Chapter 91: Radiation Therapy and the Treatment of the Cervical Lymph Nodes

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Treatment of the regional lymph nodes is frequently an integral part of the overall management of malignant tumors of the head and neck. This chapter should therefore be considered in conjunction with the accounts of malignant tumors at specific sites to be found elsewhere in these volumes. Several aspects of radiation treatment specific to management of the lymph nodes are discussed in this chapter:

1. Anatomy and pathology

2. Squamous cell carcinomas

(a) Elective irradiation of clinically normal lymph nodes

(b) Therapeutic irradiation of cancerous lymph nodes

3. Treatment of neck node metastases from an unidentified primary site

4. Salivary gland carcinomas

5. Melanomas

6. Toxicity of radiation therapy of the cervical lymph nodes.

Anatomy and Pathology

In contemplating treatment of the cervical lymph nodes, it is essential to have an understanding of normal anatomic patterns, of the patterns of metastases associated with different malignancies, and of the difficulties in determining whether nodes are affected by metastatic malignancy. Also, certain features peculiar to the lymph node metastases may affect prognosis and influence the choice of treatment.

Normal anatomic patterns

Approximately one third of the more than 500 lymph nodes in the body lie above the clavicles. The pathways of lymph flow have been studied directly by lymphography (Fisch, 1968; Larson et al, 1965) and indirectly by review of the patterns of lymph node metastases observed from cancers arising in different sites (Lindberg, 1972; Molinari et al, 1977). In general, malignant tumors that arise laterally away from the midline spread to ipsilateral lymph node groups. However, tumors that arise at or close to the midline and those originating anywhere in the nasopharynx or posterior third of the tongue may spread contralaterally as a result of the patterns of development and lymphatic flow determined in the embryo (Fisch, 1968). Once normal pathways are interrupted for any reason, contralateral lymphatic spread may occur even when the primary tumor remains well lateralized.

The most important pathway of communication to the contralateral neck is through the submaxillary and upper deep cervical lymph nodes (Fisch, 1968). Other possible routes of lymphatic flow that may become important when normal deep pathways are interrupted include retrograde flow, flow through dermal lymphatics, and lymphaticovenous communications (Larson et al, 1965).

In the lymphographic studies, deep lymphatic vessels underneath the superficial cutaneous fascia in the retroauricular region (Fisch, 1968) or lymphatics in the tongue or floor of the mouth (Larson et al, 1965) were cannulated and injected. From the radiographs obtained, Fisch produced schematic diagrams of the type shown in Fig. 91-1. Although there are several groups of lymph nodes named according to the anatomic structures with which they lie (Rouvière, 1932), the boundaries between the different groups are not distinct.

Both lymphography and neck dissection specimens identify an important group of 20 or more lymph nodes in the upper neck that function as a unit and lie at the junction between the jugular and spinal lymph node systems. These junctional nodes include the regional drainage from much of the nasopharynx, oropharynx, and upper part of the larynx and hypopharynx and also receive the efferent lymphatic vessels from the circle of lymph nodes that lie where the head and neck merge (this circle includes the submental, submaxillary, retropharyngeal, lingual, parotid, retroauricular, and occipital groups). These junctional nodes are often termed *jugulodigastric* or *subdigastric* lymph nodes.

From the junctional group of nodes, two topographically distinct lymph node chains run caudally. The jugular lymph nodes run medially and inferiorly in association with the jugular vein and usually deep to or just anterior to the sternomastoid muscle. The second chain is the posterior cervical or spinal accessory chain that lies in the posterior triangle of the neck, communicating with the junctional lymph nodes superiorly and the nuchal and supraclavicular nodes posteriorly and inferiorly. Fig. 91-2 shows the normal donward and medial pattern of lymph flow as demonstrated by lymphography. The lymph nodes in the paralaryngeal and paratracheal regions are not demonstrated by subcutaneous lymphography, suggesting that lymph nodes from these regions normally flows laterally into the jugular system or downwards into the mediastinum.

Patterns of cervical node metastases

Lindberg (1972) reviewed the locations of clinically metastatic lymph nodes found at the time of diagnosis in 2044 patients with previously untreated squamous cell carcinomas of the head and neck. Abnormal nodes were present in 57% of the patients, and the nodes were assigned for classification to one of 10 node regions (Fig. 91-3). The subdigastric region in this topographical system includes the upper jugular nodes as well as the tonsillar nodes; it approximates the junctional node region described by Fisch (1968). The data reported by Lindberg (1972) have been tabulated in Table 91-1. The subdigastric nodes were the most commonly involved group for all of the primary tumor sites studied. The jugular chain was involved more frequently than the posterior cervical chain, which was important only when the primary carcinoma was situated in the nasopharynx. Contralateral neck node metastases were more common than involvement of the ipsilateral posterior cervical chain. Contralateral nodes were found most commonly in the subdigatric group. Lindberg did not state how many patients had carcinomas that involved the midline, but the rates of contralateral lymph node spread shown in Table 91-1 are similar to those in other reports.

Although clinical observation suggests that the metastatic involvement of the various lymph node regions usually progresses in an orderly way from superior to inferior in the neck, lymph node groups may be bypassed even in the normal lymphogram (Fisch, 1968; Larson et al, 1965). Discontinuous, or "skip" patterns of metastases were noted in 6 of 21 (28%) neck dissection specimens (Toker, 1963), and node metastases occurred lower in the neck after 10 of 34 (29%) negative suprahyoid lymph node dissections (Chu and Strawitz, 1978).

The risk of lymph node involvement by metastatic squamous cell carcinoma varies according to the site of origin of the primary tumor and the tumor size and histologic grade. For most sites in the oral cavity and for the soft palate, glottic larynx, nasal cavity, and paranasal sinuses, the risk increases as the size of the primary tumor increases (Cachin, 1983; Lindberg, 1972). The association between the primary tumor size and nodal status is not so pronounced for other sites. For primary carcinomas of the oropharynx, the risk of lymph node involvement is more than 50%, and the likelihood of advanced nodal disease is about equal for all stages of carcinomas of the base of the tongue or tonsillar fossa (Lindberg, 1972). Carcinomas of the supraglottic larynx, hypopharynx, and nasopharynx are associated with a progressively greater risk of lymph node metastases (about 50% for supraglottic larynx, 75% for hypopharynx, 85% for nasopharynx), and even small primary carcinomas arising in these sites are frequently accompanied by advanced lymph node metastases (Lindberg, 1972).

Assessment of the neck nodes

There are several sources of error in assessing the status of the cervical nodes. Sako et al (1964) suggested that the lower limit of palpability for a lymph node was approximately 0.5 cm diameter in a superficial area of the neck and 1 cm in a deeper area. Some regions of the neck are inaccessible to palpation. Mancuso (1984; 1990) has discussed the potential of computed tomography (CT) and of magnetic resonance imaging (MRI) in assessing neck nodes. Although clinically inaccessible areas can be visualized and criteria for radiologic identification of tumor extension beyond the lymph nodes have been developed, neither CT nor MRI can exclude enlargement of a lymph node due to reactive dysplasia or consistently identify tumor foci in a lymph node that is normal in size. Neither isotope lymphoscintigraphy nor radioimmunoscintigraphy has so far been able to improve clinical accuracy (Soo et al, 1987; Watkinson et al, 1989). Even histologic examination of the nodes is not free from potential error, and serial sections may be needed to find small deposits of carcinoma (Wilkinson and Hause, 1974). Sampling errors are one possible explanation why 4% to 8% of patients develop later tumor recurrence in the neck after nodal dissection, even though no carcinoma had been identified on histologic examination of their radical neck dissection specimens (Decroix and Ghossein, 1981; DeSanto et al, 1982; Strong, 1969).

Histologically positive nodes have been found when the neck was considered negative on palpation, from 4% (Beahrs and Barber, 1962) to 60% (Lyall and Schetlin, 1952), with most reports being in the 20% to 40% range. In one series (DeSanto et al, 1982), a clinically negative neck was as likely to contain multiple histologically positive lymph nodes (13%) as a single positive node (16%). The accuracy of clinical assessment does improve as nodes in the lower neck become involved (Farr and Arthur, 1971). Not all enlarged nodes are involved by metastatic cancer, although the 8% to 35% range of false positives is generally less than that for false negatives (Beahrs and Barber, 1962; Sako et al, 1964) and the rate of false-positive assessments decreases when lymph node masses are larger than about 3 cm in size (Fletcher and Lindberg, 1987). DeSanto et al (1982) found that 14% (49 of 359) of those with a single enlarged node and 4% (8 of 188) of those with multiple clinically abnormal nodes had negative histologic findings.

Prognostic factors associated with lymph node metastases

Prognosis has been correlated with the presence or absence of lymph node metastases and is invariably worse for all sites when lymph nodes are involved. Clinical staging systems subdivide lymph node metastases according to whether the nodes are unilateral or bilateral, single or multiple, and mobile or fixed, and according to size (usually less than or greater than 2 or 3 cm in diameter). Each of these features has prognostic value, with the former category of each of the attributes mentioned having the better prognosis. The International Union Against Cancer (UICC) and the American Joint Committee (AJC) for Staging and End Results Reporting have recently agreed on a common staging system, which should facilitate the comparison of results from different centers. This staging system is based on the absence or presence of single or multiple nodes, laterality, and node size (< 3 cm, 3-6 cm, or > 6 cm). However, inconsistencies between observers and errors in measurement are likely to remain potentially confounding factors in this as in other staging systems (Eapen et al, 1990).

Histopathologic features with prognostic discriminatory value have also been described, including extranodal extension of cancer and nodal plasmacytic inflammatory response (Zoller et al, 1978) and the presence of tumor cell emboli within lymphatics (Richard et al, 1987). The most detrimental factor is extranodal tumor extension, which significantly worsens the prognosis (Cachin et al, 1979; Richard et al, 1987) (Table 91-2). Cachin (1983) found capsular rupture with carcinomas of all sites and with all grades of squamous cell carcinomas, and rupture in even a single node was as significant as rupture in multiple nodes. He identified capsular rupture in 40% of histologically involved lymph nodes that were less than 2 cm in diameter and in 80% of those that were 4 cm or more in diameter. Carter et al (1987) found that the risk of recurrence in the neck was nearly ten times greater in patients with macroscopic transcapsular tumor spread than in those with microscopic or no extranodal cancer extension.

Squamous Cell Carcinomas

Elective irradiation of clinically normal lymph nodes

Elective regional lymph node irradiation (ENI) has enjoyed considerable support because of the relatively high incidence of histologically positive nodes found in patients with clinically normal nodes, and because during follow-up of patients in whom only the primary tumor was treated, an appreciable proportion later demonstrate neck node metastases (Table 91-3). The risk of node involvement at some time in the course of the disease is at least 20% for most primary cancer sites, although wide variations exist between different series.

The elective treatment of clinically normal lymph node groups depends on the following propositions:

1. Elective treatment is more effective than the treatment necessary for patients in whom neck node metastases become apparent after definitive management of the primary carcinoma.

2. ENI is at least as effective as elective lymph node dissection and is not associated with any greater morbidity than dissection.

The evidence in support of both these propositions is mostly indirect and inferential rather than established by direct comparison and formal clinical trials.

In three random trials elective treatment of neck nodes has been compared with therapeutic treatment. Pointon (1982) compared ENI to therapeutic neck dissection. Patients with oral cavity carcinomas were randomized after radiation treatment of the primary tumor. The radiation dose to the whole ipsilateral neck node chain was 5000 centiGray (cGy) given in 15 fractions over 3 weeks. Although fewer patients in the irradiated group subsequently required neck dissection, the survival rates in each group were approximately the same. Vandenbrouck et al (1980) treated 75 patients with primary carcinomas of the oral tongue by interstitial irradiation, and 6 weeks later randomized them to either elective or therapeutic radical neck dissection. When nodes were positive on histologic examination, postoperative radiation was given to the neck. In the group treated by elective dissection 19 of 39 (49%) had histologically positive nodes. Out of the 36 patients who underwent therapeutic dissection the nodes became enlarged in 19 and were histologically abnormal in 17 (47%). The lymph node capsular rupture rate almost doubled, from 13% to 25%, in the therapeutic dissection group, but this normally poor prognostic feature was not reflected in the survival rates, which were almost identical in the two groups. Both these trials suggest that if patients remain under regular observation so that therapeutic dissection can be carried out without delay, there may be no advantage to elective treatment of the neck nodes. However, it should also be noted that therapeutic dissection could not be performed on 2 of the 19 patients who later developed neck node metastases in the series by Vandenbrouch et al (1980) because of the rapidity of nodal growth. A group in India is currently conducting a randomized trial of the value of prophylactic versus therapeutic neck dissection in patients with early-stage carcinoma of the oral tongue (Fakih et al, 1989). The early results favor those undergoing prophylactic dissection.

In a review of the surgical literature, Nahum et al (1977) concluded that the possible benefits of elective neck dissection had not been clearly defined and that most of the papers reviewed suggested that no more than 5% of patients would benefit from elective neck dissection. The mortality attribute to neck dissection is from 1% to 5% (Lee an Krause, 1975; Nahum et al, 1977). In nonrandom series, opinions on the merits of elective dissection vary widely. Farr and Arthur (1971) reported a 5-year survival rate of 33% in patients who were found to have histologically positive nodes at the time of elective dissection, a rate similar both to that of patients with ipsilateral clinically positive nodes at presentation an to that of patients in whom late clinical node involvement occurred. On the other hand, Lee and Krause (1975) found a 48% 5-year survival in those with positive lymph nodes at elective en bloc radical neck dissection, compared to 33% after secondary dissection for late-developing nodes. Discerning the relative merits of the various approaches is difficult because details of the primary tumor stage and site and other factors differ from series to series. Friedman et al (1990) have argued that the improved sensitivity and specificity of CT and/or MRI of the cervical noes suggest that the need for elective treatment of clinically normal nodes should be reassessed. The interpretation of different series will become even more difficult with the introduction of the additional subset of clinically negative but radiologically abnormal lymph nodes. In practice it will also be necessary to review the cost-effectiveness of extensive imaging relative to the physical and monetary costs of elective surgical or radiotherapeutic treatment and the delays in treatment that may occur where access to sophisticate imaging is limited.

Notwithstanding the absence of unequivocal evidence that elective treatment of the neck nodes improves survival and the variable success of early attempts to use ENI systematically (Dancot and Blavier, 1960; Schreiner and Mattick, 1933), several lines of argument are advanced in favor of elective treatment.

According to general radiobiologic principles radiation should be more effective when there are fewer tumor cells. Similarly, the risk of development of adverse prognostic features, such as capsular rupture, increases as the size of a node increases (Cachin, 1983).

Most retrospective series indicate that the survival rate of patients in whom neck node metastases are found some time after the initial treatment of the primary tumor is inferior to that of patients who do not develop such nodes. For example, Farr and Arthur (1971) found that the 5-year survival rate for patients who presented without clinically abnormal nodes was 48%, compared to 25% when nodes were clinically enlarged at presentation and 32% when nodes appeared later. Also, the procedures needed to treat the neck metastases when they do become clinically apparent carry some morbiity and control of the neck nodes may not be achieved (Vermund et al, 1984).

It has been argued that the development of clinically detectable nodes in the neck is associated with an increase in distant metastases and that control of neck node metastases at the earliest possible time may reduce the incidence of distant metastases. Jesse et al (1970) found distant metastases in 11% of those who develope late neck node metastases after presenting with a clinically negative neck, compare to only 3% of those who presented with a single enlarged neck node but who did not experience later recurrence in the neck. Northrop et al (1972) reported distant metastases in only 12% (16 of 134) of those who presented with unilateral lymph nodes and who had no recurrence of cancer in the neck after initial treatment, compare to 24% (11 of 46) of those who suffered recurrence at the site of the original nodes or new metastases elsewhere in the neck.

ENI has been reported to prevent late tumor relapse in two situations in the neck that is clinically negative at the time of presentation. In the first, the patient presents without clinical lymph node metastases and, after ENI, never develops node failure. In the second, the patient presents with one or more clinically abnormal nodes, and after successful treatment of the primary tumor and abnormal nodes plus ENI, no further cancer occurs in cervical node groups that were free of disease at first presentation.

The results of ENI in patients who have no abnormal nodes at presentation are shown in Table 91-4. None of these studies was randomized, and a variety of primary tumor sites and stages were included. However, because ENI appears to be equally effective for all sites, the detailed results from the various series have been pooled here. The reasons why some patients and not others received ENI were usually not stated in the various papers, and policies differed in individual centers over the extent of the neck to be irradiated. Despite these caveats the number of patients who developed late lymph node metastases after ENI is impressively small. When the primary tumor remained controlled, late neck node metastases were found in only 5% (18 of 379) of those who received ENI to the whole neck, and in only 11% (46 of 409) of those in whom part of the neck was treated, compared with a failure rate of 37% (24 of 65) when no neck irradiation was given.

Contralateral lymph nodes developed in only 3% (8 of 237) of those who received bilateral neck irradiation, compared to 25% (53 of 215) of patients who presented with unilateral nodes from primary carcinomas in similar sites but were not treated with ENI (Barkley et al, 1972; Fletcher, 1972). Berger et al (1971) found node metastases in new areas of the neck in 13% (22 of 163) of those who received ENI to part of the neck but in only 3% (7 of 227) of those in whom the whole neck was treated. These results should not be interpreted as an indication that bilateral irradiation of the whole neck is always necessary. O'Sullivan (1988) found that if well-lateralized cancers of the tonsil or oral cavity were selected for treatment with homolateral radiation techniques, the risk of failure in the contralateral neck did not increase (contralateral node relapse in 1 of 82 N0 and in 2 of 34 N1 cases).

From these results it appears that the development of new node metastases in areas of the neck that are clinically normal when the patient is first seen can be kept to about 5% by ENI when the primary tumor site remains controlled. This very low level of late node failure and the notion that prevention of nodal relapse is better than the therapeutic management of nodes that become detectable clinically stimulate continued interest in ENI, especially for patients whose primary tumor is treated by external beam irradiation and in whom the radiation fields can be extended to cover the cervical lymph nodes with minimal increase in morbidity.

Disappointingly little data exists on the possible influence of ENI on survival. Most of the references cited in Table 91-4 do not give survival statistics in a format that permits appropriate analysis. These is also considerable case selection and reports concentrate mostly on whether or not regional node control was achieved an maintained. Consequently, the suggestion that ENI changes only the pattern of disease and not its outcome remains to be refuted.

Information about the most effective radiation dosage for ENI is limited. The first-echelon lymph nodes must usually be irradiated in continuity with the primary carcinoma and consequently receive high doses. Radiation fields have generally been arranged so that a minimum dose of 4000 to 4500 cGy in 4 weeks is given to the lymph nodes at greatest risk. Table 91-5 shows the results of pooling data from various sources. Doses less than 3000 cGy in 3 weeks appear to be relatively ineffective. However, considerable uncertainty exists as to the minimum effective dose, and many of the authors cited in Table 91-5 use different conventions in specifying the radiation dose given. The usually recommended dose of 4500 to 5500 cGy in 4.5 to 5.5 weeks appears reasonable and is accompanied by little morbidity. The most frequent side effect is reduced salivary flow as a result of incidental salivary gland irradiation, but xerostomia is usually seen only after irradiation of primary oropharyngeal or nasopharyngeal carcinomas (see Toxicity of Radiation Treatment of Cervical Nodes). These is no associated mortality, unless inadvertent overdosage is given to the spinal cord. This may be contrasted with the 1% to 5% mortality attributed to neck dissection (Lee and Krause, 1975; Nahum et al, 1977).

The lymph node groups irraiated are determined by the need to encompass the primary carcinoma adequately in the radiation field, by the patterns of lymph node metastases usually associated with different tumor sites (Lindberg, 1972; Molinari et al, 1977), and by anatomic studies of normal lymphatic pathways (Fisch, 1968; Rouviere, 1932). Analysis of tumor failure patterns suggests that there woul be no advantage to extending radiation fields to cover the mediastinal lymph nodes (Merino et al, 1977). Some formal trials comparing the effectiveness of ENI to different areas of the neck have been performed, although their results are not universally accepted. In a study of patients with supraglottic carcinomas treated with 250 kV irradiation, Skolyszewski (1981) observed no lymph node failures if the primary tumor was controlled, with radiation fields from 90 to 120 cm^2 in area. However, smaller fields of 30 to 42 cm^2 were associated with lymph node failure in 9% (7 of 77). This preference for larger radiation fields for supraglottic carcinomas is consistent with the practice of most centers. In a small random trial for patients with stage 1 (T1N0) nasopharyngeal carcinomas, no patients relapsed in the neck nodes alone when cervical radiation had not been given, and only 1 of 34 relapsed after ENI (Ho, 1978). Despite this study, most North American centers recommend ENI to the whole neck in all patients with nasopharyngeal cancer including those with stage 1 disease. The uncertainty about the most appropriate radiation doses and volumes for most sites can be resolved only by carefully designed trials with appropriately matched controls.

The management of a patient who has had ENI and who subsequently develops a recurrence of primary carcinoma is not compromised. It is presumed that the cervical nodes are at risk of "reseeding", and the possibility of synchronous regrowth of unsterilized tumor in the neck nodes as the primary carcinoma recurs cannot be excluded. Some evidence exists that the risk of cervical node metastases from a recurrent primary carcinoma is reduced in patients who have previously had ENI (Mendenhall et al, 1980). However, performing neck node dissection in continuity with resection of the recurrent primary carcinoma is usually advisable.

The decision whether to recommend ENI depends on how the primary carcinoma is to be managed and whether the patient is considered at high risk of nodal metastases. It is a matter of curiosity and perhaps a reflection of the perceived morbidity of the different treatment approaches that ENI often seems to be recommended when the risk of occult nodal metastases is thought to be 10% to 15% or greater, whereas elective neck dissection is generally not suggested until the risk of nodal metastases is more than about 20% to 30%. Table 91-6 presents an outline approach to ENI, based on several sources an reflecting the practice in Toronto. Many variations are possible within these guidlines, and further clinical trials are needed to clarify the benefits of elective treatment of the neck.

Therapeutic irradiation of cancerous lymph nodes

For most primary tumor sites in the head and neck the relative 5-year survival rate when clinically detectable cervical nodes are present at diagnosis is only about 15% to 35% (Cancer Patient Survival Report, 1976). The recognition that there is no inherent difference in radioresponsiveness and radiocurability between the primary carcinoma and its lymph node metastases has led to the use of megavoltage radiation therapy as the sole method of treatment for cervical node metastases in some patients; more commonly this method is combined with neck dissection.

Radiation or neck dissection alone

Fischel (1933) suggested that satisfactory response to radiation occurred only in hyperplastic lymph nodes and not in true metastases. However, Wizenberg et al (1972) reported the successful use of radiation in 113 patients, in all of whom there was histologic proof of lymph node involvement as obtaine by needle biopsy. The overall control rate for the primary tumor and nodes was 52%; failure occurred in the nodes alone in only 8%. Similarly, Hanks et al (1969) failed to control large, multiple, or fixed lymph nodes in only 1 of 69 patients when the primary tumor was controlled. These and many other examples show that radiation can successfully sterilize some lymph node metastases.

The effectiveness of radiation depends on the raiation dose used, the number and size of the involved lymph nodes, and to a lesser extent on the site of the primary carcinoma. Lymph node metastases from carcinomas arising in the nasopharynx or tonsillar fossa appear to respond better to radiation than do metastases from other sites (Bartelink et al, 1982; Fletcher, 1979; Hanks et al, 1969).

Radical radiation doses similar to those used for the primary carcinoma are required. Fewer than 10% of enlarged nodes were controlled by 4000 cGy in 3 to 4 weeks (Horiuchi and Adachi, 1971). Single nodes 3 cm or less in diameter were controlled by 5000 cGy in 5 weeks in fewer than 50% of cases (Northrop et al, 1972) and in 90% of cases by a dose equivalent to 6500 cGy in 6 weeks, with no apparent increase in control by doses above that level (Bataini et al, 1982; Schneider et al, 1975). Bataini et al (1982) observed isolated node failure in only 11% (62 of 575) of those who presented with fixed nodes, although others have described persistent or recurrent tumor in the neck in up to half the patients who presented with fixed or bilateral cervical nodes (Votava et al, 1972). Bernier and Bataini (1986) examined dose-response relationships in cervical node metastases from oropharyngeal and hypopharyngeal and lateral epilaryngeal cancers. There was no clear-cut dose control relationship for nodes smaller than 3 cm in size within the dose range of 5500 cGy to 8000 cGy in 6 weeks equivalent, with an overal control rate of 90% (498 of 551). For nodes 3 to 6 cm in diameter, control was achieved in 86% (77 of 90) by doses of 7000 to 8500 cGy in 6 weeks equivalent, and in 65% (9 of 14) by doses of less than 7000 cGy. For larger nodes over 6 cm, the control was about 75% (32 of 43) for doses above 7500 cGy, and 50% (10 of 20) for doses in the range of 5500 to 7500 cGy in 6 weeks equivalent. Doses such as these may be achieved by boosting the areas of nodal metastases through localized external beam therapy. Bernier and Bataini (1986) favor a technique that employs an additional small boost field within the large field to encompass the primary tumor and regional node groups. However, although Bataini et al (1987a) successfully used high-dose radiation to eradicate neck node metastases and reported that neck surgery could be performed after such doses without undue morbidity, the risks of morbidity following surgery after very high doses of radiation have prompted most centers to treat patients who present with large node masses with doses from 5000 cGy in 5 weeks to about 7000 cGy in 8 weeks, followed by neck dissection. Further radiation is given only if the nodes cannot be excised completely.

The rate of regression of cervical nodes following radiation has been studied by several groups. Bataini et al (1987a) found that the clearance rate of the primary cancer was significantly higher than that for the nodal metastases at the completion of radiation treatment, but that the percentage of cases with resiual disease at the primary or nodal sites was almost the same 2 months after treatment. The larger the node, the slower the clearance rate. Two months after radiation 83% (422 of 507) of nodes less than 3 cm in size had regressed completely, compared with 63% (94 of 148) of nodes 3 to 6 cm in size, and 45% (30 of 67) of nodes larger than 6 cm.

Because some large nodes regress relatively slowly after irradiation, Bataini suggested that salvage surgery be considere at 2 months when the initial size of the node had been less than 6 cm, and at 4 to 5 months when the nodes had been larger than 6 cm. When nodes completely regress, the risk of later nodal failure in some series is low (8% to 17%) (Bartelink et al, 1982; Bataini et al, 1987a). However, others have found that up to about half of the patients with no residual palpable tumor after the irradiation of large node masses still have tumor demonstrated histopathologically if dissection is performed (Goodwin and Chandler, 1978; Northrop et al, 1972). This may be due to differences in the radiation doses given, the different intervals between the completion of radiation and surgery, and the fact that radiation damage to chromosomes is manifest only when a cell progresses to mitosis; cells that have not yet reached mitosis may appear intact when examined microscopically after exposure to radiation. Most authors suggest at least limited dissection of the area of the node masses and preferably functional or radical dissection of the whole ipsilateral neck following the irradiation of large or multiple lymph nodes, except in patients with nasopharyngeal carcinomas for whom such surgery does not appear to be necessary if the nodes regress completely (Jesse and Fletcher, 1977).

Even limited surgical resection of the residual node masses is not possible on some patients. If further treatment is considered appropriate, palliative radiation by implantation of radioactive isotopes is sometimes a convenient method of treatment (Hilaris et al, 1987; Wang, 1985).

The alternative to radiation therapy is neck dissection (see Chapter 92). Following radical neck dissection alone for metastatic squamous cell carcinomas, tumor recurrence in the neck has been reported in about 20 to 30% of those in whom the primary tumor remains controlled (DeSanto et al, 1982; Strong, 1969). This recurrence rate is related to the number of lymph nodes involved and the presence of node capsular rupture (Cachin et al, 1979; Strong, 1969). Recurrences in the neck after previous neck dissection are rarely cured (Fletcher and Evers, 1970; Pearlman, 1979). The appearance of contralateral lymph node metastases after unilateral dissection may also be a problem from primary carcinomas in sites such as the hypopharynx and supraglottic larynx (Marks et al, 1978).

Combined radiation and surgery

Because neck dissection and radiation therapy alone each have limited effectiveness, many centers have adopted policies of planned combined radiation therapy and surgical resection. Radiation therapy may be given either prior to or following neck surgery. Preoperative radiation is administered to reduce the size of the carcinomatous deposits and to decrease the likelihood of regrowth locally or beyond the neck by any irradiated tumor cells not removed at surgery. Preoperative radiation is generally given to a relatively restricted volume that encompasses only the lymph node groups at risk and immediately adjacent tissues. The treatment of the primary carcinoma is not dealt with in this chapter but must also be considered.

High-dose preoperative radiation may increase the morbidity of surgical resection. Increased complication rates for pharyngeal anastomoses have been reported following doses above about 5000 cGy in 5 weeks (Marks et al, 1978), and for soft-tissue healing after subcutaneous doses above about 6000 cGy in 6 to 7 weeks (Mendenhall et al, 1986). When the primary cancer is managed by raiation therapy, there is no evidence that treating clinically positive nodes by preoperative radiation followed by neck dissection decreases the likelihood of successful resection should cancer recur later at the primary site (Mendenhall et al, 1988). Postoperative radiation is intended to control any carcinoma that remains following surgery and lies within the volume irradiated. Postoperative radiation should encompass all of the tissues disturbed at surgery because carcinoma cells may have implanted anywhere within that volume. The volume irradiated after surgery must usually be larger than that for preoperative treatment, and the shielding of sensitive structures such as the larynx and spinal cord may be more difficult. Also, theoretically some neck tissues may be relatively avascular after resection, so tumor cells in those areas may be relatively hypoxic and thus less radiosensitive than well-oxygenated cells. The relative merits of preoperative and postoperative radiation have not yet been resolved, nor is there agreement that combined-modality treatment is better than single-modality treatment.

In one study 348 patints were randomized according to birth date to either radical neck dissection alone or to preoperative radiation of 2000 cGy in 5 fractions ni 1 week to the whole ipsilateral neck, followed by neck dissection (Strong, 1969). The recurrence rate in the neck when the primary carcinoma remained controlled was reduced from 29% in those having surgery to only 18% in those who received radiation additionally. The postoperative complication rate in each group was similar. There was no difference, however, in the survival rates at 3 years. Barkley et al (1972) described decreased failure rates in the neck in virtually all patients with primary carcinomas of the tonsillar fossa, base of tongue, supraglottic larynx, or hypopharynx who received combined therapy (mainly preoperative irradiation of 5000 cGy to 6000 cGy in 5 to 6 weeks to the whole neck, followed by neck dissection, or postoperative radiation of 6000 cGy in 6 weeks). Only for patients who presented with single nodes less than 3 cm in diameter from oropharyngeal carcinomas were neck dissection, radiation alone, and combined treatment equally effective. In an extension of these unrandomized studies, the MD Anderson Hospital group has concluded that combined therapy is indicated for most patients with involved neck nodes, and that preoperative and postoperative irradiation are equally effective (Jesse and Fletcher, 1977).

Some investigators have expressed the opinion that the addition of radiation does not improve the results of neck dissection. In a retrospective analysis of the case material of the Mayo Clinic, DeSanto et al (1982) found that the likelihood of recurrence in the neck was similar whether the patient was treated by neck dissection alone or whether dissection was preceded or followed by radiation doses of 4000 cGy or more delivered within 4 months of surgery. In their nonrandom series Schuller et al (1979) reported that survival and neck node control were no better in those who received preoperative irradiation than in those treated by surgery alone.

It has been suggested that there may be benefit from combined therapy only when carcinoma has extended through the lymph node capsule (Bartelink et al, 1982; Cachin, 1983) and that failure to stratify patients by this parameter may confound the interpretation of studies of combined therapy (Carter et al, 1987; Johnson et al, 1981). Many authors do regard nodal extracapsular tumor extension as an indication for radiation therapy after neck dissection (Cachin, 1983), although others regard any positive finding in a neck dissection as significant and recommend postoperative irradiation to the whole neck with an additional boost to areas where capsular rupture was found (Jesse and Fletcher, 1977; Vandenbrouck et al, 1980). The delivery of radiation after a neck dissection in which histologically involved lymph nodes are found appears to reduce the risk of neck recurrence in most series. The apparent ability of bilateral elective neck irradiation to prevent the appearance of new nodal metastases in the contralateral neck has been discussed previously, and ENI provides a useful alternative to synchronous or staged bilateral neck dissection.

The radiation dose usually recommended for preoperative radiation is 500 cGy in 5 weeks, although higher doses may be needed for large or fixed node masses. The dose recommended postoperatively has frequently been 6000 cGy in 6 weeks to the upper neck, and not less than 5000 cGy in 5 weeks to the lower neck; the higher ose is intended to counter any relative hypoxia in the tissues disturbed by surgery and is possible because problems with postoperative healing are no longer a consideration. However, Suen et al (1980) found that 6000 cGy at the rate of 1000 cGy each week produced unacceptable acute mucositis, fibrosis, and xerostomia; they recommended that no more than 5000 cGy be given over 5 weeks. Others have achieved a postoperative dose of 6500 cGy by reducing the weekly dose rate to 850 or 900 cGy and using a reducing field technique (Amdur et al, 1989).

The optimum interval between surgery and radiation is not known, although intuition suggests that this interval should not be excessive. Vikram et al (1984) reported that when radiation was started within 6 weeks after surgery, only 2% (1 of 53) of those who had had pathologically proven node metastases subsequently developed neck recurrence. When radiation did not commence until more than 6 weeks after surgery, 22% (9 of 41) developed recurrence. Doses were 5000 to 6000 cGy in 5 to 6 weeks to the upper neck and 4500 to 5500 cGy in 4.5 to 5.5 weeks to the lower neck. Although there was some suggestion that radiation doses above 6000 cGy could compensate for any delay longer than 6 weeks, Vikram and his colleagues did not study enough patients to establish this clearly. Amdur et al (1989) delivered a mean dose of 6300 cGy at 185 cGy per day and did not find that intervals ranging from 1 to 10 weeks between surgery and the initiation of irradiation were of major prognostic significance. The optimum interval between preoperative radiation and surgery has not been studied systematically. After short 1-week courses of radiation, the interval is usually only a few days (Strong, 1969). Following higher doses such as 5000 cGy in 5 weeks it is more usual to allow from 4 to 8 weeks to elapse so that the size of the nodes and primary tumor may decrease and the acute inflammatory reaction induced by radiation may settle. Given the evidence that there may be an increased proliferation rate of surviving tumor clonogens during or after irradiation (Peters et al, 1988), this strategy should be reassessed.

It woul be helpful to resolve the various claims for improved control from combined therapy and to establish the optimal radiation doses and timing in controlled clinical trials. In one such trial the Radiation Therapy Oncology Group randomized patients to preoperative radiation (5000 cGy in 5 weeks, surgery 4 to 8 weeks later) or to postoperative radiation

(6000 cGy to primary site, 5000 cGy in 5 weeks to the lower neck, beginning within 4 weeks of surgery) (Kramer et al, 1987). For all tumor sites combined in 277 evaluable patients, locoregional control was significantly better after a median follow-up of 60 months for those patients assigned to receive postoperative radiation (65% versus 48%, p = 0.04), and survival also showed a trend in favor of postoperative radiation (p = 0.10). Rates of severe complications from surgical and radiation therapy were similar overall. In retrospect it is unfortunate that the same radiation dose was not given both preoperatively and postoperatively because the different treatment schedules partly confound the interpretation of the results.

The order in which radiation therapy and surgery are performed is based on the joint decision of the treatment group about how the primary carcinoma should be managed. In Toronto the policy for tumor sites such as the larynx and hypopharynx has generally been one of delayed combined treatment (Harwood and Keane, 1982), with surgical resection being deferred to permit observation of the primary carcinoma and preservation of organs such as the larynx to the greatest extent possible; radiation is usually the initial modality. For cancers of the oral cavity this sequence is reversed because good function can be obtained by reconstructive surgery, and preservation of normal anatomy is a less pressing consideration. Table 91-7 shows a general plan of management for cervical lymph node metastases. Many variations are possible and these are guidelines only.

Experimental treatment methods

A variety of experimental treatment methods have been evaluated or are still undergoing study in efforts to improve locoregional control and cure rates for head and neck cancers. These treatments have been developed in efforts to exploit various facets of tumor and normal tissue biology. None of the treatments mentioned has yet become standard therapy.

The differential rates of cell regeneration between cancers and some normal tissues have prompted studies that use radiation schedules that depart from the conventional single treatment each day and attempt to shorten the overall duration of the course of treatment (Peters et al, 1988).

The recognition that hypoxia produces radioresistance relative to normally oxygenated cells has led to studies of techniques intended to alter the sensitivity of the hypoxic tumor cells or those that use radiation sources that are not so dependent on normal cellular oxygen levels. The likelihood of complete response to radiation has been correlated with the measured oxygen distribution in large cervical lymph nodes (Gatenby et al, 1988). Some of the various experimental techniques studied (most having equivocal results so far) include placing the patient on hyperbaric oxygenation during treatment (Dische, 1979), administering drugs that sensitize hypoxic cells to radiation (Dische, 1989), and treatment with neutron beams that are less oxygen dependent in producing cellular damage (Duncan, 1985).

Another experimental approach currently undergoing extensive trials is the combination of hyperthermia and radiation (Overgaard, 1987; Valdagni et al, 1988).

Although not generally thought of as experimental, the combination of radiation therapy with chemotherapy should be considered in that light. Many trials of such combinations have been reported or are in progress (Stell and Rawson, 1990; Tannock, 1989). Although improved rates of response in both primary cancers and cervical nodes have sometimes been reported with either preradiation chemotherapy (induction or neo-adjuvant chemotherapy) or concurrent radiation and chemotherapy, such improved responses have generally not resulted in improved survival.

Neck Node Metastases from Unidentified Primary Tumors

Despite detailed clinical and radiologic investigations, the primary site remains unidentified in 3% to 9% of patients who present with metastatic cervical lymphadenopathy (Richard and Micheau, 1977). Direct biopsy of the node should be deferred until clinical examination and simple radiologic investigations fail to disclose the primary tumor. However, because additional investigations and a coherent plan of management depend on the histologic diagnosis, biopsy of the abnormal node is necessary when the primary tumor is not apparent. A transcutaneous needle biopsy causes minimal disruption to the neck tissues and should be the first approach, although there are conflicting opinions on whether open biopsy influences the incidence of local tumor recurrence in the neck or survival (McGuirt and McCabe, 1978; Parsons et al, 1985; Razack et al, 1977). Open biopsy should be performed if a lymphoma is suspected or if needle biopsy fails to yield a definitive diagnosis. The most common histologic diagnoses when a primary cancer cannot be identified are squamous cell carcinoma or undifferentiated carcinoma; adenocarcinoma is relatively uncommon (Barrie et al, 1970; Fitzpatrick and Kotalik, 1974; Glynne-Jones et al, 1990; Jesse et al, 1973).

The histologic diagnosis and the site of the metastatic node in the neck together provide additional information that can prompt more intense examination of certain possible primary carcinoma sites and aid in selecting definitive treatment. A single enlarged node was present in the jugulodigastric region in 60% to 75% of patients in several large series (Barrie et al, 1970; Bataini et al, 1987b; Jesse et al, 1973; Richard and Micheau, 1977); the jugulodigastric and midjugular regions account for more than half the tumor sites in most series. Bilateral nodes were found in fewer than 10% of those with an occult primary carcinoma (Barrie et al, 1970; Fried et al, 1975; Jesse et al, 1973). Molinari et al (1977) reviewed the files of over 2500 patients with carcinomas of the head and neck and 600 patients with lymphomas or malignant tumors of the digestive tract, lungs, urogenital system, or breast. From these records they calculated the statistical probabilities of finding clinically abnormal lymph nodes in each of nine zones in the neck. These zones are similar to those used by Lindberg (1972) (see Fig. 91-3). Table 91-8 shows the results of Molinari's analysis for the probabilities of single cervical lymphadenopathy from a squamous cell carcinoma. The most commonly affected node group, the jugulodigastric (subdigastric), was involved with almost equal frequency by nasopharyngeal, oral cavity, oropharyngeal, or hypopharyngeal carcinomas. Isolated upper and midposterior triangle nodes were most likely to be from a nasopharyngeal carcinoma. A single supraclavicular node containing squamous cell carcinoma was much more likely to be associated with a primary bronchogenic carcinoma than with a head and neck primary site.

Any generalization on the most appropriate choice of treatment on the basis of published reports is impossible because of the disparities in the clinical material an the selection of subsets for reporting. Table 91-9 shows the results of representative series, with overall 3-year survival rate being generally between 20% and 40%. In most series the best outcome was achieved when a single node less than 6 cm in size had been foun in the jugulodigastric region. Prognosis was also related to lymph node factors similar to those considered when the primary cancer site is known. Thus prognosis was worse when the nodes were large, or at multiple levels, or fixed (Bataini et al, 1987b; Fried et al, 1975; Jesse et al, 1973). When the node was in the supraclavicular fossa survival rates ranged from only 3% to 20% at 3 years (Fitzpatrick and Kotalik, 1974; Glynne-Jones et al, 1990; Jesse et al, 1973). The prognosis was poor in patients with metastatic adenocarcinoma, wherever the node was located (Barrie et al, 1970).

Proponents of radiation therapy argue that inclusion of the most likely primary mucosal cancer sites and the remainder of the cervical lymph node fields reduces the risk of later presentation of either the primary tumor or new cervical node metastases. The alternative, neck dissection, may sometimes prevent the need for raiation and its side effects, but may be associated with higher rates of late primary cancer or contralateral nodal disease (Table 91-10). In practice, combined therapy is often necessary, either by resection of node masses that do not regress completely with radiation, or by radiation after neck dissection discloses extracapsular spread or multiple node metastases.

Some authors suggest that if radiation is given only to the side of the neck that harbors the presenting lymph node, later treatment of a primary tumor may be compromised. However, in some series many patients were treated with only ipsilateral radiation, with reduced subsequent morbidity as compared to that from bilateral irradiation and irradiation of most possible mucosal primary cancer sites, and resulted in reasonable local control and survival rates (Fitzpatrick and Kotalik, 1974; Glynne-Jones et al, 1990). The risk of contralateral neck failure after unilateral treatment varies from 2% (1 of 58) (Glynne-Jones et al, 1990) to 16% (16 of 97) (Jesse et al, 1973), and these results suggest that bilateral treatment is not necessary in every patient and can be reserved for those with clinical or histopathological features that suggest a high relative risk of bilateral nodal metastases. Opinions differ about whether the late finding of a primary carcinoma in the head or neck worsens the prognosis. Jesse et al (1973) found a 3-year survival of only 31% in patients in whom a primary tumor later appeared, compared to 58% in those in whom the primary site was never found. Others, who treated the lymph nodes principally by surgical dissection, found no such correlation (Barrie et al, 1970).

The guidelines generally followed in Toronto for patients with metastatic squamous cell carcinomas or undifferentiated carcinomas in cervical nodes are as follows:

1. Lymphoepithelioma or poorly differentiated squamous cell carcinoma or anaplastic histology in a high posterior triangle node: treat as primary nasopharyngeal carcinoma.

2. Lymphoepithelioma or poorly differentiated squamous cell carcinomas or anaplastic histology in a jugulodigastric or midjugular node: treat as primary nasopharyngeal carcinoma, but omit larynx shield to avoid shielding unrecognized supraglottic or hypopharyngeal carcinoma.

3. Single, mobile node, less than 6 cm in diameter, well or moderately well-differentiated squamous cell carcinoma, in upper or midjugular chain: radiation therapy to fields that include the ipsilateral tonsillar fossa, posterior tongue, pyriform fossa, and ipsilateral neck nodes. Some physicians prefer to treat these patients with radiation to both sides of the neck and include the nasopharynx, oropharynx, and hypopharynx, accepting that all patients become xerostomic following such irradiation.

4. Multiple, or bilateral nodes: treat as primary nasopharyngeal carcinoma, but omit larynx shield.

5. Consider neck dissection in all patients treated radically who have residual node mass 2 to 3 months after radiation.

6. Supraclavicular node only: palliative irradiation.

7. The radical radiation doses used are usually those that would be given for a stage T1 primary cancer, with additional boost treatment to the region of the metastatic node according to the size of the node. Some authors recommend somewhat lower doses to the mucosa and use doses analogous to those given for elective irradiation of clinically normal cervical lymph nodes (Harper et al, 1990).

Salivary Gland Carcinomas

Following the resection of salivary gland carcinomas, postoperative radiotherapy reduces the incidence of local recurrence at the primary tumor site in high-risk patients (Armstrong et al, 1990; Fu et al, 1977; King and Fletcher, 1971; McNaney et al, 1983; North et al, 1990). There do not appear to be any major differences in radiation response between the different histologic types of malignant salivary gland tumors (Fu et al, 1977; King and Fletcher, 1971).

Lymph node metastases in a patient with a salivary gland carcinoma are a poor prognostic factor, although often such nodes cannot be separated from factors relating to an uncontrolled primary tumor. In one series the 5-year survival rate was only 9% in those who had lymph node metastases at admission, and 17% in those who later developed nodes, compared to 74% for patients who never had node metastases (Spiro et al, 1975). However, following treatment of the primary carcinoma, regional failure in the neck nodes is much less common than recurrence at the primary site or development of distant metastases.

There is considerable variation in the frequency with which different malignant salivary gland tumors metastasize to the cervical lymph nodes. This variation is determined by the salivary gland in which the tumor arises and by the histologic type and grade of the tumor. The overall incidence of lymph node metastases at the time of presentation reported by Rafla-Demetrious (1970) was 24% (43 of 179); there were cervical node metastases from 24% (16 of 66) of parotid carcinomas, 38% (8 of 21) of submandibular and sublingual gland carcinomas, and 20% (19 of 92) of minor salivary gland carcinomas. There were very few node metastases from carcinomas that arose in the palate or paranasal sinuses. These percentages are consistent with the general literature. A detailed study of the location of the lymph nodes involved was possible for 34 of 43 cases (Rafla-Demetrious, 1970), although the number of patients with involvement of more than one node group was not described. The lymph node groups harboring metastases were the submaxillary (20%), subdigastric (44%), upper deep cervical (41%), midjugular (12%), lower jugular (6%), posterior cervical (6%), and preauricular (3%). The incidence of intraparotid node metastases was not described. Contralateral lymph node metastases were not discussed but such metastases from lateralized salivary gland carcinomas are very rare. Spiro et al (1975) reviewed 288 cases of primary carcinoma of the parotid gland and related the histopathology of the primary cancer to the risk of node metastases. Systematic neck dissection was not performed, but 20% of all patients had histologic node involvement at presentation, and involvement became apparent later in 6%. Lymph node metastases occurred in 70% of epidermoid carcinomas, 44% of grade II or III mucoepidermoid carcinomas, 36% of adenocarcinomas, 21% of malignant mixed tumors, 18% of acinic cell carcinomas, and 10% of adenoid cystic carcinomas; no lymph node metastases occurred in grade I mucoepidermoid carcinomas. Node metastases are very common in undifferentiated carcinomas: 80% in the series of Skolnik et al (1977).

The reduction of local-regional failure rates and improvement in survival rates in patients who presented with cervical node metastases and who received postoperative radiation as compared to the rates in those who were not irradiated has been reported from matched-pair analysis (Armstrong et al, 1990) and from comparison with historical controls (King and Fletcher, 1971; North et al, 1990). There have been no randomized trials that address this issue. Armstrong et al (1990) found a lower risk of failure in the regional lymph nodes after a median dose to the neck of 5600 cGy (fractionation not specified) than in those who did not receive radiation, and King and Fletcher (1971) reported recurrence in the neck in only 2 of 48 patients who had received 5000 to 6000 cGy in 5 to 6 weeks. Despite the apparent success of radiation in preventing relapse in the neck in these series it should be noted that in the series reported by Fu et al (1977) the neck was not systematically irradiated if the nodes were clinically normal, only 9% (8 of 86) of patients who did not have initial lymph node metastases subsequently developed such metastases, and in 5 of those 8 patients the primary cancer was not controlled.

However, if it is assumed that a risk of subclinical lymph node metastases of about 20% justifies elective radiation of the regional lymph node groups, a treatment policy may be formulated as follows. Systematic irradiation of the neck nodes is not necessary after complete resection of low-grade mucoepidermoid carcinomas or in patients with small malignant mixed carcinomas, acinic cell carcinomas, or adenoid cystic carcinomas who have no evidence of cervical lymph node metastases. Irradiation of the ipsilateral neck nodes is recommended for:

1. Those for whom postoperative irradiation to the primary site is indicated (any one of the following primary tumor features: unresectable or incompletely resected, ulcerated or fixed, larger than 4 cm, multiple tumor nodules, or seventh cranial nerve dysfunction due to cancer).

2. Those who have histologically positive nodes.

3. Those who have undifferentiated carcinomas, epidermoid carcinomas, grade II or III mucoepidermoid carcinomas, or adenocarcinomas.

It is usual to treat the whole ipsilateral neck, and the radiation doses commonly recommended are 6000 cGy in 6 weeks to the primary site and upper neck and 5000 cGy in 5 weeks to the lower neck, or equivalent doses. Residual unresectable node masses may receive additional boost treatment.

Melanomas

Melanomas of the skin of the head and neck represent about 20% of all cutaneous melanomas. Uncommonly, melanomas may also arise from the mucosa, especially of the oral cavity, nasal cavity, and paranasal sinuses. The likelihood of regional lymph node metastases varies with the type of melanoma: approximately up to 1% for lentigo maligna, 10% for lentigo maligna melanoma, 20% to 30% for superficial spreading melanoma, 30% to 50% for nodular melanoma, and 50% or more for oral cavity and other mucosal primary sites (Chaudhry et al, 1958; Harwood, 1984).

Elective neck dissection reveals microscopic metastases in about 20% to 30% of patients, similar to the rate of development of clinical neck node metastases in those who do not undergo elective dissection (Ames et al, 1976). However, because many believe that therapeutic neck dissection can control the majority of neck node metastases when they become clinically apparent, and the incidence of distant metastases and the survival rates are similar in both electively and therapeutically treated groups, the role of elective neck dissection remains the subject of debate.

Melanomas are not radioresistant, although the role of radiation therapy in the management of both primary and metastatic melanomas is unclear (Harwood and Cummings, 1981). Several radiobiological and clinical studies have suggested that many melanomas respond better to fractional doses of radiation that are higher than the standard doses (Overgaard et al, 1986). Somewhat unexpectedly this observation was not confirmed in the preliminary report of a randomized trial in which patients with measurable melanomatous tumor masses received either 4 treatments, each of 800 cGy, at 7-day intervals in 21 days overall, or 20 treatments, each of 250 cGy, in 26 to 28 days overall at the rate of 5 treatments each week (Sause et al, 1989). The complete and partial response rates to each regimen were similar. Most radiation oncologists have favored treating melanomas with fractional radiation doses of at least 300 cGy or more.

Several recent studies have addressed the role of radiation therapy a an adjuvant to the treatment of regional nodes. Ang et al (1990) treated 35 patients who had had resection of a primary melanoma of the head or neck that extended at least 1.5 mm deep, who did not have palpable lymphadenopathy, and who did not undergo neck dissection. Radiation was given to the tumor bed and at least to the first two echelons of the draining lymphatics in doses of 600 cGy twice a week to a total of 3000 cGy in 2.5 weeks. Only 2 of 35 patients developed recurrence in the regional nodes, and the 2-year crude survival rate was 80%. There was no serious acute or late morbidity. A randomized trial of adjuvant radiation following regional lymphadenectomy for melanoma of the trunk and extremities showed some delay in the median time to recurrence in those who received radiation but no other advantages (Creagen et al, 1978). The radiation schedule used in that trial was 5000 cGy in 28 fractions each of 180 cGy over 10 weeks (split course) and was probably suboptimal in its use of a low daily fractional dose and in its protraction.

There have been several nonrandom studies of adjuvant treatment with large dose-per-fraction radiation schedules combined with limited dissection of regional node metastases in primary or recurrent melanoma. Local control was achieved for the balance of the patient's survival or for at least 2 years in 45 of 48 patients who received radiation doses of 2400 to 3000 cGy in four to five fractions each of 600 cGy over 2.5 weeks (Ang et al, 1990), and in 18 of 22 who were treated with 2400 cGy in three fractions each of 800 cGy over 3 weeks (Harwood and Cummings, 1981). Considerable care must be taken with such schedules to protect the brain and spinal cord from overdosage.

Results such as these suggest that further trials that integrate regional node irradiation in the management of melanomas of the head and neck are warranted.

Toxicity of Radiation Treatment of the Cervical Lymph Nodes

A general account of the biophysiology of radiation therapy is found in Chapter 4. The response of normal tissues to radiation varies according to the organ irradiate, but in general the higher the radiation dose given, the greater is the likelihood of irreversible damage and loss of function. Rubin and Casarett (1968) have presented a detailed account of the response and tolerance of normal tissues. Million et al (1989) have discussed the effect of radiation on several normal tissues in the head and neck. The most significant effects of the radiation doses - 5000 cGy to 6500 cGy in 5 to 6.5 weeks - used most frequently in treating cervical lymph nodes are described in the following paragraphs.

Xerostomia. Fig. 91-4 shows that whenever it is necessary to irradiate the subdigastric nodes and the submaxillary nodes, a substantial part of the parotid and submandibular salivary glands will also be irradiated. Extension of the radiation fields to cover a primary carcinoma in the nasopharynx or oropharynx usually means irradiating the whole of these two major salivary gland pairs. When the major salivary glands receive a dose equivalent to 5000 to 6000 cGy in 5 to 6 weeks, total salivary output decreases during the course of treatment by more than 80% (Marks et al, 1981). The remaining saliva, which comes principally from the sublingual and minor mucosal salivary glands, is sticky and mucoid. Although some symptomatic improvement usually occurs with time, the saliva never returns to normal volume or composition, and artificial salivary substitutes are of limited value. Patients under the age of about 50 yeears can frequently tolerate doses of up to 4500 cGy in 5 weeks without developing permanent symptomatic xerostomia. The shielding of even part of one parotid gland from the radiation beam reduces the severity of xerostomia.

Dental caries and osteoradionecrosis. In addition to the changes in the saliva, the oral bacterial flora are altered and the risk of dental caries is increased (Beumer et al, 1979). The direct effects of high-dose radiation on the mandible and occasionally on the maxilla may lead to osteoradionecrosis in up to 5% of patients, and xerostomia and dental problems increase the risk of necrosis (Larson et al, 1983; Murray et al, 1980). The risk of necrosis is dose related and usually follows the higher doses used to treat a primary carcinoma or metastatic nodes rather than those used for elective neck irradiation.

Soft-tissue damage. Irradiation of the mucosa of the pharynx and oral cavity causes acute radiation mucositis and alteration of taste sensation, which with the decrease in salivary flow leads to dysphagia so that there may be significant weight loss (Donaldson, 1977). Taste sensation is generally recovered but body weight often stabilizes at a level below the pretreatment baseline.

Partial atrophy of the sternomastoid muscle was reported after full neck irradiation to 6600 cGy in 6 weeks (Bagshaw and Thompson, 1971), and excessive soft-tissue morbidity occurred when anterior and posterior opposed neck fields were used to deliver 5500 to 6000 cGy in the midplane of the neck at the rate of 1100 cGy per week (Goffinet et al, 1975). The risk of such side effects can be reduced by using only an anterior field to irradiate the lower neck (Fig. 91-4, A). A given dose of 5000 cGy in 5 weeks appears adequate when there are no clinically detectable nodes in the radiation field, and higher doses need be given only to the small volume where node masses were palpable. Bataini et al (1990) observed severe or moderately severe complications in 9% of 1646 patients and considered that in 3% these complications were due to treatment of neck disease rather than to irradiation of the primary tumor. The most common complication was cervical fibrosis (39 patients, 2%) sometimes associated with cranial nerve palsies affecting especially the hypoglossal nerve. The risk of cranial nerve palsy due to fibrosis was 4% when the dose exceeded 7000 cGy in 6 weeks equivalent compared to 2% for lower doses. The mean delay to the onset of nerve palsy after radiation was 64 months. Complications from coincidental radiation to the larynx for which a tracheostomy was required were seen in 4 patients (0.3%).

Elerding et al (1981) reported abnormal carotid phonoangiograms in 25% of 118 patients who had received various oses of external beam irradiation to the neck and recommended a prospective study of the tolerance of these major arteries. The patency of the carotid arteries prior to irradiation and the presence of any co-morbid factors for arterial damage were not known in Elering's study.

Hypothyroidism. There is a small risk of hypothyroidism after irradiation of the lower neck. Clinically overt hypothyroidism was diagnosed in about 1% and biochemically detectable thyroid abnormalities were found in 10% of patients who received lower neck irradiation of 5000 cGy in 4 weeks (Stone, 1984). Extension of the midline laryngeal shield to the lower border of the lower neck field protects part of the thyroid gland, but such shielding must be omitted if lymph node masses approach the midline in the lower neck. Biochemical thyroid abnormalities were found in 60% (40 of 66) of those who had received radiation to the pituitary gland and hypothalamus in addition to treatment of the lower neck during radiation therapy for nasopharyngeal or paranasal sinus carcinomas (Samaan et al, 1982).

Immunosuppression. It has been suggested that irradiation of lymph nodes may interfere with the immune system and promote dissemination of metastases. Although various disturbances of the immune system do follow irradiation, the majority are temporary, and there is no conclusive evidence that regional irradiation has clinically significant adverse effects on host-tumor interactions (Tubiana, 1981).

Spinal cord. The most serious potential complication of cervical irradiation is spinal cord necrosis. Fig. 91-4 shows that the spinal cord lies under the lymph nodes in the posterior triangle of the neck. Care must be taken to prevent the radiation dose to the cord from exceeding the tolerance limit of about 4500 cGy in 5 weeks. This may be done by shielding the cord from penetrating photon radiation beams and by treating the lymph nodes overlying the cord with less penetrating sources of radiation such as electron beams. Transverse myelitis is a rare complication, but it can be fatal (Abbatucci and Quint, 1989; Bataini et al, 1990; Fitzpatrick and Kotalik, 1974).

Interaction of radiation and surgery. Some degree of morbidity follows planned combined radiation and surgery in about 35% of patients (Joseph and Shumrick, 1973; Marcial et al, 1982); about 10% to 20% of such complications are rated serious (Cachin and Eschewege, 1975; Kramer et al, 1987; Marcial et al, 1982). Careful attention to radiation dose schedules and to surgical technique usually can keep serious complications to a level low enough to allow combined therapy to offer a net gain in the carefully defined situations discussed earlier in this chapter. In a randomized prospective trial comparing primary surgical resection with resection 4 to 6 weeks after administering 5000 cGy in 5 weeks for advanced carcinomas of the oral cavity, oropharynx, supraglottic larynx, and hypopharynx, there was no substantial increase in the surgical morbidity, mortality, or length of hospital stay in the combined treatment group (Marcial et al, 1982). In a further discussion of this study, Kramer et al (1987) reported that the rates of severe treatment complications in those who received 5000 cGy in 5 weeks preoperatively were 14% (18 of 133) for radiation complications and 18% (18 of 102) for surgical complications. This was similar to the rates in those who received 6000 cGy in 6 weeks following surgery when 14% (18 of 127) experienced severe surgical complications and 20% (24 of 121) had severe radiation complications. Ballantyne (1974) has discussed the modifications in surgical technique necessary in irradiated tissues.

Summary

The various patterns of lymph node metastases in the neck and the radiation fields needed to encompass these nodes are well defined. Techniques that allow the delivery of effective doses of radiation without undue toxicity are available. There is good evidence that both elective irradiation of clinically normal nodes in the high-risk patient and therapeutic irradiation of clinically metastatic lymph nodes can influence the patterns of tumor failure in patients with squamous cell carcinomas. Radiation plays a role in improving the control of regional metastases from salivary gland carcinomas and probably also from melanomas. The influence of treatment of the cervical nodes on survival rates is more difficult to determine because survival depends also on successful treatment of the primary tumor, on the risk of more distant metastases, and on deaths from intercurrent disease.

The relative roles of surgery and radiation therapy - either as single modalities or in combination - in the management of cervical lymph node metastases are argued vigorously and inconclusively in the literature. Clearly, both are capable of controlling metastatic nodes in appreciable numbers of patients, but the indications for each treatment method must be better defined.