Radiotherapy for Head and Neck Cancer

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ABSTRACT

Treatment for patients with head and neck cancer requires a multidisciplinary approach. Radiotherapy is employed as a primary treatment or as an adjuvant to surgery. Each specific subsite dictates the appropriate radiotherapy techniques, fields, dose, and fractionation scheme. Quality of life is also an important issue in the management of head and neck cancer. The radiation-related complications have a tremendous impact on the quality of life. Modern radiotherapy techniques, such as intensity-modulated radiotherapy and image-guided radiotherapy, can offer precise radiation delivery and reduce the dose to the surrounding normal tissues without compromise of target coverage. In the future, efforts should be made in the exploration of novel strategies to improve treatment outcome in patients with head and neck cancer.

KEYWORDS: Radiotherapy, intensity-modulated, head and neck cancer, brachytherapy

Head and neck cancer comprises a heterogeneous group of tumors arising from the upper aerodigestive tract, paranasal sinuses, and salivary and thyroid glands. The optimal management of head and neck cancer requires a multidisciplinary approach. Surgery and radiotherapy are the major treatment modalities.

The major goal of radiotherapy is to achieve local control of the tumor while minimizing damage to the critical organs. Radiotherapy for patients with head and neck cancer is extremely complex and has evolved greatly in the past decade, owing to the advent of conformal and intensity-modulated radiotherapy techniques. Considerable variation in practice policy exists among institutions. The extent of primary tumor and neck lymphadenopathy of various subsites and the pathologic findings dictate the appropriate radiation fields, dose, and fractionation. Customization of the treatment techniques is essential.

For most locally advanced head and neck cancer, surgery and postoperative radiotherapy are complementary, a combination of the two modalities achieving the optimal result. Surgical removal of gross tumor may eliminate the major source of irradiation failure, and radiotherapy may sterilize microscopic tumor spread beyond the surgical margins, which is the major source of recurrence after surgery. Recently, the combination of chemotherapy and radiotherapy has been introduced to increase tumor control and preserve organ integrity.[1–4] Meta-analyses have demonstrated an increased 5-year survival of ~8% with concurrent chemoradiotherapy compared with that for radiotherapy alone.[5,6]

GENERAL MANAGEMENT OF SPECIFIC CANCERS BY REGION

Paranasal Sinuses

These tumors are usually managed by complete surgical resection. Postoperative radiotherapy is preferred for locally advanced primary tumors (T3 or T4 lesions), positive or close surgical margins, and adverse pathologic

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findings (high-grade perineural, lymphatic, and vascular invasion). Definitive radiotherapy or a combination of chemotherapy and radiotherapy may be used for unresectable disease. A higher 5-year local control rate has been reported for patients with paranasal sinus and nasal cavity cancers receiving combination therapy compared with those receiving radiotherapy alone (79% vs. 48%).[7]

Nasal Cavity

Radiotherapy is generally preferred over surgery for carcinoma of the nasal vestibule because of the associated deformity after surgical excision. Surgical excision is performed only in cases of small and superficial lesions. Local control was achieved in 97% of patients treated with definitive radiotherapy.[8] For patients with early-stage carcinoma of the nasal cavity, radiotherapy and surgery are equally effective. For advanced-stage nasal cavity cancers, surgery followed by postoperative radiotherapy is preferred. Locoregional control rates obtained with definitive radiotherapy in patients with early-stage lesions and with combined surgery and postoperative radiotherapy in patients with advanced-stage lesions ranged from 60 to 80%.

Oral Cavity

The oral cavity consists of the upper and lower lips, buccal mucosa, upper and lower gingiva, alveolar ridge, retromolar trigone, floor of the mouth, hard palate, and anterior two-thirds of the tongue. Surgery and radiotherapy are the standard of care for cancers of the oral cavity. The choice of treatment modalities depends on the complications, cosmetic changes, and functional outcomes that the treatment modality is expected to produce. The optimal treatment plan is also dictated by the T and N classification of an individual patient. For early-stage lesions, either radiotherapy or surgery produces a high likelihood of cure, whereas for locally advanced tumors, neither modality by itself is adequate. Combined-modality treatment is generally the treatment of choice for advanced lesions. For some small T3 lesions with no lymphadenopathy, single-modality treatment is sufficient. Chemotherapy has been reported to have a role in the treatment of advanced diseases. Surgery could remove the tumor burden more quickly and cause fewer dental and salivary complications. Advances in reconstruction using microvascular techniques have led to improved functional outcomes for patients with locally advanced disease. Radiotherapy has better anatomic and functional preservation, but it also results in xerostomia, altered taste, and necrosis of soft tissue and bone.

LIP

In early-stage cancers, surgery and radiotherapy are equivalent treatment options in terms of local control. The choice of local treatment modalities is based on the extent of disease, medical status, patient preference, and the anticipated functional and cosmetic results. Some very small or superficial cancers are managed more expeditiously with surgical excision, without resultant functional deformity or poor cosmetic result. Definitive radiotherapy is advocated for a moderately large, infiltrative cancer and is indicated for tumors occupying the commissure because of the difficulty in achieving adequate cosmetic and functional results with surgical excision. External beam radiotherapy, interstitial implants, or both could be used as definitive treatment, depending on the size of the tumors. Interstitial irradiation is suitable for smaller lesions. Postoperative radiotherapy is advised for positive margins, perineural invasion, cervical lymph node metastasis, and locally advanced disease. Elective neck irradiation can be avoided in patients with early-stage disease and a clinically negative neck, whereas patients with advanced or recurrent diseases should have neck irradiation. Local control rates with irradiation exceed 80%, and the 5-year survival rate is in excess of 95%.[9]

BUCCAL MUCOSA

Early-stage tumors of the buccal mucosa are often amenable to either surgery or radiotherapy. For intermediate tumors and those involving the oral commissure, definitive radiotherapy, which has good functional and cosmetic outcomes and a high local control rate, is preferred. For locally advanced lesions involving the bones, the gingiva, and buccogingival sulcus, radical surgery and reconstruction, followed by postoperative radiotherapy, are typically recommended. Postoperative radiotherapy can be started as soon as wound healing is satisfactory, usually 2 to 6 weeks after surgery. A prospective randomized trial evaluating the role of postoperative radiotherapy in patients with stage III and IV carcinoma of the buccal mucosa showed that the 3-year disease-free survival rate was 68% versus 38% for patients with and without postoperative radiotherapy. The 3-year overall survival rates were 94% versus 84%, respectively.[9]

ORAL TONGUE

Small lesions of the oral tongue are generally managed with surgery. For small, posterior located or ill-defined lesions, definitive radiotherapy is preferred. Locally advanced lesions are generally best treated with surgery, followed by radiotherapy. Postoperative radiotherapy is also recommended for close or positive margins and perineural or lymphovascular invasion. In cases that are inoperable, radiotherapy in combination with chemotherapy could be used. For patients receiving definitive radiotherapy, the reported local control rates were 79 to 83% for T1 lesions and 64 to 74% for T2 lesions.[9]

GINGIVA

Because of frequent bone involvement and the risk of bone exposure after irradiating the gingival tumors, surgery is the treatment of choice for carcinoma of the gingiva. Small superficial gingival tumors without bony invasion can be treated with radiotherapy alone. Postoperative radiotherapy is added in patients with locally advanced diseases. When radiotherapy is given, the irradiation portals should encompass the entire hemimandible. For patients with advanced primary lesions or positive neck lymph nodes, the neck lymphatics may be irradiated. The reported local control rates are 71.5% for T1, 70% for T2, and 59% for T3 tumors.[9]

FLOOR OF THE MOUTH

Early-stage lesions of the floor of the mouth are readily managed with surgery or radiotherapy. Definitive radiotherapy can be considered for lesions that invade the tongue but is not favored for lesions that are adherent to the mandible. A combination of surgery and postoperative radiotherapy is recommended for operable advanced-stage diseases, especially for lesions with involvement of the mandible, multiple cervical lymph nodes, and the tongue musculature. For locally advanced, inoperable diseases, a combination of radiotherapy and chemotherapy could serve as an alternative treatment modality. Radiotherapy modalities for carcinomas of the floor of the mouth include external beam radiotherapy, interstitial implants, and intraoral cone irradiation. Interstitial implant and intraoral cone irradiation are suitable for small, superficial, or exophytic tumors. The reported 5-year local control rates were 93% for T1 lesions and 88% for T2 lesions.[9]

RETROMOLAR TRIGONE

Early-stage disease is treated with surgery or radiotherapy. In general, surgical excision is the preferred modality. Locally advanced diseases require surgery and postoperative radiotherapy. The reported ultimate local control rates of patients treated with definitive radiotherapy and surgical salvage of irradiation failure is 100% for T1, 94% for T2, and 92% for T3 tumors.[9]

HARD PALATE

Carcinomas of the hard palate are generally treated with surgical excision. For high-grade mucoepidermoid and adenoid cystic carcinoma, postoperative radiotherapy is added. Due to the relative rarity of tumors of the hard palate, limited information about treatment outcomes is available in published reports.

Nasopharynx

In general, surgical intervention is extremely difficult for nasopharyngeal carcinoma due to the anatomic location and the propensity for early involvement of retropharyngeal lymph nodes. Radiotherapy is the mainstay of treatment, and intensity-modulated radiotherapy is replacing conventional radiotherapy. Although surgery is not advised for the primary nasopharyngeal tumors, neck dissection is advocated for persistent neck lymphadenopathy after radiotherapy. For patients with locoregionally advanced diseases, a randomized Intergroup trial showed that radiotherapy plus concurrent and adjuvant chemotherapy was superior to radiotherapy alone in terms of 5-year progression-free and overall survival rates.[10]

For locally recurrent disease, radiotherapy is also the mainstay of salvage treatment. Because of the rapid fall-off of radiation dose with increasing distance from the radioactive source, brachytherapy with intracavitary insertion or interstitial implants has been used as a boost treatment modality after external beam irradiation in the treatment of primary or recurrent disease.[11–13] In general, brachytherapy is not suitable for nasopharyngeal tumors with intracranial extension.

Oropharynx and Soft Palate

For early-stage tumors of the soft palate, either surgery or definitive radiotherapy has provided excellent local control. Radiotherapy is generally preferred because the treatment results are satisfactory and the functional outcome is probably better. Patients with locally advanced lesions usually undergo surgical excision, followed by postoperative radiotherapy. A recent randomized trial demonstrates that concurrent chemoradiotherapy improved overall survival and locoregional control rates compared with radiotherapy alone and did not statistically increase severe late morbidity.[14] Therefore, concurrent chemoradiotherapy should be considered as an alternative treatment option for locally advanced oropharyngeal cancers.

Tonsillar Region

Early-stage tumors of the tonsillar regions can be treated by surgery or definitive radiotherapy. Primary radiotherapy is the preferred definitive treatment for most T1, T2, and exophytic T3 tumors of the tonsillar regions. Radiotherapy is preferred because the functional outcome is better. To reduce the incidence of xerostomia, the contralateral parotid gland should not be irradiated. For locally advanced lesions in the tonsillar region, surgery combined with postoperative radiotherapy is recommended. For patients treated with definitive radiotherapy and surgical salvage of irradiation failure, the 5-year local control rates for T1 through T4 have been reported to be 92%, 89%, 77%, and 65%, respectively. The 5-year disease-specific survival rates by 1997 American Joint Committee on Cancer stage were as follows: I, 100%; II, 86%; III, 82%; and IVa, 63%.[15] For

advanced disease treated with surgery followed by postoperative radiotherapy, local control was achieved in 94% of T3 lesions and 75% of T4 lesions.[16]

Base of the Tongue

Either surgery or radiotherapy could be used for early lesions of the base of the tongue. In general, the majority of patients are treated with definitive radiotherapy because of the improved functional outcomes and quality of life. For advanced-stage disease, surgery followed by postoperative radiotherapy is traditionally recommended. A nonsurgical approach, such as concurrent chemoradiotherapy for organ preservation, may also be considered as an alternative treatment option. Definitive radiotherapy has achieved a local control rate of ~80 to 90% for T1 to T2 lesions and 70 to 85% for T3 lesions.[17] For locally advanced cancers of the base of the tongue treated with surgery and postoperative radiotherapy, the 7-year local control rates have been reported to be 94% for T3 tumors and 75% for T4 tumors.[16]

Oropharyngeal Wall

Radiotherapy or surgery can be used for early lesions of the pharyngeal wall. Radiotherapy is preferred because it confers less functional impairment and the results are good. Locally advanced lesions are best managed with surgery followed by postoperative radiotherapy. For pharyngeal wall cancers, the reported local control rates after radiotherapy were ~100% for T1, 67 to 92% for T2, 43 to 80% for T3, and 17 to 50% for T4 tumors.[17]

Hypopharynx

The primary goals in the treatment of hypopharyngeal cancer are to maximize the control rates and preserve the swallowing function.

For T1 or T2 carcinomas of the piriform sinus, radiotherapy or surgery alone is preferred. The reported ultimate local control rates in patients receiving radiotherapy alone with surgical salvage were 95% and 91% for T1 and T2 lesions, respectively.[18] A combination of radical surgery and radiotherapy serves as the standard management for locally advanced diseases. Some institutions prefer to use irradiation and reserve radical surgery for salvage with and without preservation of the larynx. A randomized trial of larynx-conserving treatment (induction chemotherapy followed by definitive radiotherapy in patients who showed a complete response to chemotherapy or by surgery in those who did not respond well) by the European Organization for Research in Cancer Therapy (EORTC) showed that the larynx-preserving procedures provided survival rates similar to those of conventional treatment and allowed two thirds of the survivors to retain their larynxes.[19]

Tumors of the posterior pharyngeal wall are usually considered unresectable, and definitive radiotherapy with or without concurrent chemotherapy is preferred. If surgery is selected as the primary therapy, postoperative radiotherapy is usually administered. For patients treated with radiotherapy alone, 5-year local control rates of 70 to 100% for early lesions and 20 to 50% for advanced lesions have been reported.[18]

Larynx

The choice of treatment modality for laryngeal cancer is based on the preservation of speech function and maintenance of the airway. The majority of early-stage laryngeal cancer can be effectively treated with either radiotherapy or surgery.[20,21] In general, definitive radiotherapy is preferred for T1 and T2 glottic tumors.[22,23] Surgery is reserved for salvage after radiotherapy failure. Because early glottic cancers seldom metastasize to the regional lymph nodes, elective irradiation of neck lymphatics is not advised. Five-year local control rates for T1 glottic tumors were 78 to 93% after definitive radiotherapy.[22,24,25] For T2 glottic tumors treated with radiotherapy alone, 5-year local control rates of 72 to 73% have been reported.[22,25] Patients with T3 lesions confined mostly to one side of the larynx are advised about surgery or definitive radiotherapy with surgical salvage. For advanced T3 and T4 glottic tumors, total laryngectomy followed by postoperative radiotherapy is almost always required. Definitive radiotherapy or concurrent chemoradiotherapy is advised for those whose tumors are medically inoperable or who decline to receive laryngectomy. Recently, a combination of chemotherapy and radiotherapy has been used in patients with locally advanced carcinoma of the larynx for larynx preservation, and surgery is reserved for salvage of treatment failure.

Early-stage supraglottic cancers can be managed with surgery or radiotherapy. Either surgery or radiotherapy could allow the voice to be preserved. Results of definitive radiotherapy are comparable with those of patients treated with supraglottic laryngectomies. Compared with glottic cancers, supraglottic cancers have relatively poor response to radiotherapy, with 5-year local control rate of 58% for T1 lesions.[24] Locally advanced supraglottic cancers often require a combination of surgery and postoperative radiotherapy.

Subglottic cancers are relatively rare and are generally managed with surgery. Postoperative radiotherapy is advised in case of cartilage invasion or positive surgical margins.

Salivary Glands

Inoperable primary or previously unirradiated recurrent malignant tumors of the salivary glands can be treated with radiotherapy. In general, the indications

for postoperative radiotherapy include primary T4 and recurrent tumors; high-grade lesions, including adenoid cystic carcinoma; positive or close surgical margins; perineural, vascular invasion; and regional lymph node metastasis. A matched-pair analysis demonstrated that postoperative radiotherapy significantly improved the local control and survival in patients with advanced-stage malignant salivary gland tumors.[26] For patients receiving postoperative radiotherapy, the 5-year local control and survival rates were higher than for those undergoing surgery alone (local control rates 51% vs. 17%; survival rates 51% vs. 10%).

Thyroid Gland

Surgery and radioiodine therapy are the mainstays of treatment for thyroid cancer. Radiotherapy can be considered for certain patients. For patients with differentiated thyroid cancers, the indications for radiotherapy include inoperable lesions, recurrence after maximal radioiodine therapy, tumors showing poor uptake of radioiodine, and bulky residual tumors after surgery, which are unlikely to take up adequate radioiodine to reach a therapeutic radiation dose. For medullary carcinoma, radiotherapy is used when the tumors are inoperable. For anaplastic thyroid cancer, a combination of surgery, irradiation, and chemotherapy yields the best results.

INTENSITY-MODULATED RADIATION THERAPY

Recent advances in radiation physics, computer technology, imaging technology, and radiotherapy facility have dramatically improved the treatment planning and delivery of radiotherapy. Technologic advances such as inverse treatment planning and the multileaf collimator-equipped linear accelerator have led to the successful implementation of intensity-modulated radiation therapy (IMRT). IMRT is an advanced form of three-dimensional conformal radiotherapy using computer-optimized inverse treatment planning and a computer-controlled multileaf collimator. With these techniques, the intensity of radiation can be modulated so that a higher radiation dose can be delivered to the targets with a sharply conformal target volume coverage, while at the same time the dose to the surrounding normal tissues is markedly reduced.[27,28] Therefore, radiotherapy can be delivered in ways that preserve as much of critical organs and functions as possible. IMRT has been prevalent in recent years in the treatment of head and neck cancers,[29] which have proved to be the ideal target for its implementation. In the head and neck region, organ motion is practically negligible. Many radiosensitive critical organs, such as the spinal cord, brain stem, and parotid gland, are in close proximity to the targets. Successful implementation of IMRT requires highly precise patient setup and immobilization, optimal imaging modalities, adequate target volume delineation, and appropriate determination of dose-volume constraints. The optimal fractionation scheme for IMRT has not been conclusively defined, despite extensive research efforts. More research is needed to evaluate different fractionation schemes.

BRACHYTHERAPY

The term *brachytherapy* means treatment with radioactive sources at a short distance from the irradiated target (*brachy* is the Greek word for "short"). The procedure of surgical insertion of radioactive sources or applicators designed to hold the radioactive sources is known as interstitial implantation. Intracavitary brachytherapy consists of inserting applicators that will hold the radioactive sources into a body cavity in close proximity to the targets. The development of computer-controlled remote afterloading devices has the potential to reduce drastically the radiation dose to which radiation oncology staff will be exposed. Iodine-125 seeds are the most commonly used isotope for permanent interstitial brachytherapy. Iridium-192 is the most commonly used radioactive isotope for temporary interstitial and intracavitary brachytherapy.

RADIATION DOSE

The optimal radiation dose depends on the size and location of the primary tumors and the neck lymph nodes. In general, primary tumors and gross lymphadenopathy require a total of 70 Gy or more, with a daily fraction of 2 Gy. Radiation to low-risk neck nodal regions requires a total of 50 Gy or more. For postoperative radiotherapy, higher doses of radiation (60 to 66 Gy) are generally required for microscopic disease to decrease the risk of locoregional failure resulting from interruption of the normal vasculature, scarring, and relative hypoxia in the postoperative tumor bed.

FRACTIONATION

No single fractionation schedule has proved to be optimal for all head and neck cancers. Conventional fractionation consists of daily fractions of 1.8 to 2 Gy, five treatments per week. Attempts to improve the treatment outcomes for head and neck cancers have led to the development of alternative radiotherapy delivery schedules. During the past two decades, two dominant altered fractionation schedules—hyperfractionation and accelerated fractionation—have been under study. The hyperfractionation schedule delivers two or more small-dose fractions on each treatment day and keeps the overall treatment time the same or slightly reduced.

The use of smaller-dose fractions allows a higher biologically effective dose to be delivered to the tumors and increases the tolerance of late-responding normal tissues. Some randomized trials showed that the hyperfractionation schedule was associated with significantly higher locoregional control and survival rates than the corresponding rates of standard fractionation schedule.[3,30] Considering the normal tissue effect, hyperfractionation is associated with more severe acute mucositis, but the incidence of late complications was within the range observed with conventional fractionation schedules.

Accelerated fractionation refers to a schedule in which the overall treatment time is reduced, but the number of dose fractions, total dose, and size of dose per fraction are unchanged or somewhat reduced. The basic rationale for accelerated fractionation is that reduction in overall treatment time decreases the opportunity for tumor cell regeneration during the treatment course. Clinical research on accelerated fractionation showed that the reduction in treatment time yielded a significant improvement in locoregional control and survival rates.[31] The accelerated schedules caused severe acute mucositis but no detectable increase in late complications.

For both hyperfractionation and accelerated fractionation schedules, an interval of 4.5 hours or more between fractions is required for normal tissue repair of sublethal radiation injuries.[32]

DENTAL CARE

Proper dental care before the initiation of radiotherapy is mandatory. Before radiotherapy begins, all patients must be examined by a dentist. The teeth and soft tissue of the oral cavity should be carefully examined. Routine extraction of all teeth within the irradiated volume is not recommended. Only the teeth that do not have long-term viability need to be extracted. Prophylactic antibiotics are prescribed routinely if teeth are extracted before or after radiotherapy. Routine dental follow-up examination is essential during and after the course of radiotherapy. All patients need to be instructed in a good oral hygiene program. Frequent mouth irrigation with a salt and baking soda solution, topical fluoride applications, and use of fluoride-containing toothpaste should be continued permanently after radiotherapy to minimize the risk of dental caries.

COMPLICATIONS

The large treatment volume used in head and neck cancers can induce acute and late complications. Complication rates are increased in patients with concurrent chemotherapy or coexisting medical diseases such as diabetes. With modern three-dimensional conformal radiotherapy techniques, radiation-related complication rates can be reduced.[27,33]

Acute Complications

Acute mucositis reflects primarily the direct damage of the irradiated mucosa and represents the most common dose-limiting side effect of radiotherapy. Patients may experience soreness of throat and mouth. As a preventive measure, patients should be instructed in an individualized oral-hygiene regimen. For definitive radiotherapy, the goal is to achieve mucositis that is patchy or confluent (grade 2 to 3). Simple injected mucosa usually means that the treatment protraction is too long and tumor proliferation during radiotherapy will be too great.[9] Ulcerative mucositis (grade 4), which requires hospitalization or parenteral nutrition support, should be avoided. Pain, generally secondary to mucositis, is also a common acute and subacute complication. Both mucositis and pain usually respond well to conservative medical treatment.

Taste buds lining the tongue may be affected by radiation. The sweet sensation is reported to be affected more than the salty sensation. Although taste changes may recover within a few months after radiotherapy, some patients experience persistent change of taste. These patients should be encouraged to eat foods that still retain some taste sensation and to chew foods longer to allow more contact of the foods with the taste buds.

Due to radiation-induced xerostomia and the subsequent associated changes in the oral pH values and oral flora, oral candidiasis is a common complication during radiotherapy for head and neck cancers. This complication can be effectively controlled with topical or systemic antifungal agents.

Almost all patients will have some degree of acute skin reaction during radiotherapy. The following parameters of radiotherapy may affect the development and severity of skin reactions: total dose, daily fraction size, type of radiation (electron or photon), beam energy, and beam modifiers. Creams or lotions containing steroids can be applied to the skin lesions but should be avoided on areas of moist desquamation to decrease the possibility of superimposed infection. Epilation of irradiated hair-bearing areas, with loss of sweat and sebaceous gland function, usually occurs by the fourth week of treatment.

Laryngeal edema accompanied by hoarseness is a common acute morbidity during radiotherapy. Care should be taken to avoid life-threatening airway obstruction.

Patients tend to have nutritional problems as treatment progresses. Due to loss or impairment of the sense of taste, acute mucositis of the oral cavity and pharynx, pain caused by mucositis, and decreased saliva secretion, oral intake may be compromised in patients who are undergoing radiotherapy for head and neck cancers. Counseling by a dietitian may help by providing well-balanced diet recommendations. Patients can be instructed to eat smaller amounts more often. For

patients who have difficulty chewing and swallowing, liquid or semiliquid meals or foods moistened with soups and sauces are recommended to make eating easier. If the patient does not eat enough food because of severe mucositis, nutritional supplements via nasogastric tube or percutaneous gastrostomy can be considered to meet the dietary demands.

Late Complications

Xerostomia was by far one of the most common radiation-related complications. Xerostomia usually occurs by the third week of radiotherapy and persists after the completion of treatment. The degree of xerostomia is largely dependent on the radiation dose and the volume of the major salivary glands within the radiation fields. Loss of function of salivary glands is usually permanent after radiation doses of 35 Gy.[34] Xerostomia is responsible for difficulty in swallowing, nutritional deficiency, compromised oral hygiene, poor dental condition, altered taste sensation, impaired speech function, and poor sleep quality.[35,36] It can lead to poor quality of life and poor social activity. Many efforts have been made to prevent or treat this complication. Radioprotective agents such as amifostine have been reported to significantly reduce the parenchymal damage to the salivary glands.[37] However, it is still unclear whether administration of amifostine carries a risk of tumor protection.[38] Acupuncture and oral pilocarpine have been reported to be beneficial for xerostomia.[39,40] Surgical transfer of submandibular glands has been attempted to prevent radiation-induced xerostomia.[41] Implementing IMRT for head and neck cancers has been reported to have a positive impact on the reduction of salivary toxicity. The goal in planning is to keep the mean dose to the parotid gland below 26 Gy.[27,33]

Dental caries occurs as a result of altered salivary consistency and decreased amount of saliva. Dental prophylaxis with topical fluoride and good dental care can reduce the incidence of dental problems. The carious teeth should be extracted before radiotherapy. After radiotherapy, the teeth must be maintained in good condition because aggressive extraction of carious teeth predisposes to osteoradionecrosis.

Due to diminished vascular supply, reduced number of osteoblasts and osteoclasts, altered metabolism of bone, and impaired healing ability in response to various injuries, osteoradionecrosis may develop in patients after head and neck irradiation. Osteoradionecrosis typically involves the mandible and the maxilla, and patients may have bone complications varying from simple exposure to severe bone necrosis with ensuing osteomyelitis and intolerable pain.

Brachytherapy applied close to the mandible is also associated with the development of osteoradionecrosis. The risk and severity of osteoradionecrosis are usually related to the radiation dose to the irradiated bones. The incidence of osteoradionecrosis can be reduced with proper dental care. Osteoradionecrosis is usually managed with conservative treatment, likely antibiotics and analgesics. Hyperbaric oxygen can help by stimulating angiogenesis, increasing neovascularization, and enhancing osteoblast and fibroblast activity.[42]

Irradiating the masticator spaces and temporomandibular joint can result in trismus. Trismus occurs as a consequence of fibrosis and contraction of the pterygoid muscles or fibrosis of the temporomandibular joint. Mandible exercise may prevent progression of the trismus. Occasionally, surgical intervention is advised to relieve severe trismus.

Subcutaneous fibrosis of the soft tissues often resulted from use of a large fraction size.[43] Use of daily fractions less than 2 Gy may reduce the incidence of soft tissue fibrosis.

Laryngeal edema may persist after the completion of radiotherapy in patients whose larynxes were included in the irradiated volume. The incidence of persistent laryngeal edema is ~15 to 25%.[44] Greater radiation dose, large field size, large fraction size, and advanced tumor invasion were associated with a higher incidence of laryngeal edema. The incidence of severe laryngeal edema has been reported to be 1.5 to 4.6%.[44] Persistent laryngeal edema after radiotherapy can initially be managed with conservative measures and close follow-up examination. Empirical antibiotics may be used if infection is suspected. Steroids should be used when the airway is significantly compromised. If the laryngeal edema is progressive and refractory to conservative treatment and the primary tumors initially involved the larynx, persistent or recurrent disease should be suspected. Salvage surgery is advised if biopsies are positive.

Chondronecrosis, necrosis of soft tissue, necrosis of skin, stricture of pharynx and larynx, and carotid stenosis occur infrequently.

Neck irradiation can cause hypothyroidism. Radiation fields encompassing the sphenoid sinus, base of skull, and cavernous sinus can result in hypopituitarism.

Chronic otitis media and hearing impairment can occur in patients whose middle and inner ears were irradiated. The incidence of hearing impairment was radiation dose–related and was significantly higher in patients receiving more than 50 Gy to the cochlea.[45] Hearing loss is more common in patients treated with a combination of radiation and cisplatin, which is ototoxic.[46] Formation of cataracts may develop after doses less than 10 Gy. Painful dry eye may be caused by irradiation of the lacrimal glands.

The most severe complications of radiotherapy for head and neck cancer are neurologic complications. Cranial nerve injury, especially to nerves IX to XII, may result from soft tissue fibrosis along the course of the nerves and entrapment in the lateral retroparotid and

parapharyngeal spaces. If the orbit and optic chiasm are irradiated and the radiation dose is not kept under the limits of tolerance, optic nerve injury or radiation retinopathy can occur, and blindness may result. Optic nerve injury can occur after 50 Gy; the incidence increases with large daily fractions.[47] The spinal cord and brain stem are susceptible to high-dose radiation while radiating concave pharyngeal tumors. Transverse radiation myelitis has been reported in some patients as well. With the aid of computed tomography scans, magnetic resonance imaging, and conformal radiotherapy techniques, these devastating complications may be prevented.

A variety of abdominal viscera has been used to reconstruct the alimentary tract after head and neck surgery. One of the major concerns of surgeons is the influence of postoperative radiotherapy on the displaced visceral grafts. Emami et al have compiled and published the normal tissue tolerance doses.[48] These normal tissue tolerance data were defined for uniformly irradiated partial volumes (1/3, 2/3, and 3/3) of the normal tissues and organs for conventional fractionation schedules of 1.8 to 2 Gy per fraction, five fractions a week. The radiation tolerance doses were 45 to 55 Gy for the colon, 50 to 60 Gy for the stomach, and 40 to 50 Gy for the small intestine. A survey of published reports showed a wide range in the normal tissue tolerance of radiation. The radiation tolerance dose of the displaced jejunum has also been reported to be higher than the accepted dose for the small intestine in its native location. McCaffrey et al reported that postoperative radiotherapy with radiation doses of 61 to 64 Gy to patients receiving free jejunal reconstruction of the pharynx and cervical esophagus did not increase the risk of complications.[49] Cole et al documented that postoperative radiotherapy with a total dose of 58 to 63 Gy to patients having resection of advanced head and neck cancer and reconstruction with jejunal autografts did not cause late complications related to the autograft.[50] Further studies are needed to define a reasonable, widely accepted value of normal tissue tolerance of radiation for routine clinical practice.

CONCLUSION

The advent of IMRT has offered excellent precision of radiation delivery. Technical advances in radiotherapy are continuously emerging. Image-guided radiation therapy is a revolutionary technique that delivers real-time, image-guided IMRT. The use of proton therapy will also be increasing as the costs of the facilities are lowered by standardization of manufacture. During the past decade, advances in radiotherapy have improved the treatment outcomes of patients with head and neck cancer. Unfortunately, these improvements have been achieved at the cost of increased morbidity and compromised quality of life. In the future, research will be continued in the exploration of novel strategies to improve survival and quality of life in patients with head and neck cancer.

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