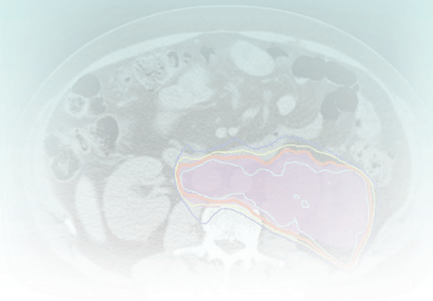
Overview



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Although representing about 4% of cancers, a variety of neoplasms with diverging natural histories arise in the relatively small body region of the head and neck. Essential basic physiologic functions that are critical for one's expression, respiration, nutrition, and social interactions are all located within the head and neck region, including one's personal appearance. Depending on the site, size, and pattern of spread, head and neck cancers can cause various degrees of structural deformities and functional handicaps, compromising comfort and social integration. Treatments used in the management of head and neck tumors can induce additional mutilations and malfunctions, worsening the quality of life. Consequently, optimizing outcomes in terms of survival, tumor control, function, and quality of life is challenging.

Knowledge of the basic principles of oncology and expertise in patient assessment and in individual specialties are essential for the optimal staging workup of patients and for appropriate treatment selection. Integrated interdisciplinary collaborations among surgical, radiation, medical, and dental oncologists as well as interactions among oncologists and pathologists, radiologists, reconstructive surgeons, physical medicine and rehabilitation physicians, psychiatrists, nurses, speech and swallowing therapists, dieticians, social workers, chaplains, and other health and spiritual care personnel are essential for optimal management and rehabilitation of patients with head and neck cancer. Well-functioning, integrated, and coordinated care is essential to yield the highest complication-free cure rate with maximal functional and cosmetic outcome. Close collaborations among radiation oncologists, dosimetrists, medical physicists, radiotherapists, and oncology nurses are important to deliver quality radiotherapy.

Long-term investment in cancer research has come to fruition for certain cancers. The mortality rate for most cancers in the United States increased for decades, but since 1975 the rate has decreased.[1] Many advances have been achieved in the understanding of the biology, natural history, and treatment of head and neck cancers.

This summary highlights a few interesting and evolving concepts and recent findings of clinical interest in the carcinogenesis, biology, and treatment of head and neck cancers. Site-specific issues are discussed in the subsequent chapters.

MOLECULAR BIOLOGY AND ECOGENETICS

The molecular tumor progression model was initially proposed by Fearon and Vogelstein.[2] This model states that tumors progress by activation of oncogenes and inactivation of tumor suppressor genes (TSGs), with each process producing a growth advantage for a clonal population of cells, and that specific genetic events usually occur in a distinct order (i.e., multistep carcinogenesis) that is not necessarily the same for each tumor.

For head and neck carcinomas, Califano et al[3] described a preliminary tumor progression model using allelic loss or imbalance as a molecular marker for oncogene amplification TSG inactivation. They identified *CDKN2A* (formerly designated *p16*; 9p21), *TP53* (17p), and *RB1* (13q) as candidate TSGs, and *CCND1* (cyclin D1 gene; 11q13) as a candidate proto-oncogene. The results of this work support the initial observations of the colorectal molecular progression model in that clonal genetic changes occur early in the histopathologic continuum of tumor progression. About one third of histopathologically benign squamous hyperplasias contain a clonal population of cells with shared genetic anomalies characterizing head and neck cancers. Identification of such early events facilitates discovery of genetic alterations associated with further transformation and aggressive clinical behavior. Genetic mutations of the PI3K/Akt/mTOR pathway have been reported in most head and neck squamous cell carcinomas (HNSCCs).[4] Mutation rates are low in human papillomavirus (HPV)-positive squamous cell carcinomas of the head and neck when compared to HPV-negative cancers. PIK3CA is the most commonly mutated oncogene pathway in HPV-positive cancers.[5] With further validation, this knowledge will contribute greatly to the development of screening strategies, focusing on previous steps of the estimated 10 or more genetic alterations required to generate an invasive tumor phenotype and to the conception of early pharmacologic or genetic therapy approaches.

Tobacco and alcohol exposure has long been recognized as the dominant risk factor in head and neck carcinogenesis. Although the use of these substances was estimated to account for approximately three fourths of oral and pharyngeal carcinomas,[6] neoplasms develop in only a small fraction of exposed individuals. This intriguing information raised the notion of the contribution of genetic susceptibility or predisposition and other cofactors (e.g., viral infection) to carcinogenesis. The potential pathways are thought to include genetic polymorphism influencing environmental carcinogen absorption and detoxification, individual sensitivity to carcinogen-induced genotypic alterations, and so on. These ideas can now be tested properly because of progress in molecular biology concepts and assay methodology. The ability to identify smokers at high risk for the development of cancer, for example, has important practical clinical implications, such as in selecting individuals for more aggressive screening programs or for enrollment in intensive chemoprevention trials (discussed later).

RECEPTOR TYROSINE KINASES

Intensive research efforts sparked by the characterization of epidermal growth factor receptor (EGFR, also known as HER1 or ERBB1) in the late 1970s generated insights into the structures and functions of receptor tyrosine kinases (RTKs) and their roles in the ligand-mediated signaling pathways governing proliferation, differentiation, survival, and other key cellular processes.

More than two decades after the initial characterization of the EGFR, it is known that receptor tyrosine kinases are highly related in structure and domain arrangements despite their unique biologic roles. This class of receptors comprises 58 members distributed among 20 subfamilies (reviewed by Gschwind et al[7]). EGFR-mediated signaling and its deregulation in pathogenesis and as the target of therapeutic intervention of human tumors have also been reviewed.[8,9] Its value as a prognostic-predictive biomarker and as a target of therapeutic intervention in head and neck carcinoma is addressed in the section on "Biomarkers and Molecular Targeting."

Deregulation of the *RET* gene-encoded transmembrane receptor tyrosine kinase plays an important role in the pathogenesis of papillary and medullary thyroid cancer (reviewed by Santoro et al[10]). The *RET* gene is located in the pericentromeric region of the short arm of chromosome 10. Alternative splicing of the RET product results in two protein isoforms: RET9 and RET51. RET shows that a single gene can induce different types of cancer, depending on the mutation. The genetic characteristics of papillary thyroid carcinoma (PTC), the most common thyroid neoplasm, are chromosomal inversions or translocations leading to several types of combinations of intracellular kinase-coding RET domain with heterologous genes, producing the *RET*/PTC chimeric oncogenes. In vitro and in vivo irradiation was found to induce the formation of a RET/PTC1 rearrangement,[11] and RET/PTC rearrangements have been found in more than 60% of post-Chernobyl accident papillary thyroid carcinomas.[12] These findings contribute to the understanding of the pathogenesis of radiation-induced thyroid carcinoma.

In contrast to the rearrangement observed in papillary thyroid carcinoma, germline point mutations in *RET* cause three types of related dominantly inherited cancer syndromes: multiple endocrine neoplasia type 2A (MEN2A), MEN2B, and familial medullary thyroid carcinoma (FMTC).[13-15] Most RET mutations in MEN2A and FMTC affect cysteine in the extracellular cysteine-rich domain (i.e., codon 634 [particularly, C634R] in MEN2A) or are evenly distributed among various cysteines in FMTC. Mutations in the kinase domain have also been observed. The most common mutation in MEN2B is M918T in the kinase domain. Somatic mutations of V804, M918, and E768 occur in about one half of sporadic medullary thyroid carcinomas (MTCs).[13-16] Functionally, RET cysteine mutants form covalent dimers leading to constitutive kinase activity, whereas the M918T mutation causes a change in the substrate specificity.[17]

VIRAL CAUSES

Nasopharyngeal carcinoma (NPC) has been an excellent model for studying viral causes of human cancer. Although the association between Epstein-Barr virus (EBV) and NPC has been recognized for about four decades, significant progress in this field has been made only more recently. For example, the EBV genome was characterized (reviewed by Liebowitz[18]) and found to consist of a linear, 172-kb, double-stranded DNA having five unique sequences, separated by four internal repeats along with two terminal repeats. The DNA circularizes by homologous recombination at random locations within terminal repeats in the nucleus of infected cells. The length of terminal repeat is therefore specific for each infected cell, and this is the basis for clonality assay, which may be useful in determining the putative primary tumor in patients presenting with nodal metastasis from an unknown source. The genome encodes several families of proteins, such as early antigens (EAs), EB nuclear antigens (EBNAs), and latency membrane proteins (LMPs). Many of these proteins control viral behavior and affect cell proliferation regulatory mechanisms, and they are thought to play a role in transformation and carcinogenesis and to influence the tumor response to therapy. EBNA-1 regulates viral genome replication during cell division and was found to induce growth and dedifferentiation of an EBV(–) NPC cell line.[19] LMP-1 seems to alter growth of epithelial cells, induce well-differentiated squamous carcinomas from human epithelial cell-line transfectants, and is associated with BCL2 expression in tumors.[20,21]

More work has been done on the molecular genetics of NPC. Many NPCs were found to have deletions of the short arm or some regions of the short arm of chromosomes 3 and 9, suggesting the possibility of the existence of TSGs in these regions.[22,23] For example, some studies[24,25] revealed that the combined frequency for chromosome 3p and 9p (bearing *CDKN2A* and *RASSF1A*) losses in the normal nasopharyngeal epithelium among southern Chinese individuals in Hong Kong, a population at high risk for NPC, was 82.6%, compared with 20% in the low-risk populations. In contrast, latent EBV infection was detected only in high-grade nasopharyngeal dysplasia or NPC. Consequently, it was postulated that the abnormal genetic changes in chromosomes 3p and 9p predispose nasopharyngeal cells to sustain latent EBV infection, and this combination promotes a cascade of events leading to malignancy. One study revealed that in patients with nonmetastatic NPC, the plasma level of EBV DNA, particularly when assayed after completion of therapy, is a robust prognostic biomarker (see section "Biomarkers and Molecular Targeting").

The causal relationship between HPVs and some human neoplasms has been established, particularly for carcinoma of the uterine cervix. Most cervical cancers contain integrated HPV DNA, most commonly of high-risk types HPV-16 and HPV-18.[26] Cell culture studies clearly demonstrated that the high-risk HPVs can transform and immortalize epithelial cells from the cervix, foreskin, and oral cavity.[27-29] In contrast, HPV-6 and HPV-11, associated more often with benign lesions, do not possess this capability.[30,31] Expression of E6 and E7 open reading frames of the HPV-16 or HPV-18 genome is sufficient for immortalization.[32,33]

The potential role of HPV in head and neck carcinogenesis has attracted attention (reviewed by Blitzer[34]). Carcinomas of the tonsil, oral tongue, and floor of the mouth were found to have a relatively high prevalence of HPV DNA.[35-37] A high proportion of verrucous carcinomas, rare locally invasive carcinomas with papillomatous morphology, are associated with HPV.[38,39] Verrucous carcinomas of the larynx predominantly contain HPV-6, HPV-11, HPV-16, or related DNA.[40] The evidence for the role of HPVs in carcinogenesis of tonsillar carcinomas is increasing because these tumors contain HPV DNA in most of the cells and express readily detectable levels of HPV RNA.[41] In a series of 253 patients, Gillison et al[42] detected HPV in 25% of tumors, with HPV-16 present in 90% of the positive neoplasms. HPV presence was most common in oropharyngeal carcinoma, occurring in individuals with no history of smoking and alcohol consumption, and having a basaloid subtype without *TP53* mutation. Laboratory data showing that transcriptionally active, integrated HPV-16 DNA persisted in an oral carcinoma cell line having features indistinguishable from those of the primary tumor[43] provide strong evidence for an active role of HPV in carcinogenesis.

Ang et al[44] reported that tumor HPV status is a strong and independent prognostic factor for survival among patients with oropharyngeal cancer. They performed a retrospective analysis of the association between tumor HPV status and survival among patients with stage III or IV oropharyngeal squamous cell carcinoma who were enrolled in a randomized trial comparing accelerated fractionation radiotherapy with standard fractionation radiotherapy, each combined with cisplatin (Radiation Therapy Oncology Group [RTOG] 0129). Proportional hazards models were used to compare the risk of death among patients with HPV-positive cancer and those with HPV-negative cancer. With a median follow-up of 4.8 years, patients with HPV-positive tumors had significantly better 3-year rates of overall survival (OS). After adjustment for age, race, tumor and nodal stage, tobacco exposure, and treatment assignment, patients with HPV-positive tumors had a 58% reduction in the risk of death. These results have been confirmed by others.[45]

Understanding HPV infection and the mechanisms of HPV-induced malignant conversion is essential for developing strategies for preventing HPV infection and virus-associated carcinogenesis, such as blocking expression of its E6 and E7 proteins.

TREATMENT OF RELATIVELY LOCALLY ADVANCED CANCERS

Refinement in surgical resection and reconstructive techniques and advances in radiotherapy planning and delivery technology have produced good outcomes for most patients with early-stage head and neck cancers. Unfortunately, for more locally advanced cancers, the current standard therapy consisting of surgical resection and preoperative or postoperative irradiation achieves poor results in terms of disease control, preservation of organ function, or both. Consequently, there has been a continuous search for better treatment approaches. This quest plus the simplicity of clinical evaluation and a well-characterized pattern of relapse make head and neck carcinomas ideal models for testing the relative efficacy of novel therapy concepts and modalities. For example, most clinical radiobiologic investigations have been conducted in patients with head and neck cancers.

Clinical Radiobiology: Fractionation Schedules

Radiobiologic concepts derived from more than two decades of integrated laboratory and clinical investigations led to the conception of two classes of new fractionation schedules for the treatment of head and neck cancers. These altered fractionation regimens are referred to as *hyperfractionation* and *accelerated fractionation schedules*. Hyperfractionation exploits the difference in fractionation sensitivity between tumors and normal tissues manifesting late morbidity. In contrast, accelerated fractionation attempts to reduce tumor proliferation as a major cause of radiotherapy failure. Although there are many permutations in accelerating radiation treatment, the existing schedules can be conceptually grouped into two categories: pure and hybrid accelerated fractionation regimens, depicting the absence and presence of concurrent changes in other fractionation parameters, respectively.

These radiobiologically sound fractionation regimens have been extensively tested in patients with intermediate and more locally advanced head and neck carcinomas, mainly of the oropharynx. This line of clinical research has concluded. Results of the completed phase III clinical trials have been reviewed,[46,47] and the results and conclusions are briefly reviewed here.

Hyperfractionation

The clinical trial results, most notably those of the European Organization for Research on Treatment of Cancer (EORTC), show a moderate (10% to 15%) but consistent improvement in the local control of T2 to T3, N0 to N1 oropharyngeal carcinomas.[48] The incidence of late toxicity with a 10% to 15% total dose increment delivered twice daily in smaller than standard fraction sizes was within the range observed with conventional fractionation schedules, although none of the studies was designed to test the equivalency of late morbidity.

Accelerated Fractionation

The trial results indicate that mucosal toxicity limits the magnitude of overall time reduction to at most 2 weeks without decreasing the total dose. With *pure accelerated fractionation* (no or minimal change in the total dose and fraction size relative to a conventional schedule), delivery of 10 fractions per week (Vancouver trial[49]) induced severe acute mucositis. Administration of continuous daily irradiation without a weekend break (CAIR trial[50]) caused severe late effects, which were thought to be consequential.

With *hybrid accelerated fractionation*, delivery of three fractions of 1.6 Gy per day, separated by an interval of approximately 6 hours, without reduction of the total dose (EORTC trial[51]) increased late complications such as soft-tissue fibrosis, peripheral neuropathy, and myelopathy. Based on the repair kinetic data obtained from experimental spinal cord and skin models and from human skin, these late morbidities can be ascribed in part to the occurrence of compounding incomplete cellular repair of sublethal injury. A 12-Gy total dose reduction (as in continuous hyperfractionated accelerated radiation therapy [CHART][52]) seemed more than sufficient to offset the compounding incomplete repair associated with the delivery of three fractions per day and thereby resulted in lesser severity of a number of late complications, including skin telangiectasia, mucosal ulceration, and laryngeal edema. However, CHART did not improve tumor control in patients with a variety of locally advanced head and neck carcinomas. This study showed that it is possible to substitute radiation dose by overall time reduction and thereby provide indirect evidence for the importance of tumor clonogenic proliferation in determining local cure by irradiation. Theoretically, this regimen should benefit a subset of patients with rapidly proliferating tumors. Based on subset analyses, the investigators postulated that this subgroup might be those with T3 to T4, well-differentiated carcinomas of the larynx. This study warrants further analysis.

A pure accelerated fractionation regimen delivering six fractions per week (Danish trial[53]) and a hybrid variant by concomitant boost (RTOG trial[54]) yielded improved local control rates for locally advanced head and neck cancers without increasing the morbidity. The Danish trial (DAHANCA 7) randomized a total of 1485 patients eligible for primary irradiation alone to receive 66 Gy to 68 Gy in 33 to 34 fractions given in 5 or 6 fractions per week. The compliance rate to both regimens was high. The incidence of acute severe mucositis and dysphagia was higher in patients receiving 6 fractions per week, but there was no difference in the incidence of late edema or fibrosis. The 5-year actuarial locoregional control rates in 1476 evaluable patients were 70% and 60% for accelerated and conventional regimens, respectively ($p = 0.0005$). The benefit for acceleration resulted primarily from improvement in primary tumor control.

The RTOG randomized trial 90-03 compared the relative efficacy of three altered fractionation regimens with the standard dose of 70 Gy in 35 fractions over 7 weeks.[54] The test

radiation schedules were hyperfractionation (81.6 Gy in 68 fractions over 7 weeks, with 1.2 Gy given twice daily), split-course accelerated fractionation (67.2 Gy in 42 fractions of 1.6 Gy twice daily over 6 weeks, including a 2-week break), and a concomitant boost regimen (72 Gy in 42 fractions over 6 weeks, with 1.8 Gy daily for the first 3.6 weeks and 1.8 Gy [large field] plus 1.5 Gy [boost field], 6 hours apart, for the last 2.4 weeks). Analysis of results for the 1073 patients enrolled showed that the concomitant boost and hyperfractionation regimens yielded significantly higher locoregional control than standard fractionation. The split-course accelerated regimen did not improve locoregional control rates over the standard fractionation regimen. The acute mucosal reactions were more severe in patients receiving altered fractionation regimens, but there was no difference in the complication rates at 6, 12, 18, and 24 months after therapy. With long-term follow up (5 years), only patients treated with hyperfractionation had improved locoregional tumor control and improved OS, without an increase in late toxicity, when compared to standard fractionation.[55]

Conclusions

More than two decades of intensive clinical investigations of altered fractionation schedules have produced conceptually interesting and clinically important findings. Trials addressing hyperfractionation show that this biologically sound regimen yields a moderate but consistent improvement in locoregional control and OS of moderate or more locally advanced HNSCC, with no observed increase in late toxicity.

The results of accelerated fractionation indicate that acute mucosal toxicity limits the magnitude of overall time reduction to at most 2 weeks and that late complications resulting from compounding incomplete repair compromise delivery of three fractions of 1.6 Gy per day without a reduction in total dose. Acceleration by concomitant boost also appears to be associated with a higher rate of late complications. However, acceleration of radiotherapy by delivering six fractions per week yielded significantly improved local tumor control rates relative to standard fractionation without increasing the morbidity in the treatment of predominantly locally advanced carcinomas.

All in all, well-organized clinical trials enrolling more than 6000 patients to test the relative efficacy of various altered fractionation regimens have generated important data. In terms of radiobiological findings, the trial results demonstrated the existence of differential fractionation sensitivity between head and neck carcinomas and late-responding normal tissues and firm evidence that tumor clonogenic proliferation is a major obstacle to curing advanced head and neck cancers with fractionated radiotherapy. Clinically, the results of these trials call for changing radiotherapy practice for the treatment of moderate or advanced head and neck carcinomas. Because of the magnitude of therapeutic gain achieved with six fractions per week, economic and logistic considerations determine the choice of the new standard treatment. For reasons of cost, resource utilization, and patient convenience, many centers have adopted the relatively simple six-fractions-per-week regimen as the standard radiotherapy for patients with intermediate-stage head and neck carcinomas and those with locally advanced cancers either not eligible for protocol studies (having contraindications to chemotherapy or biologically targeted agents) or choosing to receive irradiation alone.

The data open the challenge for conceiving creative approaches to integrate altered fractionation regimens with cytotoxic or biologic agents to further improve the therapeutic outcome. Several concepts have been tested or are undergoing preclinical and clinical testing.

Combination of Radiation with Chemotherapy

Sequential versus Concurrent Radiation and Chemotherapy

Most combined irradiation-chemotherapy regimens tested have evolved empirically by administering drugs found to have some activity against tumors of interest in a dose and time sequence known to be tolerated in a single-modality therapy setting. Meta-analyses of available data of randomized trials in head and neck cancer undertaken a few years ago showed that despite a high initial response rate, multiagent chemotherapy given before radiation treatment (neoadjuvant setting) has a small impact on the locoregional control and survival rates.[56] Concurrent irradiation and chemotherapy yielded an almost 10% higher survival rate relative to irradiation alone.[57] Unfortunately, the complication rates of combined regimens are also higher than those of radiotherapy only.[57]

The Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) Collaborative Group undertook an extensive meta-analysis. The project investigators obtained updated patient data of 93 randomized trials enrolling a total of 17,346 patients. This study revealed tremendous heterogeneity in eligibility criteria and results between studies exploring chemotherapy for patients with nonmetastatic head and neck carcinoma, which made a simple conclusion on the role of chemotherapy difficult. Nonetheless, the analysis revealed a small statistically significant benefit with the addition of chemotherapy to locoregional therapy, which consists of a 4.5% improvement in survival at 5 years. The benefit primarily reflected the favorable effect of concurrent irradiation and chemotherapy, resulting in a 6.5% overall improvement in the survival rate. The study authors conclude that the benefit of concomitant chemotherapy is confirmed and is greater than the benefit of induction chemotherapy. They suggest that future clinical trials should compare concurrent chemotherapy with induction and concurrent chemotherapy to see if the reduction in distant metastasis seen with induction chemotherapy will further improve survival and to determine if induction chemotherapy adversely affects the compliance to concomitant chemoradiation, the most important component of sequential therapy.[58] Unfortunately, to date, in the patient populations studied and with the cytotoxic agents administered in three Phase III clinical trials, there has been no improvement in survival when induction chemotherapy was added to concurrent chemoradiotherapy.[59-61]

Results of many published Phase III trials[62-68] confirm the finding of meta-analyses that chemotherapy given concurrently with irradiation yields better locoregional control and survival rates than irradiation alone in patients with locally advanced HNSCC. Two trials have also shown the benefit of concurrent irradiation and chemotherapy given in the postoperative adjuvant setting.[69,70]

The combined irradiation-chemotherapy regimen most extensively tested is the combination of conventionally fractionated irradiation (70 Gy in 35 fractions over 7 weeks) with cisplatin. In previous trials, cisplatin was given in a dose of 100 mg/m^2, administered during weeks 1, 4, and 7 of radiotherapy (approximately one third of patients were not able to tolerate the last dose). The systemic and mucosal toxicities of such a high-dose, intermittent cisplatin regimen are rather severe. There are four trials showing locoregional control or survival benefit of alternative cisplatin regimens, such as five doses of 20 mg/m^2 over 5 consecutive days or four doses of 25 mg/m^2 over 4 sequential days during weeks 1, 4, and 7[71,72]; weekly fixed doses of 50 mg during the 7- to 9-week course of postoperative radiotherapy[73]; or 6 mg/m^2/day for 5 days each week during the 7-week course of radiotherapy.[68]

Unfortunately, recording and reporting of the late morbidity of combined irradiation and chemotherapy have not been sufficiently consistent and systematic.[74] A thorough report of the long-term results of a French cooperative group (GORTEC) trial reveals that the late complication rate of the combination of irradiation with concurrent carboplatin and fluorouracil was significantly higher than that of irradiation alone.[65] Because of the lack of adequate reporting, controversy still exists about whether the late toxicity of the combination of standard irradiation with 100 mg/m^2 of cisplatin given every 3 weeks may be higher than irradiation alone. It is hoped that longer and more complete follow-up data on late morbidities will be reported in the future. Despite this uncertainty, many oncologists consider 100 mg/m^2 of cisplatin given during weeks 1, 4, and 7 of conventionally fractionated irradiation as the standard of care for patients with locally advanced head and neck carcinomas who are found to be medically fit to receive chemotherapy. The majority of current ECOG and RTOG clinical trials are using 40 mg/m^2 cisplatin given weekly during radiotherapy.

Principles for Optimizing Combined Radiotherapy and Systemic Therapy

A clear understanding of the therapy objective is essential for designing a logical combined-therapy regimen. The purpose of combining irradiation and systemic therapy in the treatment of neoplastic diseases can be to eliminate hematogenous micrometastases that have occurred before initiation of locoregional therapy or to improve the probability of eradicating primary tumors and involved regional nodes. Depending on the pattern of failure, one or both objectives may be desirable in given clinical settings. The primary objective determines the choice of the agents and the timing of drug administration relative to irradiation. If the main aim is to reduce the probability of metastatic relapse, it is logical to select the least toxic agents with proven antitumor activity and administer irradiation and systemic therapy sequentially, rather than concurrently, to minimize direct drug-irradiation interactions that may increase normal tissue toxicity within the radiation treatment volumes. If the major purpose is to increase local tumor control, it is logical to select drugs based on mechanisms of action and administer systemic therapy concurrently with irradiation to maximize drug-radiation interactions. In the latter scenario, therapeutic benefit occurs only when the combined therapy enhances tumor response more than it increases normal-tissue toxicity.

Analysis of the data from the randomized trial RTOG 90-03 on altered fractionations for locally advanced head and neck carcinomas enrolling more than 1000 patients, 60% of whom had stage IV disease, revealed that locoregional relapse is the predominant pattern of failure. Overall, the actuarial locoregional tumor recurrence rate was close to 50%, compared with less than 20% for distant metastasis.[54] Consequently, for the time being, effort should preferentially focus on developing combined therapy aiming at improving locoregional control for patients with locally advanced HNSCC, especially in patients with a more than a 10-pack a year smoking history, HPV-negative cancer, or an oral cavity, hypopharynx, or larynx primary cancer. The finding that concurrent irradiation and systemic therapy improved outcome but that sequential combined therapy did not improve outcome is consistent with this first principle. Such confirmation should be taken into account in the design of future trials.

Despite three decades of clinical research, many scientific questions related to combinations of irradiation and chemotherapy are still not answered. Newer cytotoxic agents with higher efficacy are needed. Factors to be taken into account in selecting agents for combination with irradiation include mechanisms of drug-radiation interaction, pharmacodynamic characteristics, and clinical activity in inducing tumor response in a single-modality therapy setting. A large number of laboratory studies have been undertaken to optimize the combination of irradiation with chemotherapy, particularly using newer cytotoxic and biologic agents such as taxanes, inhibitors of growth factor receptor signaling pathways, and so on.

HIGH-PRECISION RADIOTHERAPY

Advances in computerized radiotherapy planning and delivery technology offered the possibility of conforming irradiation to an irregular tumor target volume (i.e., conformal radiotherapy).[75] It is feasible to reduce the radiation dose to more of the critical normal tissues surrounding the tumor without compromising dose delivery to the intended target volume, resulting in a reduction in morbidity. Reduced toxicity permits escalation of the radiation dose or combining of irradiation with intensive chemotherapy, each of which has the prospect of improving HNSCC control. Basic expertise in anatomy, imaging, and patterns of tumor spread are vital for clinical application of precision radiotherapy.

Precision radiotherapy can be accomplished by the use of an array of x-ray beams individually shaped to conform to the projection of the target, which is referred to as three-dimensional conformal radiation therapy (3DCRT). Technology is also available to modify the intensity of the beams across the irradiated field as an added degree of freedom to enhance the capability of conforming dose distributions in three dimensions. This irradiation technique is called *intensity-modulated radiation therapy* (IMRT). Proton beams offer an even higher magnitude of normal tissue sparing, which is desirable for the treatment of head and neck tumors. Carbon ion beams may offer enhanced normal tissue sparing compared to proton beams, with the added benefit of being biologically more effective, particularly for malignant tumors considered to be resistant to photon and proton irradiation (i.e., hypoxic tumors, inoperable melanoma and salivary gland cancers).

The roles of 3DCRT and, particularly, IMRT in reducing morbidity and perhaps improving the control of squamous cell carcinoma through radiation dose escalation are being tested in a number of medical centers. Results already reveal that these modalities are effective in sparing the parotid glands from receiving a high radiation dose and, thereby, they diminish radiation-induced permanent xerostomia in selected patients.[76-79] Improved OS has also been reported with the use of IMRT.[80]

Single-institution studies testing the role of IMRT in the management of NPC and oropharyngeal cancers have yielded exciting results. In patients with NPC, IMRT was given alone or, for locally advanced stages, in combination with chemotherapy consisting of concurrent cisplatin and adjuvant cisplatin plus 5-fluorouracil.[81] In a series of 67 patients with a median follow-up of 31 months, the 4-year estimates of local progression-free, locoregional progression-free, distant metastasis-free, and OS rates were 98%, 97%, 66%, and 88%, respectively. The worst acute toxicity was grades 1 to 2 in 51 patients (76%), grade 3 in 15 patients (22%), and grade 4 in 1 patient (2%). The worst late morbidity was grade 1 in 20 patients (30%), grade 2 in 15 patients (22%), grade 3 in 7 patients (10%), and grade 4 in 1 patient (2%). Xerostomia was less pronounced than after 3DCRT and decreased with time. At 3 months after IMRT, 8% of patients had no dry mouth, 28% had grade 1 xerostomia, and 64% had grade 2 xerostomia. Of the 41 patients evaluated at 2 years, 66% had no dry mouth and 32% had grade 1 xerostomia, and only 1 patient had grade 2 xerostomia.

In a series of 74 patients with oropharyngeal carcinoma reported by Chao et al,[82] 14 received IMRT alone, 17 had IMRT combined with cisplatin-based chemotherapy, and 43 underwent surgery followed by postoperative IMRT. With a median follow-up of 33 months, the 4-year estimates of locoregional control, distant metastasis-free, disease-free survival (DFS), and OS rates were 87%, 90%, 81%, and 87%, respectively. Grades 1 and 2 cases of late xerostomia were reported for 32 and 9 patients, respectively. Late skin toxicity occurred in three patients (two had grade 1 toxicity, and one had grade 2 toxicity), mucositis in three patients (all had grade 1 toxicity), and trismus in three patients.

Inspired by encouraging single-institution data, a number of prospective multiinstitutional trials addressing the role of IMRT in the treatment of head and neck carcinomas were completed. RTOG 0022 evaluated the efficacy of IMRT in the treatment of 69 patients with T1 to T2, N0 to N1, M0 oropharyngeal cancer. The patients underwent bilateral neck irradiation without concurrent chemotherapy. A dose of 66 Gy in 30 fractions of 2.2 Gy each was administered to the gross tumor planning target volume (PTV), 60 Gy in 30 fractions of 2 Gy each to the intermediate-risk PTV, and 54 Gy in 30 fractions of 1.8 Gy each to the low-risk elective lymph node region PTVs. With a median follow up of 2.8 years, the 2-year estimated locoregional failure rate was 9% (and only 6% in the 49 patients without a major underdose deviation). The maximal late grade 2 or greater toxicity was skin 12%, mucosa 24%, salivary 67%, esophagus 19%, and osteoradionecrosis 6%. The incidence of grade 2 or higher xerostomia was 55% at 6 months, 25% at 12 months, and 16% at 24 months. The authors concluded that IMRT for early-stage oropharyngeal cancer results in high local and regional tumor control rates with lower salivary toxicity when compared with patients treated in previous RTOG clinical trials.[83]

RTOG 0225 evaluated IMRT in the treatment of 68 patients with stage I to IVB NPC (94% were World Health Organization [WHO] type 2 or 3). The PTV for the gross tumor at the primary tumor site and within involved lymph nodes received 70 Gy in 33 fractions of 2.12 Gy each. Regions at risk for subclinical disease and electively treated lymph nodes received 59.4 Gy in 33 fractions of 1.8 Gy each to the PTV. Patients with T2 to T4 primary tumors or with nodal disease beyond N1 category received concurrent cisplatin chemotherapy and adjuvant cisplatin and 5-fluorouracil chemotherapy. The estimated 2-year local progression-free survival (PFS) was 92.6%, regional PFS was 90.8%, local and regional PFS was 89.3%, and the distant metastasis-free survival was 84.7%. The estimated 2-year PFS was 72.7%, and 2-yr OS was 80.2%. Late grade 3 toxicity included esophageal toxicity in 4.7% of patients, mucous membrane toxicity in 3.1%, and xerostomia in 3.1%. The incidence of grade 2 xerostomia at 1 year was 13.5%. Only two patients developed grade 3 xerostomia. No patient developed grade 4 xerostomia. The authors concluded that it is feasible to administer IMRT with or without chemotherapy to patients with NPC and that such treatment is effective with 90% locoregional PFS and minimal grade 3 xerostomia.[84]

Proton beam therapy is being evaluated for patients with locally advanced head and neck cancers.[85-104] Liebsch et al[105] at Massachusetts General Hospital have used proton beam therapy with or without chemotherapy in the treatment of 17 patients with NPC. They escalated the dose to 73.6 Gy by taking advantage of the Bragg peak physical characteristics of the proton beam. With a median follow-up of 43 months, they reported a 3-year relapse-free and OS rate of 91%, which is quite encouraging. Slater et al[106] from Loma Linda University Medical Center treated 29 patients with oropharyngeal carcinoma with proton beam therapy. They were able to escalate the dose to 75.9 Gy in 45 fractions over 5.5 weeks (concomitant boost). With a median follow-up of 28 months, they reported a 2-year locoregional control rate of 92%, DFS rate of 81%, and grade 3 or higher late toxicity of 11%. Proton beam therapy has also been shown to be safe and effective in the treatment of a variety of head and neck malignant tumors located in the region of the skull base adjacent to critical normal tissues, including the eyes, optic nerves, brainstem, and brain. Promising reports are emerging for neuroendocrine tumors of the sinonasal tract, skull base adenoid cystic carcinoma, olfactory neuroblastoma, and sphenoid sinus malignant disease.[107-110] Prospective studies in well-defined patient cohorts are ongoing to determine the outcomes, cost, and value of proton therapy.

Carbon ion therapy holds promise in the treatment of selected head and neck malignant disease. Potential advantages of carbon ion therapy include improved tumor control resulting from even more conformal and precise tumor targeting than photons and protons, thus allowing for dose escalation to the tumor, reduction of dose to normal tissues, and greater radiobiologic effectiveness because of high linear energy transfer (LET), and completion of therapy with at least 50% fewer treatments. Examples include the treatment of inoperable salivary gland malignant tumors and mucosal melanomas. Mizoe et al[111] from the National Institute of Radiological Sciences (NIRS) in Chiba, Japan, treated 8 patients with advanced inoperable salivary gland cancers with carbon ion therapy (64 GyE to 70.2 GyE in 16 to 18 fractions over 4 to 6 weeks). With a median follow-up of 90 months, they report 100% tumor control and no grade 3 or higher late morbidity. Similarly, Castro et al[112] from Lawrence Berkeley Laboratory treated 9 patients with inoperable salivary gland tumors with neon ions (8 patients) or helium ions (1 patient) (52 GyE to 70 GyE, 2 GyE per fraction, four fractions per week). With a median follow-up of 17 months, they reported a 78% tumor control rate, with no grade 3 or higher late effects. These results appear to be better when compared with the RTOG/MRC randomized trial comparing photons with neutrons,[113] but the series are small. Finally, Yanagi et al[114] from NIRS have treated 72 patients with mucosal malignant melanoma of the head and neck with carbon ions (52.8 GyE to 64 GyE in 16 fractions over 4 weeks). With a median follow-up of 49.2 months, they reported no grade 3 or higher late effects and a 5-year local control rate of 84.1%. The 5-year OS and cause-specific survival rates were 27% and 39.6%, respectively.

More developments are needed to fully benefit from these new sophisticated technologies. Challenges to treating the head and neck region with charged particle therapy include the presence of air cavities and dental restorations. Current treatment planning is limited by field size and the need to patch and match scattered proton or carbon ion beams. Full development of intensity-modulated proton and carbon ion pencil beam scanning is well under way, has been found to be feasible, and has been instituted in the clinic. Prospective clinical trials evaluating larger numbers of patients with long-term follow-up are needed to compare the outcomes of photons, protons, and carbon ions. Areas needing improvement to refine margins of coverage include immobilization devices, topographic and biologic tumor imaging to better define target volumes, and quantification of day-to-day anatomic variations occurring during the course of radiotherapy as a result of motion and changes in tumor and normal tissue volume.

Although results of IMRT and proton beam therapy are encouraging, the observation that most recurrences originate from the high-dose region indicates that radiation dose escalation with low LET irradiation alone will improve the tumor control outcome only for a subset of patients. Further advances in the treatment of solid tumors will likely come through application of newer knowledge about tumor biology, as

exemplified by translational research addressing the role of EGFR in tumor progression and as a target for therapeutic intervention and high LET irradiation.

BIOMARKERS AND MOLECULAR TARGETING

Progress in searching for useful markers for early detection of tumor, estimation of tumor burden, prediction of response to therapy, and monitoring of disease progression has been slow. However, some studies of head and neck carcinomas have generated optimism.

A review of the literature data up to a few years ago identified TP53, EGFR and one of its ligands, transforming growth factor-alpha (TGF-α), and cyclin D1 as promising prognostic biomarkers for HNSCC.[115-117] A few studies[118-120] corroborated the prognostic value of EGFR. A study using HNSCC specimens of patients enrolled in a Phase III trial of the RTOG[54] and randomized to receive standard irradiation,[120] for example, revealed no correlation between EGFR expression and T category, N category, American Joint Committee on Cancer (AJCC) stage grouping, and recursive partitioning analysis (RPA) classes[121] (r = –0.07 to 0.17). However, patients with more than median EGFR-expressing tumors, as measured using an image analysis-based immunohistochemical (IA-IHC) assay, were found to have significantly lower OS and PFS rates because of a significantly higher locoregional relapse rate. Multivariate analysis showed that EGFR expression was a strong, independent predictor of survival and of locoregional relapse.

A completed follow-up study, using a validation set of patients enrolled in the same trial, revealed high reproducibility of the IA-IHC assay and confirmed the absence of correlation between EGFR expression and tumor stage and other clinical prognostic variables (r = –0.20 to 0.18). The results validated previous findings that higher tumor EGFR expression predicted worse rates of OS, PFS, and locoregional relapse, with hazard ratios of 1.97, 2.15, and 3.12, respectively. However, the questions of whether EGFR predicts for the risk for metastasis and whether EGFR is a marker for tumor clonogen proliferation have not been resolved.

Recognition of the importance of the ERBB family of tyrosine kinase receptors in coregulating cell proliferation, death, and angiogenesis led to development of several strategies targeting the EGFR signaling pathway for cancer treatment. Two of these strategies, a monoclonal antibody (e.g., cetuximab) and small-molecule kinase inhibitors (e.g., gefitinib, erlotinib) have gone through various stages of preclinical and clinical development for several types of cancers. Several reviews summarize the status of these clinical investigations.[8,9,120,122] Randomized trials of treatment for colorectal adenocarcinoma[123] and HNSCC[124] showed that cetuximab given in combination with irinotecan or cisplatin yielded higher objective response rates (23% and 26%, respectively) than chemotherapy alone. However, the higher response rates for combined therapies have not translated into improved OS rates relative to monotherapy. Two Phase III trials enrolling patients with non–small cell lung cancer showed that gefitinib did not improve the response rate or survival rate when it was added to cisplatin-gemcitabine or carboplatin-paclitaxel doublets.[125,126]

In contrast to the results of combinations of EGFR antagonists with chemotherapy, data regarding the combination of cetuximab with radiotherapy in patients with locally advanced HNSCC are impressive. A completed international Phase III trial (IMCL CP02-9815) revealed that compared with irradiation alone, adding cetuximab to irradiation resulted in a significant improvement in OS and locoregional control rates without increasing mucositis or dysphagia.[127] These findings validate the notion that selective enhancement of the tumor response leading to durable locoregional control can be achieved by "designer drugs" targeting a specific molecular pathway.

Progress has been made in identifying prognostic markers in patients with NPC. The study of Chan et al[128] showed in a series of 170 patients that the posttreatment plasma level of Epstein-Barr virus (EBV) DNA was strongly correlated with PFS and OS rates, more so than the pretreatment titer. For example, the relative risk for NPC recurrence was 11.9% (95% CI, 5.53 to 25.43) for patients with a posttreatment EBV DNA titer, compared with 2.5% (95% CI, 1.14 to 5.7) for patients with higher pretreatment titers of EBV DNA. The positive and negative predictive values for recurrence for higher posttherapy EBV DNA were 83% (58% to 98%) and 98% (76% to 89%), respectively. NRG Oncology (NRG HN001) is evaluating this marker to see if it is useful in identifying high-risk patients for testing more aggressive therapy and monitoring their response to treatment. Eligible patients include those with detectable plasma EBV DNA before treatment. All patients will be treated with 69.96 Gy in 33 fractions with 6 weekly doses of cisplatin 40 mg/m^2. Plasma EBV DNA will be determined again 1 week after completion of treatment. Patients with undetectable plasma EBV DNA will undergo Phase III randomization to either observation or three cycles of cisplatin (80 mg/m^2) and 5-FU (1000 mg/m^2/d) for 4 days by intravenous continuous infusion every 28 days starting 4 weeks after completion of radiation therapy. Patients with detectable plasma EBV DNA will undergo Phase II randomization to either three cycles of cisplatin (80 mg/m^2) and 5-FU (1000 mg/m^2/d) for 4 days by intravenous continuous infusion or four cycles of gemcitabine (1000 mg/m^2) days 1 and 8 and paclitaxel (80 mg/m^2) days 1 and 8 every 21 days starting 4 weeks after completion of radiation therapy.

Tumor HPV status (HPV DNA and p16 expression) as a strong and independent prognostic factor for survival among patients with oropharyngeal cancer has been discussed.[44,45] This appears to be independent of treatment by radiotherapy alone or combined with concurrent chemotherapy.[129] It is possible that patients with HPV-positive tumors are being overtreated with concurrent irradiation and chemotherapy and are experiencing excessive toxicity despite an excellent prognosis. Current studies are evaluating dose de-escalation by reducing the radiotherapy dose, decreasing the cisplatin dose, or replacing cisplatin with cetuximab or some other biologically targeted agent. In the RTOG 1016 clinical trial, patients with HPV-related oropharynx cancer are randomly assigned to either accelerated RT to 70 Gy administered over 6 weeks with concurrent high dose cisplatin (100 mg/m^2) days 1 and 22 or the same IMRT with cetuximab (400 mg/m^2 loading dose pre-IMRT, then 250 mg/m^2 weekly during IMRT and for 1 week after IMRT). In the ECOG 3311 clinical trial, patients with HPV-related oropharynx cancer undergo transoral resection and neck dissection for T1-T2, N0-N2 disease. Low-risk patients (T1-T2, N0-N1, 0-1 positive nodes, negative margins) then undergo observation. Intermediate-risk patients (close margins [<3 mm], <1 mm extracapsular extension, and two to four positive nodes) are randomly assigned to receive either IMRT to 50 Gy in 25 treatments or IMRT to 60 Gy in 30 treatments. High-risk patients (positive margins, >1 mm extracapsular extension, or 5 or more positive nodes) receive IMRT to 66 Gy in 33 treatments with concurrent weekly cisplatin (40 mg/m^2). In the ADEPT clinical trial, coordinated by Washington University School of Medicine, patients with HPV-related oropharynx cancer undergo complete resection with negative margins by transoral surgery and neck dissection. Patients with positive nodes with extracapsular extension are

randomized to 60 Gy in 30 fractions either alone or with concurrent weekly cisplatin 40 mg/m^2.

PREVENTION OF HEAD AND NECK CANCERS

The concept of *field cancerization* was first described by Slaughter et al[130] in 1953 and has long been validated by clinical data. This evolving notion describes diffuse subcellular injury to the epithelium, resulting from interactions between prolonged carcinogen exposure and individuals' genetic profiles, rendering the whole anatomic field at risk for developing invasive cancers through stepwise, progressive accumulation of genetic alterations. It follows that an individual who develops and survives an upper aerodigestive cancer is at a higher risk (i.e., susceptible) for forming a second primary tumor in the same anatomic field during the ensuing years. The field cancerization and multistep carcinogenesis concepts form the basis for research on cancer chemoprevention.

Results of relatively large series revealed that patients cured of their first head and neck cancer had a more than 20% projected lifetime risk of development of a secondary primary tumor. The estimated annual secondary primary tumor development rate ranged from 4% to 6% for at least 8 years after the diagnosis of the first cancer.[131,132] A secondary primary tumor is the leading cause of death in patients with early head and neck cancers.[133]

This patient population has served as a model for addressing the efficacy of *adjuvant chemoprevention* regimens. An initial trial testing the role of *cis*-retinoic acid in preventing secondary primary tumors had yielded encouraging results.[134] Unfortunately, two large, multiinstitutional, randomized trials did not confirm its benefit.[135,136]

Leukoplakia and erythroplakia carry increased risk for transformation into squamous carcinomas. This patient subset has been used as a model to test *chemoprevention of malignant transformation*. The weaknesses of this model are that the natural history of leukoplakia is rather variable, with spontaneous improvement occurring in many cases, and that the malignant transformation rate at 8 years may vary from 18% to 36%, depending on the degree of dysplasia observed histologically.[137] Consequently, large series and prolonged follow-up studies are required to properly test the efficacy of a given primary chemoprevention strategy.

Identification of key genetic changes resulting in development of malignant clones and markers of multistep carcinogenesis will aid in selecting patients with the highest risk for enrollment into chemoprevention trials and thereby in reducing the required sample size. Markers can also serve as intermediate, surrogate endpoints for assessing the efficacy of chemoprevention regimens, and thereby, shorten the length of the required follow-up. Physicians can counsel their patients regarding healthy lifestyle choices, such as abstaining from using tobacco products and alcohol or from engaging in early-age sexual activity with multiple partners (including oral sex practices) and receiving the HPV vaccine. They can also advise them to practice good oral hygiene and eat a diet rich in fresh fruits and vegetables.

SUMMARY

The past two decades have been an exciting era for participation in clinical trials and laboratory research that have produced gratifying progress in understanding and treating head and neck cancer. Advances in molecular biology techniques opened new research avenues yielding new concepts and knowledge, such as the multistep tumor progression model, genetic susceptibility to environmental carcinogen-induced tumorigenesis, processes of virus-induced changes in cellular behavior, and factors and mechanisms governing the radiation response of cells and tissues. Some of the wisdom gained has already found applications in developing novel therapy strategies that have completed or are undergoing preclinical and clinical testing. Examples include altered photon fractionation regimens, charged particle therapy, mechanism- or molecular-oriented combined-therapy modalities, and conformal radiotherapy with photons and charged particles. The basic and translational research efforts have paid off in that the head and neck cancer mortality rate in the United States has declined since the inception of record keeping. For example, the annual death rate for men because of oral cavity and pharyngeal cancers in the United States decreased by an average of 1.9%, 3%, and 1.2% between 1975 and 1993, between 1993 and 2001, and between 2001 and 2010, respectively.[1]

It is likely that the pace of discovery will increase in the coming years. Sensitive methods for detecting occult tumor foci for screening and staging purposes will be developed, and new approaches in characterizing the genetic profile of cancers will accurately depict their individual virulence, predict the therapy response, and guide treatment selection. Optimism about developing rational novel therapy strategies aimed at specific molecular targets to prevent malignant transformation or reverse malignant phenotyping is also increasing. The insights and new technologies gained from further research should have a sizable impact in reducing the mortality rate caused by head and neck cancers.

The accelerated pace of new discoveries and the large number of research directions make it increasingly complex to determine what constitutes the standard therapy for a variety of patient subsets. When several treatment options can yield approximately the same locoregional tumor control rate, other determinants to be taken into account in selecting the treatment of choice include cosmetic and functional outcome, acute and long-term morbidity (quality of life), resource utilization (cost), physician expertise, patient convenience, out-of-pocket costs (transportation, time off work for the patient, family members, and friends, indirect medical costs), and patient preference.

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