Advances in Radiation Therapy in Nasal and Paranasal Sinus Cancer

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Sinus carcinoma probably expands asymptomatically by filling the air-filled cavity first, before eroding the adjacent bony wall in a centrifugal pattern. The bony partitions between the nasal cavity, sinuses, and orbits are quite thin. In addition, fibroelastic connective tissue, which is considered the most efficient barrier to disease expansion, is present in the periosteum, perichondrium, and dura, but is absent in pathologic studies. Consequently, there is little resistance to the spread of cancer. Most patients present with locally advanced T3 or T4 tumors. Lymph node metastases generally do not occur until the tumor has extended to areas that contain abundant capillary lymphatics. The retropharyngeal, submandibular, and subdigastric lymph nodes are most commonly involved. As distant metastases are found infrequently at presentation, tumor staging is predominantly a function of the locoregional extent of the tumor.

The low incidence rate and great variety of histologic types of sinus carcinoma explain why few centers have extensive experience in treating patients with these tumors. The advanced stage at presentation combined with the complexity of the anatomy and the proximity of the eye, brain, and cranial nerves render radical surgery and radiation therapy delicate, and such treatments are associated with numerous complications.

A Meta-analysis of Treatment Results from 1960 to 1999

One hundred fifty-four articles from 1960 to 1999 were identified and analysed[1). When the global survival data are classified according to the decade of treatment, the survival rates were 28, 36, 43, and 51% during the 1960s, 1970s, 1980s, and 1990s, respectively, and 41% overall. The survival rates for patients with squamous cell carcinoma were 25, 34, 45, and 50% during the 1960s, 1970s, 1980s, and 1990s, respectively (P<0.001), and survival rates improved progressively each decade for patients with maxillary and ethmoid sinus primaries. The treatment modalities used were combined surgery and radiation in 45% of patients, radiation alone in 35% of patients, surgery alone in 15% of patients, and various combinations including chemotherapy in 5% of patients. A progressive improvement was found with all four treatment modalities from the 1960s to the 1990s, with cure rates in the 1990s of 70% for patients treated with surgery alone, 56% for patients who underwent combined surgery and radiation, and 33% for patients who underwent radiotherapy alone (Table 1). The better results of those who underwent surgery are probably a result of a bias in patient selection.

Prophylactic Neck Node Irradiation

Neck lymph metastases are generally infrequent both at the time of presentation and after treatment. In some studies that were weighted heavily toward patients with advanced-stage maxillary squamous cell carcinoma, the rate of neck metastasis at the time of presentation was 20-25%. Several studies have indicated a higher incidence of alveolus and cheek metastases.

Some authors recommend prophylactic ipsilateral cervical chain radiotherapy for large tumors (T4), regardless of their histologic features, and for squamous cell carcinomas involving the infrastructure of the maxillary sinus.

High Precision Radiotherapy

Given that cancers of the nasal cavity and paranasal sinuses are typically irregular in shape and are in close proximity to radiosensitive normal tissues such as the retina, optic nerve, optic chiasm, brainstem, and salivary gland, these tumors sho-

Table 1.

Characteristic	Decade (%)			
	1960	1970s	1980s	1990s
No. of patients	3137	3877	5966	3416
Histology				
Squamous cell carcinoma	25	34	45	50
Glandular carcinoma	42	30	45	60
Adenocarcinoma	46	48	49	50
Undifferentiated carcinoma	23	42	30	28
Site				
Maxillary sinus	26	31	39	45
Ethmoid sinus	27	37	56	51
Nasal cavity	63	54	59	66
T classification				
T1	28	83	87	90
T2	22	53	62	70
T3	10	28	44	44
T4	0	18	19	28
Treatment				
Surgery	36	54	57	70
Surgery and radiotherapy	33	42	54	56
Radiotherapy	21	19	28	33
Chemotherapy	0	21	34	42
Overall	28	36	44	51

uld readily benefit from treatment with conformal and intensity-modulated radiation therapy (IMRT).

1. Volume determination and delineation

An often-repeated dogma of IMRT for head and neck cancer is the critical need for precise target definition. The International Commission on Radiation Units and Measurements (ICRU) 50 and 62 described newer ways in which to define the targets[2)3)]. The gross target volume (GTV) is the volume of the known tumor; the clinical target volume (CTV) is the volume of the suspected microscopic spread; and the planning target volume (PTV) is the marginal volume necessary to account for any variation in the treatment setup and any motion of the organ or patient.

When chemotherapy is delivered before radiation, the GTV should be based on the extent of the tumor before chemotherapy. The CTV is the volume that contains the demonstrable GTV and the subclinical malignant disease to be eliminated. There are two types of subclinical disease: that surrounding the GTV and that at a distance, such as in the regional lymphatics. Defining the CTV surrounding the target is more problematic. Decisions must be made regarding (1) how much expansion should be created around the GTV, (2) whether the expansion should be purely volumetric or anatomic, and (3) whether the expansion should be treated with the same dose as the GTV or with a lower subclinical dose. For the nasal cavity and ethmoid sinuses, the CTV generally includes the nasal cavity, bilateral ethmoid sinuses, medial orbits, nasopharynx, and the pterygopalatine and infratemporal fossae. The CTV for maxillary sinus lesions generally includes the entire maxillary sinus, palate, alveolar ridge, nasal cavity, medial orbits, nasopharynx, and the pterygopalatine and infratemporal fossae. Setup inaccuracy can be reduced substantially by using appropriate immobilization devices, and the motion of organs or patients with head and neck lesions, especially nasal and paranasal sinus lesions, is small; therefore, an additional 3 to 5 mm margin surrounding the CTV is sufficient for the PTV.

2. Biological dose distribution and increased dose intensity

Owing to the highly conformal dose conformation that can be expected with IMRT, fractionation strategies that differ from those used in conventional treatments can be envisaged. In the simultaneous modulated accelerated radiation therapy boost technique initially described by Butler et al., large fractions of 2.4Gy were delivered to the primary PTV (associated with the primary tumor GTV), whereas conventional fractions of 2Gy were delivered to the secondary PTV (associated with the regions at risk of microscopic disease) up to a total dose of 60Gy and 50Gy, respectively. The treatment was completed in 5weeks, which is a moderately shorter treatment time. The term simultaneous integrated boost (SIB) was introduced later to define treatments that delivered different doses per fraction in different target regions.

The delivery of the conventional 2Gy per fraction to the primary target results in a significantly lower dose per fraction to the secondary target, while the delivery of 2Gy per fraction to the lower and intermediate dose volumes enables a higher dose to be delivered per fraction, with as much as 2.4Gy for gross disease. The latter regimen (SIB technique) offers the biological advantage of shortened treatment duration (i.e., 70Gy over 6weeks), which has been shown to significantly increase locoregional control compared with the same dose delivered over 7weeks. The gain resulting from an increase in the equivalent dose can be achieved without an increase in late normal-tissue complications compared with the standard treatment.

3. Parotid gland sparing

The use of IMRT in head and neck cancer reduces the radiation dose to the major salivary glands, particularly the parotid glands. The extent to which this technique preserves salivary flow depends on the volume of salivary tissues receiving a subthreshold dose. It is generally accepted that 50Gy delivered to the entire parotid gland results in xerostomia. Recently, investigators testing conformal techniques designed to achieve parotid sparing have predicted possible threshold doses. Eisbruch et al. measured saliva flow rates for 152 glands. Parotid glands that received a mean dose of less than 26Gy (for stimulated saliva) showed substantial preservation of flow rates with continued improvement through the first year after radiation therapy. Glands receiving higher doses had poor flow rates and little recovery.

Additional factors influencing post-IMRT xerostomia include the oral cavity dose owing to the irradiation of minor salivary glands, the pre-radiation baseline flow, concurrent medications, and the dose to the submandibular glands. The influence of the submandibular glands is often under appreciated. These glands account for 70% of the resting saliva, and intriguing surgical data suggest that transplanting one submandibular gland outside a radiation field results in a significant reduction in xerostomia, even if the other three major glands receive high doses.

A recent randomized trial testing the radioprotector amifostine revealed that 57% of patients in the control arm, all of whom received a minimum of 40Gy to at least 75% of their parotid glands, developed chronic xerostomia.

4. Clinical outcome

The data suggest that geographic misses are uncommon. Disease recurrence has been reported to occur mostly in the high-dose volume. Chao et al. reported that the majority of local disease recurrences in their patients treated with IMRT occurred in CTV1 (the high-dose volume). There was only one marginal failure adjacent to the parotid glands. Dawson et al. also reported that the majority of local-regional recurrences were in field, or in the areas judged to be at high risk for disease recurrence.

Reports have suggested that IMRT does not reduce the rates of acute mucositis, but encouraging data regarding a reduction in the incidence of xerostomia, as well as better recovery of salivary flow over time, have been reported. Data regarding changes in the development of second primaries and other forms of late tissue toxicity will take years to accumulate.

The disease control and patterns of disease recurrence have been reported, and the data are encouraging. However, in these reports, IMRT was often combined with other treatments in a multimodal setting or a mix of patients is described, making these single-institution experiences difficult to interpret.

5. Carcinogenesis

The risk of secondary malignancies after radiotherapy is controversial. One of the reasons for the uncertainty is that patients undergoing radiotherapy for head and neck cancers are at higher risk of secondary tumors because of their particular lifestyle and exposure to tobacco, which could predispose them to such disease. Indeed, this factor could outweigh the radiation risks. There are two reasons why IMRT may result in an increased rate of secondary malignancies. First, IMRT uses more extensive fields, which exposes a larger volume of normal tissue to lower radiation doses. Second, the delivery of a specified dose to the isocenter from modulated fields requires a longer beam time compared with the same dose delivered with a nonmodulated field. The IMRT treatment plan then results in an increase in the number of monitor units by a factor of 2 to 3, increasing the dose outside the boundary of the primary collimator as a result of leakage and scattered radiation. Consequently, the total body dose received is increased substantially. In a comparison between a conventional technique and a slice-by-slice arc rotation technique delivering 70Gy, it was estimated that the equivalent total body dose increased from 242mSv (conventional) to 1,969 mSv (arc technique), resulting in an increase in the risk of secondary malignancies by a factor of 8.

Advances in Head and Neck Cancer

The most significant recent therapeutic advances for treating head and neck squamous cell carcinoma are the validation of altered fractionation, concurrent radiotherapy and chemotherapy, and the introduction of high-precision intensity-modulated radiation therapy. Functional imaging is a very challenging yet extremely promising technique.

References

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