapy reduces metastatic dissemination. Clin Cancer Res. 2005;11(11): 4212–6.
97. Rischin D, Peters L, O'Sullivan B, et al. Tirapazamine, cisplatin, and radiation versus cisplatin and radiation for advanced squamous cell carcinoma of the head and neck (TROG 02.02, HeadSTART): a phase III trial of the Trans-Tasman Radiation Oncology Group. J Clin Oncol. 2010;28(18):2989–95.
98. Seiwert TY, Salama JK, Vokes EE. The chemoradiation paradigm in head and neck cancer. Nat Clin Pract Oncol. 2007;4(3): 156–71.
99. Brizel DM, Dodge RK, Clough RW, Dewhirst MW. Oxygenation of head and neck cancer: changes during radiotherapy and impact on treatment outcome. Radiother Oncol. 1999;53(2):113–7.
100. Rischin D, Hicks RJ, Fisher R, et al. Prognostic significance of [18F]-misonidazole positron emission tomography-detected tumor hypoxia in patients with advanced head and neck cancer randomly assigned to chemoradiation with or without tirapazamine: a substudy of Trans-Tasman Radiation Oncology Group Study 98.02. J Clin Oncol. 2006;24(13):2098–104.
101. Le QT. Identifying and targeting hypoxia in head and neck cancer: a brief overview of current approaches. Int J Radiat Oncol Biol Phys. 2007;69(2 Suppl):S56–8.
102. Lee NY, Le QT. New developments in radiation therapy for head and neck cancer: intensity-modulated radiation therapy and hypoxia targeting. Semin Oncol. 2008;35(3):236–50.
103. Lin Z, Mechalakos J, Nehmeh S, et al. The influence of changes in tumor hypoxia on dose-painting treatment plans based on 18F-FMISO positron emission tomography. Int J Radiat Oncol Biol Phys. 2008;70(4):1219–28.
104. Chung CH, Wong S, Ang KK, et al. Strategic plans to promote head and neck cancer translational research within the radiation therapy oncology group: a report from the translational research program. Int J Radiat Oncol Biol Phys. 2007;69(2 Suppl):S67–78.