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Head and Neck Cancers, Version 1.2015:

Featured Updates to the NCCN Guidelines

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Abstract

These NCCN Guidelines Insights focus on recent updates to the 2015 NCCN Guidelines for Head and Neck (H&N) Cancers. These Insights describe the different types of particle therapy that may be used to treat H&N cancers, in contrast to traditional radiation therapy (RT) with photons (x-ray). Research is ongoing regarding the different types of particle therapy, including protons and carbon ions, with the goals of reducing the long-term side effects from RT and improving the therapeutic index. For the 2015 update, the NCCN H&N Cancers Panel agreed to delete recommendations for neutron therapy for salivary gland cancers, because of its limited availability, which has decreased over the past 2 decades; the small number of patients in the United States who currently receive this treatment; and concerns that the toxicity of neutron therapy may offset potential disease control advantages.

Overview

More than 600,000 cases of head and neck (H&N) cancers occur worldwide, with 300,000 patients dying of the disease each year.[1] The incidence of human papilloma virus (HPV)–related oropharyngeal cancers is increasing, but this specific subset of H&N cancers is associated with improved survivorship and increased long-term survival.[2–7] More than 11,000 new cases of HPV-related H&N cancers occur each year in the United States, with progression-free survival rates anticipated to be more than 85% in patients with a minimal history of smoking.[8] It is important to continue to maintain the excellent rates of disease control obtained in these certain classes of H&N cancers; however, for all patients with H&N cancers, it is equally important to minimize the acute effects of their therapies and the late effects in long-term survivors.

Over the past 15 years, intensity-modulated radiotherapy (IMRT) has displaced other techniques in the treatment of most H&N malignancies.[9–15] Reports indicate that xerostomia has decreased because of the transition to IMRT from older 2-dimensional and 3-dimensional radiotherapy techniques,[9,11] but there are likely some tradeoffs as a result of low-dose redistribution to other surrounding normal tissues. For example, IMRT can create new, unexpected acute toxicities to organs radiated in the beam path.[16,17] In addition, the long-term effects, even with using IMRT, can still result in a substantial decrease in quality of life.[18–23] Few long-term studies of IMRT outcomes are available for longer than 2 to 5 years, but older studies quantify the long-term effects of conventional forms of radiation therapy (RT), either alone or in conjunction with concurrent chemoradiation.[21,24] For example, RTOG 95-01 included patients with oral cavity, oropharyngeal, laryngeal, or hypopharyngeal cancer; the rates of grade 3 to 5 toxicity were 24.9% for patients receiving chemoradiation versus 20.5% for RT alone after more than 9 years.[24] RTOG 91-11 included patients with locally advanced laryngeal cancer; the rates of grade 3 to 5 toxicity were 33% for patients receiving concurrent chemoradiation versus 38% for RT alone after 10 years.[21] Although the toxicity rates of concurrent chemoradiation versus RT alone were not statistically different in either trial, clinicians remain concerned about the potential incremental toxicity burden of adding concurrent chemotherapy to radiation over the very long term that may not be fully measured. Understandably, investigating ways to decrease the long-term toxicity burden from therapy, either radiation alone or concurrent chemoradiation, is a research priority.[15]

Principles Of Radiation Therapy[1]

DEFINITIVE

RT Alone

- Photon or photon/electron therapy or highly conformal radiation therapy techniques
- PTV:
  - High risk: Primary tumor and involved lymph nodes (this includes possible local subclinical infiltration at the primary and at the high-risk level lymph node(s))
    - Fractionation:

- 66 Gy (2.0 Gy/fraction) to 70-70.2 Gy (1.8-2.0 Gy/fraction); daily Monday-Friday in 6-7 weeks[2]

– Low to intermediate risk: Sites of suspected subclinical spread

♦ 44-50 Gy (2.0 Gy/fraction) to 54-63 Gy (1.6-1.8 Gy/fraction) [3]

POSTOPERATIVE

RT

- Preferred interval between resection and postoperative RT is 6 weeks
- Photon or photon/electron therapy
- PTV

– High risk: Adverse features such as positive margins (see SALI-3)

♦ 60-66 Gy (2.0 Gy/fraction); daily Monday-Friday in 6-7 weeks

– Low to intermediate risk: Sites of suspected subclinical spread

♦ 44-50 Gy (2.0 Gy/fraction) to 54-63 Gy (1.6-1.8 Gy/fraction)[3]

Either intensity-modulated RT (IMRT) or 3-D conformal RT is recommended.

[1] See Radiation Techniques (RAD-A) and (Discussion).

[2] For doses >70 Gy, some clinicians feel that the fractionation should be slightly modified (eg, <2.0 Gy/fraction for at least some of the treatment) to minimize toxicity. An additional 2–3 doses can be added depending on the clinical circumstances.

[3] Suggest 44–50 Gy in confromal RT and sequentially planned IMRT or 54–63 Gy with IMRT doser painting technique dependent on dose per fraction).

Most traditional RT therapy uses ionizing photon beams (x-rays). However, particle therapy, including protons, neutrons, and carbon ions, has also been investigated in an effort to decrease acute and late RT toxicities.[25,26] Several commercial machines for particle therapy have only become available in the past decade; therefore, the clinical experience using particle therapies to treat H&N cancers remains limited. Currently, whether particle therapies will significantly decrease acute and long-term toxicity for patients with H&N cancers or whether they will produce equivalent or different rates of tumor control is unknown. A major hindrance at this time to large-scale exploration of particle therapies is that great financial cost is associated with installation of commercial machines for particle therapy and their continued operations.[27] One facility serving a pediatric population reported that two-thirds of their patients received treatment at a financial loss because of the payer mix and decreased reimbursement; patients were nonetheless treated with proton therapy based on a belief in the potential favorable outcomes that would occur in the pediatric population.[28]

Neutron therapy was removed from the pathways for salivary gland cancers in the 2015 version of the NCCN Guidelines for H&N Cancers because of the extreme limitation on the availability of this treatment—one center only in the United States—and its consequently restricted clinical application (see SALI-A, page 849). Although the potential clinical value of neutron therapy for selected cases is recognized, there are lingering toxicity concerns regarding its use, and the NCCN Guidelines are meant to apply to more than 5% of the eligible patients. Although carbon ion therapy is not currently available in the United States,

it is available in Germany and Japan[29]; a few US-based centers are in the early phases of exploration and development of carbon ion therapy. These 3 specific particle therapies, including protons, neutrons, and carbon ions, are described in these NCCN Guidelines Insights. The full version of the NCCN Guidelines for H&N Cancers address all aspects of management for the different types of H&N cancers, including diagnosis, evaluation, staging, primary treatment, surveillance, and therapy for recurrence and metastasis. For a list of all recent revisions, see the "Summary of the Guidelines Updates" in the complete version of these guidelines at NCCN.org.

Particle Therapies

Neutron Therapy

Neutrons were the frst high–linear energy transfer (LET) particles used in clinical RT. The high LET and low oxygen enhancement ratio (OER) of neutrons led physicians to believe that these particles would yield a clinical benefit for cancer therapy. In 1977, results were reported in 133 patients with locally advanced cancers of the H&N. The local control was favorable, and the complications were reported as acceptable.[30] Other promising results finally led to the establishment of other neutron centers around the world. Several neutron therapy trials were associated with reasonable control rates in tumors that were considered to be locally advanced.[31,32] The Edinburgh trial and other multi-institutional trials for H&N cancers reported control rates ranging from 32% to 45%. However, the late effects were somewhat alarming, with late grade 3 to 5 toxicities of up to 40%.[33] The RTOG and Medical Research Council (MRC) conducted a trial for salivary gland tumors comparing fast neutron versus photon therapy. The trial included 25 patients with locally advanced disease. The local control at 10 years was 56% versus 17% in favor of neutron therapy, but no improvement in survival was seen.[34] The pooled analyses of several studies confirmed local control benefits with neutron therapy when compared with photon therapy for advanced salivary gland cancers.[34,35] However, the risk of late effects was high and generally found to continue to increase over time, reaching as much as 20% at 9 years.[34,36] Increased complications were thought to be related to variations in the relative biologic effectiveness (RBE) of neutron therapy and the impact on late responding tissues.[7,37,38] Notably, the efficacy advantage of neutrons compared with photons seemed to be best established for salivary gland cancers. A Cochrane Collaboration systematic review evaluating the efficacy of radiotherapy interventions for oral cavity and oropharyngeal cancer failed to demonstrate any significant difference in survival or disease-control outcomes between neutron and photon therapy.[39]

Arguably, in a field dominated by uncontrolled studies, the RTOG-MRC randomized trial played a critical role in establishing neutron therapy as a potentially more efficacious option for unresectable salivary gland cancers. That being said, it deserves emphasis that by contemporary standards, the RTOG-MRC study had significant methodological limitations that should be considered when interpreting the disease control and survival results. The sample size was small; the distribution of histologic subtypes was heterogenous and not fully balanced (eg, 23% of the patients on the neutron arm had acinic cell carcinoma vs 0% of patients on the photon arm); and other prognostically relevant factors (eg, resectability,

primary versus recurrent disease, tumor size) also varied somewhat between treatment arms. These limitations likely had a smaller impact on the toxicity data, which noted a higher incidence of severe morbidity on the neutron arm (P=.07).

These findings and limitations (ie, concerns that the toxicity of neutron therapy may offset potential disease control advantages) decreased the enthusiasm for neutron therapy research. At one point, there were 8 active neutron centers in the United States; however, almost all of these centers have now closed. The number of centers in Europe has also decreased. However, the neutron center at the University of Washington Medical Center is still open in the United States and is treating a small number of patients with neutron therapy.

For the 2015 update, the NCCN H&N Cancers Panel removed recommendations for neutron therapy for salivary gland cancers from the pathways because of the diminishing demand and closure of all but one center in the United States (see SALI-A, page 849). Although the clinical value of neutron therapy for selected patients is recognized, there are lingering toxicity concerns and the NCCN H&N Cancers Guidelines are meant to apply to recommendations that can be distributed to more than 5% of the eligible patients. Overall, the use of neutron therapy has lost traction over the years because of cost and toxicity considerations, and a lack of widely accepted clinical applications based on the limited amount of randomized trial data that remain specific to salivary gland cancers.

Proton Therapy

Clinicians have long hoped that charged particle therapy, such as protons and carbon ions, would improve the local control of tumors while sparing adjacent normal structures from unnecessary radiation. Protons and carbon ions exhibit a defined Bragg peak of ionization.[40] The proton or carbon ion dose in front of the peak is notably lower, with a very pronounced and rapid falloff of dose after the peak, whereas the megavoltage photon-based therapy (as used in IMRT) and neutrons do not have this unique property.[11] Photon beams deliver relatively higher doses of “falloff” radiation along the beam path, whereas protons or carbon ions “stop” following the peak. The proton or carbon ion beam energy can be modulated so that the peak is sustained at all of the desired depths of penetration across the tumor while minimizing the dose to the immediately adjacent normal tissue. This is accomplished by using a scattered broad beam, with range modulation and a range compensator that conforms the dose to the distal edge of the tumor but increases the relative dose to the organs proximal to the tumor. More recently, in some centers, the energy of the beams is modulated electronically to treat the tumor layer by layer from distal edge to proximal edge while using magnets to scan the beam (discrete spots or continuous lines) throughout the tumor (intensity-modulated proton beam therapy [IMPT], pencil beam scanning).[40]

Only a slight difference is detectable in the RBE between proton and photon therapy, typically set at 1.1. Theoretically, proton therapy should represent a 10% increase in the RBE. However, there are variations in the exact dose calculation with respect to tissue type. Furthermore, the application of these findings with respect to clinical treatment planning algorithms is controversial.[41] Although there is little gain in the RBE, the potential advantage of proton therapy derives from the superior dose distributions obtained, with a decrease of the incidental dose delivered to adjacent normal tissues.[11] The hope is that these

sharper dose distributions might translate into reduced side effects in the normal tissues. In certain situations, these sharper dose distributions might be used to facilitate dose escalation to the tumor while delivering doses to the normal tissues similar to those given with photon-based therapy. The exploitation of the physical dose distribution is the driving force behind the enthusiasm for proton and carbon ion therapies. However, carbon ion therapy offers an additional opportunity to exploit an increased RBE and a dose distribution advantage (see "Carbon Ion Therapy," facing page).[42]

At present, proton therapy is the predominant particle therapy under active clinical investigation in the United States.[25,43–45] Proton therapy has been used to treat oropharyngeal cancers, sinonasal malignancies, and mucosal melanomas, although the clinical data are best established for ocular melanomas and chordomas.[46–51] Single-institution outcome data have been reported for these H&N cancers,[43,47–49,52,53] but the literature does not easily allow direct comparisons between proton therapy and IMRT; historical comparisons warrant cautious interpretation, because improvements in diagnosis and staging evaluations may lead to improvements in reported outcomes independent of therapy. Mindful of these caveats, a recent systematic review and meta-analysis of noncomparative observation studies concluded that patients with malignant diseases of the nasal cavity and paranasal sinuses who received proton therapy seemed to have better outcomes than those receiving photon therapy.[54] A review of proton therapy in patients with H&N cancers was recently published that included 14 retrospective reviews and 4 prospective nonrandomized studies.[25] The 2- to 5-year local control rates were as low as 17.5% for T4 or recurrent paranasal sinus cancers and as high as 95% in other types of tumors.

In older institutional reports, outcomes for proton therapy have been reported for large unresectable H&N cancers, oropharyngeal cancers, sinonasal malignancies, chordomas, and sarcomas of the skull base.[25,53,55–59] For example, proton therapy was used for locally advanced sinonasal malignancies in 102 patients; disease-free survival rates were 49% to 90% at 5 years, depending on whether patients had partial or complete resection.[60] In comparison, conventional RT with photons has been reported to yield disease-free survival rates of 54% in patients with sinonasal malignancies.[61,62] In an older series, more than 500 patients with chordoma and chondrosarcoma were treated with proton therapy, and relapse-free survival rates were reported to be 73% and 98%, respectively, at 5 years, which is considered to be promising in these challenging disease types.[53] These older data from proton therapy were generated in the absence of sophisticated treatment planning and delivery tools currently available, such as IMPT planning systems, on-board image guidance, and technical solutions for motion management.[25,63,64]

Occasional fatal outcomes have been reported with proton therapy, including 3 deaths secondary to brainstem injury.[53,57,65] A recent report from Japan described long-term toxicities after proton therapy in 90 patients with nasal cavity, paranasal sinus, or skull base malignancies.[52] Late toxicities reached grade 3 in 17 patients (19%) and grade 4 in 6 patients (7%) (encephalomyelitis infection in 2 patients, optic nerve disorder in 4 patients). This rate of grade 3 to 4 late toxicity with protons (19%) was similar to the rate reported for conventional RT with photons (16%).[61] Other clinicians have reported low rates of serious

toxicities when using strict dose limits for proton therapy.[47,66] Proton therapy has typically been used to treat patients with the most challenging disease, for which other RT options were not felt to be safe or of any benefit.[47,50,67] Therefore, an accurate comparison of benefits would ideally take place in the controlled setting of randomized clinical trials. An alternative approach may be to develop prospectively maintained databases to raise the quality of institutional reports of clinical experiences.[53] Because of the current lack of data supporting clear or unique indications in H&N cancers for proton therapy, and the limited number of patients who may gain access to this treatment, specific recommendations for proton therapy have yet to be elucidated in the NCCN Guidelines for H&N Cancers.

Carbon Ion Therapy

Carbon ion therapy (also known as *carbon ion RT*, *heavy ion therapy*) uses particles that are more massive than protons or neutrons. The high LET that occurs with carbon ion therapy can precisely target tumors and spare surrounding normal tissue due to the Bragg peak effect (see "Proton Therapy," page 851).[40] Research using carbon ion therapy is ongoing outside of the United States.[68–72] Currently, there is no carbon ion facility in the United States, although public funding has been designated for early developmental efforts.[29] Because of its higher RBE, carbon ion therapy is thought to be promising for tumors traditionally considered resistant to standard RT. Some relatively large institutional case series have reported outcomes in patients with chordomas and chondrosarcomas of the skull base, mucosal melanomas, adenoid cystic carcinomas, salivary gland tumors, and squamous cell carcinomas of the H&N.[71,72] The optimization of carbon ion fractionation schemes and the degree to which carbon ions may be used as a supplement to photon-based RT are areas that require additional controlled investigations. Critical factors, such as accounting for tissue heterodensity and the radiobiological impact of these ions in normal tissues, need further clinical validation. However, even in the limited reports of these institutional experiences, the outcomes are encouraging.[25,69]

Because of the sharp dose distributions, high RBE, and limitations on this very expensive resource, carbon ions have frequently been used as a boost to photon-based therapy or over a shortened treatment time frame. A comprehensive review of the 20-year experience in Chiba, Japan was recently published; one of the major recommendations was the exploration of shorter treatment schedules for H&N cancers, such as 16 fractions.[71] The German experience with an intensity-controlled raster scanning technique developed at the Heidelberg Ion Therapy Center was reported in 118 patients. In these patients with H&N cancers who received photon-based therapy with carbon ion boost, the rate of grade 3 toxicities was less than 5%.[72] In the United States, carbon ion therapy is not yet reimbursable and, because of the lack of access, the NCCN Guidelines for H&N Cancers do not contain specific recommendations for carbon ion therapy.

Summary

These NCCN Guidelines Insights focus on recent updates to the 2015 NCCN Guidelines for H&N Cancers. These Insights describe the major types of particle therapy that may be used to treat H&N cancers, such as proton, neutron, and carbon ion therapy, in contrast to

traditional RT with photons (x-rays). Research is ongoing regarding the different types of particle therapy, with the goal of increasing the tumoricidal effect and/or reducing long-term side effects from RT. Particle therapy is an exciting area of exploration but requires careful evaluation to determine its true clinical benefit. New and exciting advances in RT, such as particle therapy, have initially generated great enthusiasm; however, without robust, well-controlled data to support an advantage in long-term survival and/or toxicity reduction, some of these technologies have lost traction, especially because of the cost. Lessons have been learned from the early neutron experience that can be used to advance current research.

For the 2015 update, the NCCN H&N Cancers Panel agreed to remove the specific recommendations for neutron therapy for salivary gland cancers because of the limited availability and clinical application of this technology, and concerns that the toxicity of neutron therapy may offset potential disease control advantages (see SALI-A, page 849). Although the clinical value of neutron therapy is recognized for selected patients with salivary gland cancers, the NCCN Guidelines for H&N Cancers are meant to be generalizable to greater than 5% of the eligible population. For this reason, specific recommendations for proton and carbon ion therapy also are not currently specified in the guidelines. In regard to the current high level of interest in proton and/or carbon ion therapies, either a potential decrease in treatment toxicity or a safe escalation of the total dose of radiotherapy for certain malignancies would be a worthy goal. Nonetheless, it is important to note that other ongoing, less-costly clinical trials are addressing the safety and efficacy of decreasing the total dose of standard radiotherapy in combination with surgery, concurrent chemotherapy, or induction chemotherapy, with the goal of mitigating late toxicities in patients who have HPV-associated H&N cancers (ECOG 3311, NRG-HN002, ECOG 1308). Biologically based strategies may also be integrated into toxicity reduction; for instance, a national nasopharyngeal cancer trial uses a biologic marker (Epstein-Barr virus serology) to tailor adjuvant treatment for individual patients, thus reducing their overall multimodality-induced toxicity burden (NRG-HN001). Higher quality data for evaluating proton therapy will soon be generated. Large-scale randomized clinical trials of proton therapy in glioblastoma and non–small cell lung cancer (NRG-BN001, RTOG 1308) are ongoing and are expected to advance understanding of the role of proton therapy in the treatment of clinically challenging malignancies. Public funding support for comparative studies of particle and photon therapies will assist in rigorous assessment of these technologies in the future.

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Head and Neck Cancers
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Head and Neck Cancers

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.