Actas Dermosifiliogr. 2009;100:166-81

REVIEW ARTICLE

Radiotherapy inb Dermatology

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Abstract. Ionizing radiation causes cell death through DNA damage and has a stronger effect on undifferentiated tumor cells with a high mitotic rate. The use of a fractionated radiotherapy regimen improves both efficacy and tolerance. In addition, greater fractionation, with lower doses per session, minimizes adverse effects. In the majority of tumors treated with radical radiotherapy, the tumor cells do not disappear immediately after treatment, and assessment of the final response to treatment before three months is premature. Radiotherapy is an important treatment modality in selected patients with skin cancer. Modern radiotherapy equipment and techniques achieve excellent rates of tumor control, associated with good cosmetic results, preserved function, and a low rate of complications. The choice of technique is determined by tumor size and site and the thickness. The techniques most widely used at the present time include external beam radiotherapy with linear accelerator sand high-dose-rate brachytherapy.

Key words: radiotherapy, skin cancer, electrons, high-dose-rate brachytherapy.

RADIOTERAPIA EN DERMATOLOGÍA

Resumen. El mecanismo por el cual las radiaciones ionizantes producen muerte celular es el daño al ADN, que afecta más a las células tumorales de mayor actividad mitótica e indiferenciadas. La administración de radioterapia en dosis fraccionadas aumenta la eficacia y la tolerabilidad del tratamiento; esquemas más fraccionados en dosis bajas por sesión minimizan los efectos secundarios. La mayoría de los tumores irradiados en dosis radical no desaparecen de forma rápida al final del tratamiento. Una valoración de la respuesta definitiva antes de los tres meses es prematura. La radioterapia es un tratamiento importante en pacientes seleccionados con cáncer de piel. Se obtienen excelentes tasas de control tumoral, con buen resultado cosmético, preservación funcional e infrecuentes complicaciones con los modernos equipos y las técnicas de radioterapia. La elección de la técnica se determina por el tamaño, el espesor y la localización anatómica del tumor. Las técnicas actualmente más extendidas para el tratamiento del cáncer de piel son la radioterapia externa con electrones de acelerador lineal y la braquiterapia de alta tasa de dosis.

Palabras clave: radioterapia, cáncer de piel, electrones, braquiterapia de alta tasa.

Introduction

This review examines the role of radiotherapy in nonmelanoma skin cancer, with particular reference to the natural history and prognostic factors, tumor radiobiology, radiotherapy techniques and indications, anatomic site, clinical outcomes, and adverse effects. We will also describe the indications for radiotherapy in the treatment of premalignant skin lesions, melanoma, and Merkel cell carcinoma. Finally, we will examine the use of radiotherapy to treat rare tumors such as dermatofibrosarcoma protuberans.

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Manuscript accepted for publication July 7, 2008

Epidemiology

Nonmelanoma skin cancer is the most common of all cancers and its incidence is growing with the aging of the population and the increase in exposure to ultraviolet radiation. Basal cell carcinoma is the most common type of nonmelanoma skin cancer. It accounts for 80% of all such cancers, contrasting with squamous cell cancer, which accounts for just 20%.[1,2] While melanoma represents just 3% of all skin cancers, it is responsible for 75% of skin cancer-related deaths. Other forms of skin cancer are less common.

Natural History and Prognostic Factors for Nonmelanoma Skin Cancer

Nonmelanoma Skin Cancer

Basal Cell Carcinoma

Basal cell carcinoma occurs most frequently on the head and neck[3] and can exhibit greater invasive potential at embryonic fusion planes. The cancer has been associated with mutations of the *p53* tumor suppressor gene and loss of chromosome 9q.[4] Basal cell carcinoma rarely metastasizes (<0.1% of cases) and mucosal and palmoplantar involvement is rare. The most common subtypes of basal cell carcinoma are ulcerative nodular carcinomas (45%-60%) and superficial carcinomas (15%-35%). The more aggressive sclerodermiform and infiltrative types are less common (4%-17%) and the least common type is pigmented basal cell carcinoma (1%-2%).[5-8] Sclerodermiform and infiltrative basal cell cancers have the highest recurrence rate after initial treatment, possibly due to the difficulty of accurately defining tumor margins. The risk of local recurrence in basal cell carcinoma is related to tumor size (>6 mm), infiltration into deeper layers, histologic subtype (infiltrative, sclerodermiform), location (midface region, embryonic fusion planes,) poor definition of tumor margins, tumor recurrence, immunosuppression, perineural invasion, and the presence of multifocal lesions.[9-12] Most tumor recurrences occur within 3 years of treatment.

Squamous Cell Carcinoma

Squamous cell carcinoma is a keratinizing tumor that invades the epidermis through the dermoepidermal junction and is commonly associated with mutations of the tumor suppressor gene *p53*. Despite its superficial presentation, squamous cell carcinoma can invade muscular structures, the periosteum, perineural tissue, and blood and lymphatic vessels through the subcutis. Squamous cell carcinomas that develop from actinic keratosis tend to grow slowly and rarely metastasize. They can follow a more aggressive course, however, when they arise in pressure ulcers or areas of chronic inflammation or in the case of de novo primary tumors. Lymph node and distant metastases occur in approximately 10% of cases. Death due to nonmelanoma skin cancer is rare and most deaths are caused by squamous cell carcinoma, which has the following risk factors for mortality: a tumor size of ≥4 cm, perineural invasion, and invasion through the subcutis. In an analysis of 210 squamous cell carcinomas, Clayman et al[13] reported a 3-year disease-free survival rate of 100% for patients with no risk factors and of 70% for patients with at least 1 risk factor.

The risk factors for recurrence in squamous cell cancer are tumor size and location, poorly defined tumor margins, tumor recurrence, and immunosuppression. Additional factors are underlying chronic inflammatory processes, rapid tumor growth, neurologic symptoms, poorly or moderately differentiated tumors, adenoid squamous carcinoma (featuring acantholysis), mucin-producing adenosquamous or desmoplastic squamous carcinoma, involvement of the reticular dermis or subcutaneous fat (Clark levels IV-V) or a tumor depth of ≥4 mm, and perineural or vascular involvement.[10]

Staging Nonmelanoma Skin Cancer

The staging system for nonmelanoma skin cancer is shown in Table 1.

Patterns of Spread in Nonmelanoma Skin Cancer

Extensive and recurrent tumor lesions in nonmelanoma skin cancer are very difficult, if not impossible, to eradicate due to the means by which this cancer spreads.[14]

Table 1. TNM Staging System for Nonmelanoma Skin Cancer

Primary Tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor 2 cm or less in greatest dimension		
T2	Tumor more than 2 cm, but not more than 5 cm, in greatest dimension		
T3	Tumor more than 5 cm in greatest dimension		
T4	Tumor invades deep extradermal structures		
Regional Lymph Nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant Metastasis (M)			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage			
0	Tis	N0	M0
I	T1	N0	M0
II	T2-3	N0	M0
III	T4	N0	M0
IV	T	N1	M0
	T	N	M1

Source: American Joint Committee Staging System. In: Green FL, Page DL, Fleming ID, et al, editors. AJCC Cancer Staging Manual. 6th ed. New York: Springer-Verlag; 2002.

Subclinical Invasion (Skin Spread)

This pattern of dissemination, which is characterized by irregular infiltration with finger-like projections, is common in basal cell carcinoma. Deep invasion through the subcutis is the most common pattern of spread in early-stage squamous cell carcinoma. Both basal and squamous cell carcinomas can also invade the middle dermis through the pilosebaceous units. Tumor islands may occur in the deep dermis in larger lesions.[15]

Deep Invasion

Invasion By Contiguity

Basal and squamous cell carcinoma can invade vital structures such as the eye, the eyelid, and the lacrimal duct near the orbit. Similar invasive processes in other parts of the body can cause other functional alterations. The tumor, for example, can spread through fascia and planes such as the periosteum, the perichondrium, and the muscular fascia.

Neurotropic Spread

Perineural invasion in basal and squamous cell cancer is associated with poor prognosis but this process is fortunately rare. Neurotropic spread occurs when the perineural space, located between the nerve and its sheath, becomes a pathway for the spread of skin cancer, providing direct access to the central nervous system. Mohs[16] observed perineural invasion in 0.9% of 2488 basal cell carcinomas analyzed. Basal cell carcinoma with perineural invasion occurs in locally advanced or recurrent tumors.[17,18] Between 2% and 14% of patients with squamous cell carcinoma develop perineural invasion, which in most cases affects the peripheral branches of trigeminal and facial nerves. Histologically, discontinuous tumor growth is observed along the length of the nerve. The clinical picture is insidious, with 60% to 70% of patients remaining asymptomatic. The nerve can become compressed over long periods of time, sometimes even years, giving rise to symptoms such as tingling, burning sensation followed by pain, paralysis, and impaired motor function if not treated adequately.[19-24]

Lymph Node, Skin, and Hematogenous Metastases

Lymph node involvement in basal cell carcinoma is uncommon (<0.1% of cases). It is seen in large or deep-seated tumors, tumors with ulceration, and tumors that recur despite several treatments. The regional lymph nodes are the most common site for metastasis, but the lungs, liver, and bones can also be affected.[25]

Lymph node involvement in squamous cell carcinoma has poor prognosis in 10% to 30% of cases. Periparotid and intraparotid involvement is the most common form of lymph node involvement. Identifying patients with high-risk squamous cell carcinoma is essential for agreement about choice of treatment strategy.

According to Johnson et al,[26] hematogenous spread of squamous cell carcinoma can affect the lungs, liver, brain, skin, and bones.

Five-year survival rates of 22% to 56% and 23% have been reported for patients with regional and distant lymph node metastasis, respectively.

Radiotherapy in Nonmelanoma Skin Cancer

Tumor Radiobiology

Radiosensitivity

Ionizing radiation delivers energy to the body, causing ionization and free radical production. These potent, chemically active free radicals have several biologic effects.

The main mechanism by which ionizing radiation causes cell death is by DNA damage (base loss or substitution, rupture of hydrogen bonds holding the 2 strands of the DNA molecule together, or single-strand or double-strand breaks). These alterations do not always cause cell damage as many of the changes that take place are repaired; others occur in nonreplicating regions of DNA, and others do not play an important role in protein synthesis. Other alterations, in contrast, do cause damage, to either existing cells or their descendants, and this is the basis of tumor control (complete or partial response, or tumor stabilization).

Even though the most serious radiation-induced damage occurs in DNA and chromosomes, other cell parts and functions may also be affected. Examples are altered cell membrane permeability, enzyme activity, and protein structure. High doses of radiation cause immediate death due to mitochondrial failure and impaired oxidative phosphorylation.

The principle underlying the use of ionizing radiation in medicine is to destroy more neoplastic tissue than healthy tissue. Radiation has a greater effect on undifferentiated cells that are mitotically active and have yet to undergo many karyokinetic divisions. Such cells are said to have greater radiosensitivity. The concept of radioresistance is relative, however, as all cells are radiosensitive if the radiation dose is sufficiently high.

Tumor Response

Tumors have a complex structure formed by different cells including hypoxic and well-oxygenated cells, clonogenic and nonclonogenic cells, and proliferative and nonproliferative cells. Different cell types have different radiosensitivity profiles. Histologic type and grade also play a key role in response to radiation, as does total cell volume.

Neoplasms are more heterogeneous than normal tissues, and not just in terms of hypoxia. Tumors change with time and with the administration of radiation or antineoplastic drugs. Radiotherapy is not very effective when administered as a single dose as the different cells that make up a tumor have different radiosensitivity profiles and are therefore not all immediately destroyed. Hypoxic tumor cells and cells in the synthesis phase, for example, are highly resistant to the effects of radiation compared to other cells.

The administration of radiation in fractionated doses enhances the effects of radiation via several mechanisms:

1. Reoxygenation. The proportion of hypoxic cells decreases with each fraction as an increasing number of well-oxygenated, more radiosensitive cells are destroyed.
2. Redistribution. Cells at more sensitive stages of the cell cycle process (gap [G] 2 and mitosis) are destroyed in the early phases of treatment. In subsequent sessions, more resistant cells—those in the resting phase (G0)—will enter the cell cycle and eventually be destroyed as they become radiosensitive.
3. Intracellular repair. Although the damage caused to tumor cells and healthy cells following the first dose of radiation is similar, the fact that healthy tissue has a greater capacity to repair sublethal damage provides healthy cells with a clear advantage, which increases with subsequent doses. Accumulation of sublethal damage also suppresses tumor cell activity. Finally, the proliferative capacity of healthy cells is greater and occurs in earlier stages than in the case of neoplastic cells.
4. Repopulation. One of the most noticeable effects following a dose of radiation is a reduction in tissue growth, measured using the mitotic index. This index does not recover during the first few days after treatment, but increases sharply after about 3 to 4 weeks with the rapid repopulation of surviving tumor cells. From this point on, the efficacy of each dose will decrease progressively.

Evaluating Tumor Response

The majority of tumors treated with radical radiotherapy do not disappear immediately after treatment. Any evaluation of tumor response made within 3 months of completion of treatment is therefore premature. It should not be forgotten that while radiation irreversibly impedes the mitotic capacity of many cells—sometimes after just 2 or 3 cell cycles—it does not cause immediate death.

This is why clinical and pathologic findings often differ from each other following radiation. A biopsy of clinically stable residual tumor, for example, will reveal tumor cells. These cells, however, are not viable as they will have lost their ability to enter the cell cycle process.

Tumors contain nonneoplastic vascular connective tissue stroma that is not destroyed by radiation. This is why it can take months, even years, for residual tumor to be fully reabsorbed. This is also the case with chemosensitive tumors such as lymphomas. Caution should, therefore, be exercised before subjecting patients to repeated biopsies or premature surgery.[29,30]

Radiotherapy Indications and Techniques

Indications

Radiotherapy has an important role in the management of nonmelanoma skin cancer. It enables the treatment of extensive, deeply invading tumor lesions, and can also be used, either alone or in combination with surgery, to treat tumors at embryonic fusion planes,[31] or facial tumors in which extensive resection and reconstruction might be required to achieve disease-free margins.

Surgery is the treatment of choice for small tumor lesions that can be easily removed with direct closure and no risk of functional or cosmetic sequelae.

Skin cancer with perineural invasion is difficult to control, and it is almost impossible to avoid recurrence after resection. Local control rates of 78% and 50% respectively have been reported for patients with incidental microscopic perineural invasion who received postoperative radiotherapy and for patients with neurologic symptoms and gross evidence of perineural invasion.[32,33] Magnetic resonance imaging is a useful tool in the planning of radiotherapy as it can be used to document gross tumor involvement of the nerve to define target volumes for treatments involving high doses. The recommended doses in such cases are 60 Gy to the surgical bed; 50 Gy to the area proximal to the nerve in tumors with negative margins, reaching as far as the skull base; and 66-70 Gy to the primary site in tumors with positive margins and microscopic or macroscopic evidence of residual disease.[34]

Radiation fields can be used to treat multiple lesions and regional lymph nodes. Nodes in the parotid glands are the most commonly affected lymph nodes in patients with cancer of the face, scalp, or pinnae. Treatment options include radical or postoperative radiotherapy and

prophylactic irradiation of ipsilateral cervical lymph nodes.

Bone or cartilage involvement used to be a contraindication for radiation therapy, but the emergence of modern equipment and radiation techniques has resulted in excellent control rates, good cosmetic results, and few complications in such cases.[31,34]

Postoperative radiotherapy is also an option in patients with incomplete resection. Improved local control and survival rates are achieved in squamous cell carcinoma when adjuvant radiotherapy is administered after incomplete tumor resection. Perez,[35] at the Washington University School of Medicine in St Louis, United States, reported local control rates of 87% and lymph node metastasis rates of 10% to 15% in patients who received immediate postoperative radiotherapy; the corresponding figures in patients who received radiotherapy following recurrence or tumor progression were 65% and 39%, respectively.

Residual skin damage due to reirradiation is related to fraction size and cumulative dose. Certain parts of the body may not tolerate radiation after a cycle of radical radiotherapy; in such cases, surgery is recommended for persistent or recurrent tumors. Reirradiation of skin cancer is only indicated when surgery is contraindicated and when the area in question has a healthy appearance and is well vascularized. Reirradiation seem to be beneficial when administered in lower doses per session. According to Chao et al,[36] reirradiation is a viable option in selected patients with recurrent skin cancer. In their study of 17 patients with facial skin cancer, good local control and acceptable cosmetic results were achieved with full-dose, or radical, reirradiation.

Techniques

Skin cancer can be treated using a variety of specialized radiotherapy techniques. The choice of technique depends on the size, the depth, and the location of the tumor.

The radiation quality is chosen according to the desired ratio between surface dose and deep dose, while field size is influenced by tumor location and histopathology.

The choice of treatment regimen, cumulative dose, and fractionation (dose per session and number of sessions per week) is influenced by cosmetic considerations, tolerability, and adverse effects, which are minimized using greater fractionation and low doses per session although this option might be limited by the caseload at the treating hospital.

Table 2. Orthovoltage X-Ray Therapy: Central Axis Deep Dose By Energy

Depth, cm	*Dose-Depth Percentage, %*		
	50 KV	*100 KV*	*150 KV*
0.0 (surface)	100	100	100
0.1	92	99	99
0.2	85	98	99
0.5	65	95	96
1.0	45	89	90
1.5	36	79	83
2.0	23	70	76

Radiation Quality

1. Superficial radiotherapy (orthovoltage x-ray therapy). Used to treat superficial tumors, although orthovoltage x-ray machines are becoming less common. These machines can operate at 1 or more energies, of 50, 100, 150, 200, 250, and 300 KV. Because irradiation of subcutaneous tissue increases the risk of visible scarring, it is important to choose the energy level carefully. The recommended energy for superficial basal cell carcinomas—most of which have a depth of 2 to 5 mm—is 50 KV.[37] As shown in Table 2, a typical radiation beam of 50 KV deposits 85% of the surface dose at a depth of 2 mm and just 65% at a depth of 5 mm. Low-energy radiation (50 KV) therefore should only be used to treat very superficial lesions.[38]
   One of the advantages of orthovoltage radiation is that it results in a smaller penumbra than other types of radiation, meaning that a smaller proportion of skin surrounding the tumor is irradiated.
2. Electron beam therapy (linear accelerator). Modern linear accelerators produce energy levels ranging from 6 to 20 MeV; this has the advantage of a rapid dose falloff with depth, which spares healthy tissue that does not need to be treated. Table 3 shows depth-dose profiles for the most common energies used in the treatment of skin cancer. Doses, however, need to be directly measured when treating small lesions as profile accuracy decreases with field size.
   The depth of tissue treated or covered by the electron beam depends on the energy of the beam. Because electrons deposit their maximum energy under rather than at the surface of the skin, certain dose modifications need to be made to increase the surface dose when treating superficial lesions.[31,34,39] In most cases, a tissue-equivalent material (bolus) is placed directly on the skin surface to ensure that the dose delivered to the treatment area is adequate. The bolus increases the surface dose and covers the estimated depth. The number of bolus layers (thickness) required depends on the beam energy.[40]
   Beam delivery accuracy decreases with an increase in the oblique incidence angle, and this affects the

prescribed dose for the area in question. The radiation beam must fall as perpendicularly as possible on the defined treatment area to minimize the risk of underdosage. Although tumors are often irregularly shaped and located in uneven anatomic locations, efforts must be made to obtain optimal, reproducible treatment conditions wherever possible.

3. Megavoltage photon beam therapy (linear accelerator). This technique is used to treat locally advanced skin tumors that invade deep tissue, with possible bone or cartilage involvement. The treatment depth tends to be 5 to 6 cm. Lesions are irradiated with a photon beam, generally with an energy of 6 MeV. A tissue-equivalent bolus is also used in this case to optimize the surface dose in the treatment area.

   Treatment is planned on computerized tomography (CT) scans, which are taken with the patient in the treatment position. The patient is fitted with special immobilization devices to ensure reproducibility at the different treatment sessions. The target tumor volume is defined on the CT scans. Radiopaque markers are placed on the skin to delineate the tumor and facilitate its localization on the CT scans. Critical organs are also marked on the CT scans to ensure that they receive the lowest possible dose. If the maximum tolerable dose is exceeded in any of these organs, the patient could experience serious adverse effects and functional alterations. The CT scans are then used to plan the treatment and produce the dose-volume histograms (Figure 1). This treatment method is called conformal radiotherapy with 3-dimensional (3D) planning. In many cases, the treatment is planned with a combination of high-energy photon and electron beams.
4. High-dose-rate (HDR) brachytherapy (contact therapy). This technique, which involves the use of either standard applicators (such as the flexible Freiburg Flap and the Valencia Skin Applicator) or custom temporary implants, is used to treat basal and squamous cell carcinomas located at irregular body sites or on curved areas. Brachytherapy offers both clinical and dose-related benefits thanks to the precise positioning achieved with the use of these flexible applicators. The radioactive source used is high-dose-rate Iridium^{192}, which is loaded into a digital afterloader, from where it is delivered through transfer tubes to applicators placed on the skin covering the tumor to be treated. The process is controlled remotely, meaning that health care staff are protected from direct radiation exposure. The patient is left alone in a shielded room for a few minutes, which is the length of time each session lasts. When finished, the patient is free to go home (Figure 2).

   The surface dose to deep dose ratio in HDR brachytherapy is ideal for treating early-stage skin tumors. A maximum dose is delivered to the skin surface (100% at 0 mm and treatment range of 3-5 mm) and there is an exponential dose falloff in deeper areas.[41-43]

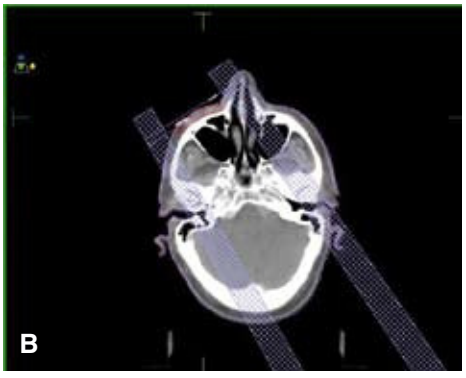
   HDR brachytherapy is indicated for radical monotherapy in early-stage (T1 or T2) basal and squamous cell carcinoma, the treatment of nonmelanoma skin carcinoma after radiotherapy with a linear accelerator, the treatment of nonmelanoma skin carcinoma after surgery with positive margins, the reirradiation of recurrent tumors, and the treatment of Bowen disease, premalignant skin lesions, keloids, and premalignant or malignant intraoral and vaginal lesions.

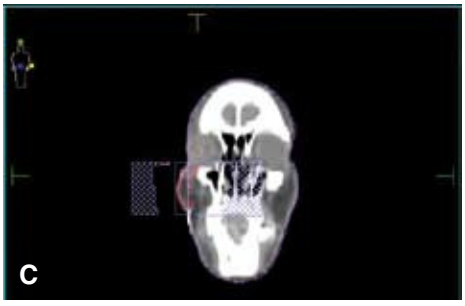
   HDR brachytherapy is associated with greater toxicity than low-dose-rate (LDR) brachytherapy in the treatment of tumors of the eyelids or the vermillion borders of the lips. Finally, it is contraindicated in the treatment of melanoma and tumors of the upper eyelid.

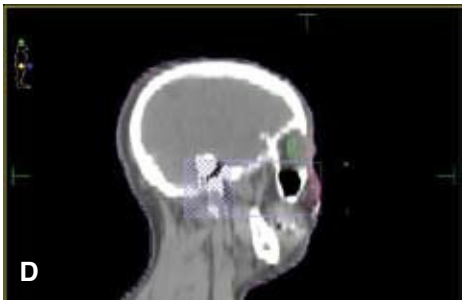
   The recommended cumulative dose for the radical treatment of nonmelanoma skin cancer is 66 to 70 Gy, with fractionated doses of 2 Gy per session in 5 sessions per week. With such a schedule, treatment last for 7 weeks. In older patients with mobility difficulties, hypofractionated regimens may be used, but at the expense of cosmetic results and tolerability.[39]
5. LDR interstitial brachytherapy. This technique can be used to treat periorificial skin tumors in embryonic fusion planes of the face. Rio et al[44] reported good tumor control (92.5%) and cosmetic results for this method using doses of between 55 and 65 Gy and fractions of ≤2 Gy an hour, which are associated with a low risk of late complications. Because LDR brachytherapy is administered in continuous sessions for hours or even days, patients must be hospitalized in

Table 3. Electron Beam Therapy: Central Axis Deep Dose By Energy

Depth, cm	*Dose-Depth Percentage, %*	
	6 MeV Electrons (0.5 cm bolus)	*9 MeV Electrons (1.0 cm bolus)*
0.0 (surface)	93	96
0.1	9	97
0.2	96	98
0.5	100	100
1.0	94	99
1.5	65	90
2.0	25	71







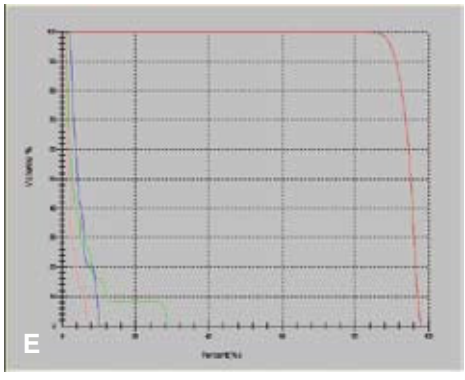


Figure 1. Conformal radiotherapy with 3-dimensional planning. A, Linear accelerator. B, C, D, definition of tumor volume (squamous cell carcinoma in right nasolabial crease) and critical organs (right retina and lens) on computed tomography scans. E, dose-volume histogram.

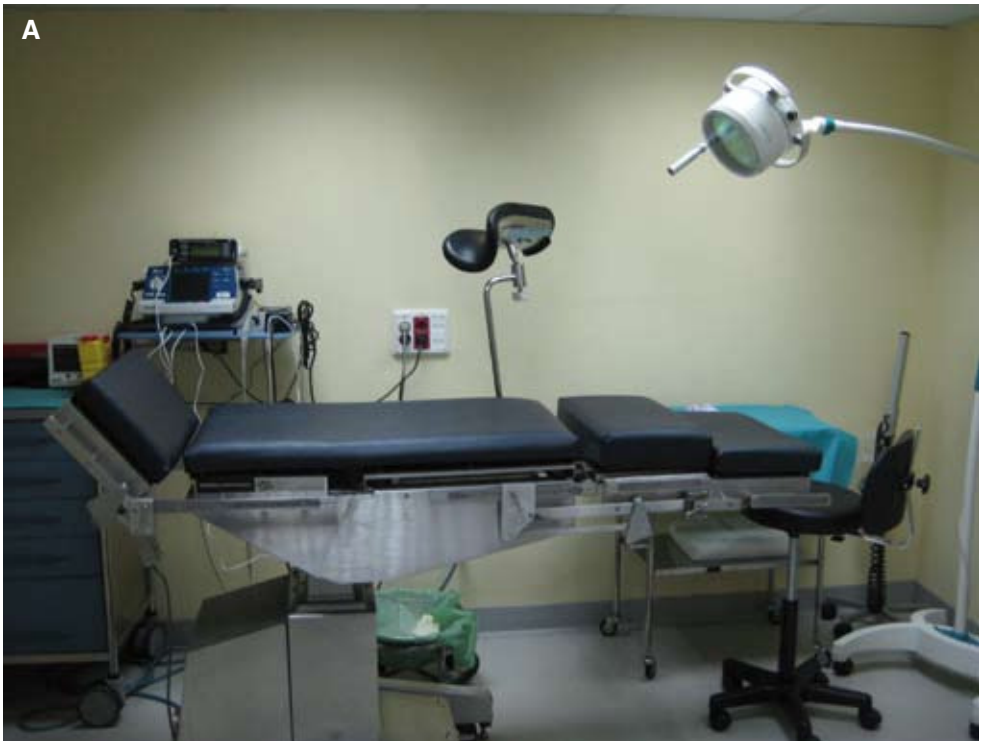


Figure 2. High-dose-rate brachytherapy.
A, Radiotherapy room.
B, Afterloader with radioactive sources.

centers with shielded rooms and adequate safety and control measures. The risk of radiation exposure is greater with LDR than with HDR brachytherapy as the radioactive sources are prepared manually.

Like orthovoltage x-ray machines, LDR brachytherapy units are also becoming harder to find, in contrast to HDR units, whose numbers are on the rise. It has indeed been hypothesized that HDR brachytherapy might soon become the treatment of choice for skin cancer of the face.[41]

Radiation Field Size and Margins

Radiation field size depends on the size and location of the tumor and the type of radiation used. On assessing resection margins in 71 patients with nonmelanoma skin cancer treated with Mohs surgery, Choo et al[45] found that microscopic tumor extension varied between 1 and 15 mm (mean, 5.2 mm). The authors concluded that it was necessary to leave a margin of 10 mm beyond the gross tumor boundary in order to have a 95% chance of a negative margin. They also found that microscopic extension increased with tumor size.

Miscalculation of margin size is the most common reason for treatment failure in nonmelanoma skin cancer. Generous radiation margins should be defined for high-grade tumors, recurrent tumors, poorly defined tumors, and sclerodermiform basal cell tumors.[39] When treating small lesions, wider lateral margins need to be considered with low-energy electron beam therapy with small field sizes than with orthovoltage x-ray therapy due to the dose distribution of electrons. These margins can be smaller when photon rather than electron beam therapy is used. Suitable margin sizes for tumors of 2 cm are 0.5 to 1 cm in the case of photon beam therapy and 1 to 1.5 cm in the case of electron beam therapy; the corresponding sizes for tumors measuring between 2 and 7 cm are 1.5 to 2 cm and 2 to 2.5 cm, respectively.[34,39]

Like margin size, the depth of tumor invasion is also often underestimated. CT scanning and magnetic resonance imaging are useful tools for calculating tumor depth. In tumors of the eyelid, pinnae, and the wing of the nose, where tissue thickness is easy to measure, the entire depth of the tumor should be covered. For tumors measuring up to 4 cm in diameter, the margin should extend 5 mm beyond the estimated depth of the tumor. More generous margins should be defined for larger tumors, recurrent tumors, high-grade tumors, and tumors located in embryonic fusion planes in particular, due to the increased risk of occult deep involvement.

Dose-Time Fractionation

Similar radiotherapy doses and fractionation schedules are used to treat basal and squamous cell tumors of a similar size and thickness, although some authors argue that higher doses are necessary for squamous cell carcinomas.[46] Several studies have shown that late skin effects such as telangiectasis, atrophy, hypopigmentation, and necrosis can be minimized with greater fractionation.[47-49] Petrovich et al[50] reported excellent cosmetic and functional results in 896 patients with skin cancer treated with daily doses of ≤3 Gy. Higher fractions cause more chronic adverse effects, and factors such as age and comorbidity should be considered when prescribing radiotherapy.

Recommended tumor bed doses are 50 to 60 Gy for subclinical disease and negative margins, 60 to 66 Gy for microscopically positive margins, and 66 to 70 Gy for macroscopic disease. The corresponding lymph node dose recommendations are 46 to 50 Gy for subclinical disease (prophylactic) and 56 to 60 Gy for macroscopic lymph node disease using a conventional schedule of 2 Gy per session 5 times a week.

Because the relative biologic effect is 10% to 20% less with linear accelerators than with orthovoltage x-ray machines, electron and photon beam doses need to be increased by 10% to 20% to achieve an equivalent antitumor effect.

It is useful to consider isoeffect time-dose-fractionation values when comparing treatment schedules. The total dose—calculated by multiplying the dose administered per session by the total number of sessions—only coincides with the effective biological dose when a standard fractionation schedule (2 Gy per session 5 times a week) is used. In all other cases, total dose must be converted to the equivalent biologically effective dose. Local tumor control doses and maximum healthy tissue doses can be calculated using the linear quadratic model.

Patient Positioning and Protection Systems

Patient immobilization devices are used to guarantee high-precision localization of the tumor and reproducibility in subsequent sessions.

In electron beam therapy, the linear accelerator can be rotated until the beam axis is perpendicular to the treatment surface. It is very important to protect adjacent healthy tissue and critical organs when treating skin cancer on the head and neck area. To this end, protective molds made of materials such as lead, bismuth, and tungsten are placed on the areas to be protected. Special protection is also needed when treating tumors near the eyes, nose, lips, and ears. Radiation doses in the range of 5 to 10 Gy, for example, can cause cataracts. To protect the eyes from damage, tungsten eye shields are often placed under the eyelids before each session to protect the surface structures of the eyes and the lenses. Tungsten eye shields reduce the dose to the eyes to less than 5% in electron beam therapy at energies of up to 9 MeV.[51]

Other structures such as gums, the oral mucosa, the ear canal, the nasal septum, and areas at risk of hair loss such as eyebrows and the scalp are also shielded.

Radiation Oncology in Practice

Treatment indications

1. Radical radiotherapy. This is used for curative treatment, either alone or in association with other treatments. It also has the advantage that it preserves organ, functional, and cosmetic integrity, and enables surgical salvage in cases of recurrence.
2. Adjuvant radiotherapy. This is used after surgery, to improve local control by reducing the risk of local recurrence, to eradicate microscopic residual tumor, and to preserve anatomic and cosmetic integrity, avoiding the need for extensive, mutilating surgery.
3. Neoadjuvant radiotherapy. This is used before surgery or as an alternative to surgery in patients with locally advanced tumors that are inoperable or require extensive surgery. It also improves survival and preserves anatomic and organ integrity.
4. Palliative radiotherapy. This is used to treat tumor symptoms such as pain, hemorrhaging, and vascular or nerve compression. It does not cause additional symptoms thanks to its rapid, precise administration system, and finally, it improves health-related quality of life.

Treatment Stages

1. Initial clinical evaluation.
2. Choice of treatment.
3. Localization of tumor by direct clinical examination, if possible, with the help of photographs and diagnostic images (CT, MRI, ultrasound, and positron emission tomography scans) to accurately determine the location and depth of the tumor and define the treatment area.
4. Definition of tumor volume and critical organs (Figure 3). This is done on CT scans taken with the patient immobilized in the treatment position or directly on the patient's skin, also with the immobilization devices in place. Axial, coronal, and sagittal images from the CT planning scans are used to delineate 3D images of the tumor and critical organs (eyes, middle ear, inner ear, etc), which must receive as little radiation as possible.
5. Clinical dosimetry. This involves configuring the radiation beam or beams using the previously defined volumes.
6. Simulation. Reproduction of prescribed treatment using a radiation simulator before it is administered to the patient through the linear accelerator.
7. Initiation of treatment: first session. Verification of treatment.
8. Administration of successive treatments.
9. Clinical evaluation of treatment, with special attention paid to tumor response and adverse effects.
10. Patient surveillance.

Adverse Effects

Treatment-related adverse effects are divided into acute (early) effects (occurring within 6 months of completion of treatment) and chronic (late) effects (occurring after 6 months of completion of treatment).

Acute effects

The skin is a rapidly renewing tissue. The epidermis is formed by 2 well-defined areas: the upper layers—composed of mature keratinizing cells—and the basal layer—composed of immature progenitor cells that give rise to mature cells that replace cells that are shed naturally and maintain functional integrity.

Two percent of skin cells are renewed every day and it takes 14 to 17 days for a progenitor cell to give rise to a mature cell and for this to reach the surface of the epidermis.

Erythema caused by capillary vasodilation and edema forms on skin after a latency period of 1 to 2 days following irradiation with a dose of 8 Gy. Histologic changes evidence the disappearance of mitotic activity in the basal layer. Clinically, erythema is followed by dry flaking (moderate doses) or moist dermatitis (high doses). In both cases, undamaged basal cells accelerate the production of new cells to restore skin integrity. This natural recovery can be quantified by counting the number of epithelial cell colonies originating from a surviving basal cell (regeneration nodules); these colonies grow until the dermis is completely covered. As can be seen in Figure 4, the number of regeneration colonies present several days after the administration of different doses of radiotherapy produces a typical cell survival curve.

Late Effects

Local effects caused by targeted radiation, generally involving high doses, occur as irradiated tissue is repaired by proliferating connective tissue cells, which replace the original cells, giving rise to morphologic and functional changes. Effects include atrophy, pigmentation changes, skin loss, telangiectasis, ulceration, and necrosis.[52]

Systemic somatic effects are the result of the stochastic effect of low doses of radiation after long periods of latency. The effects may be the result of the depletion of progenitor cells. This depletion can have 2 consequences: the loss of tissue regeneration capacity, resulting in aging or shortened life span and the appearance of genetic mutations due to the proliferation of abnormal cells, resulting in carcinogenesis.

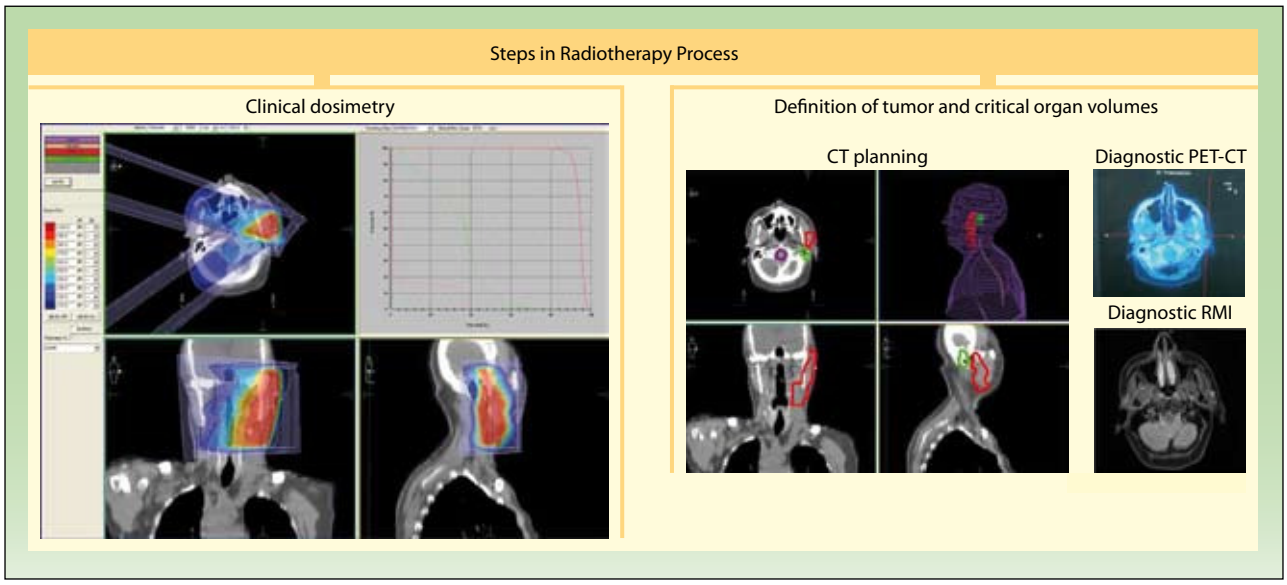


Figure 3. Steps in radiotherapy process. Irradiation of cervical-parotid lymph node metastasis from squamous cell carcinoma of the skin. Localization of tumor with the aid of positron emission tomography-computerized tomography (PET-CRT) and magnetic resonance imaging (MRI). Definition of target volumes and clinical dosimetry on CT planning scans.

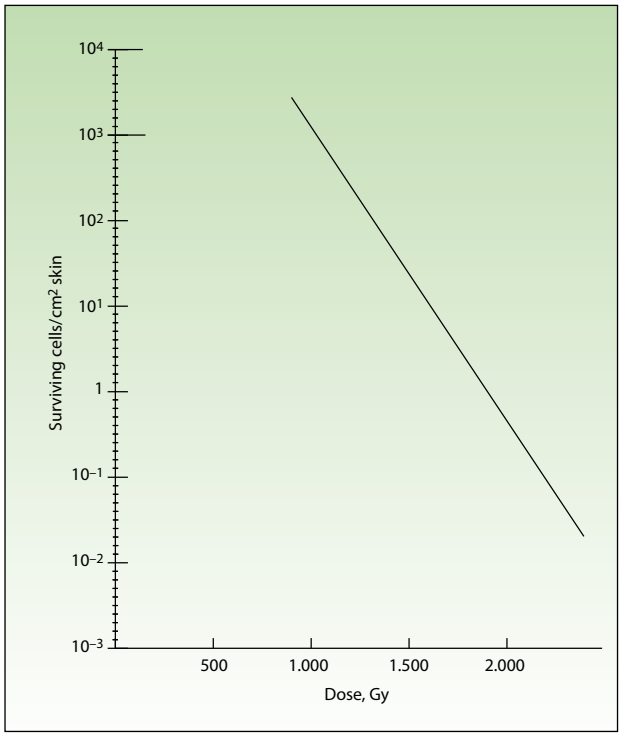


Figure 4. Cell survival curve obtained by counting regeneration colonies with incremental doses of radiation delivered to the skin.

There are 2 theories regarding the appearance of late radiation effects. The first suggests that these effects are due to damage to connective tissue stroma. The fact that this stroma is found throughout the body suggests that there is a common mechanism for the production of late effects in any organ.[53] A variant of this theory is that late effects are due to damage to endothelial cells, which are also found throughout the body.[54] The second theory suggests that early and late effects of both radiation and cytotoxic chemotherapy are due to cell depletion in affected renewing tissues. Early effects would depend on the balance between cell death and the compensatory proliferation of stem cells, while late effects would occur in cases where stem cells had a limited proliferative capacity.[55,56] Repeated or extensive cell death can deplete this proliferative capacity, possibly giving rise to tissue failure.[57]

Treatment morbidity is quantified using the subjective objective management analytic—late effects of normal tissue (SOMA-LENT) scale established in 1995 by 2 leading research groups in oncology and radiation therapy: the European Organization for Research and Treatment of Cancer and the Radiation Therapy Oncology Group.

Results of Radiotherapy for Nonmelanoma Skin Cancer

In an updated study of results for the treatment of 339 squamous cell and basal cell carcinomas, Locke et al,[46] in line with earlier findings, reported similar tumor control rates for electron beam therapy and orthovoltage x-rays. They also found a significant association between

histologic type and recurrence. The local control rate was 92% for basal cell carcinoma and 80% for squamous cell carcinoma. As in previous series, control rates were better for lesions that had not received any treatment prior to radiotherapy: 94% for basal cell carcinoma and 89% for squamous cell carcinoma. The authors stressed the importance of early treatment to optimize tumor control and cosmetic results (Figure 5).

Premalignant Skin Lesions

Bowen Disease

Bowen disease progresses to squamous cell carcinoma in 5% to 20% of patients. The treatment of choice is surgical resection, but radiotherapy may also be considered. The required dose is 56 Gy divided into fractions of 2 Gy. This schedule offers good cosmetic results, which is an important factor when treating facial lesions. Shorter treatment schedules with a biologically equivalent dose can be used but the cosmetic results are not so good. Radiotherapy is not recommended for lesions of the leg, or in elderly patients with vascular comorbidities or diabetes, for example, as difficult-to-heal chronic ulcers have been reported.[58] Local recurrence in Bowen disease is rare following radiotherapy according to results published for recent series.[59]

Keratoacanthoma

In most cases, keratoacanthoma is a benign tumor that can spontaneously regress. In some cases, however, a destructive variant of this tumor invades extensive areas of tissue. Several authors consider keratoacanthoma to be a variant of squamous cell carcinoma while others believe that the course of both tumors is related.[60] Keratoacanthoma can be treated with radiation when biopsy confirms the simultaneous presence of squamous cell carcinoma. The recommended treatment dose is a biologically equivalent dose of 56 Gy, with several treatment schedules possible.

Lentigo Maligna

Lentigo maligna can progress to invasive melanoma. It is generally treated with surgery, although radiotherapy can also be used, either as primary or adjuvant postoperative treatment, with several radiation schedules possible.[61] The recommended biologically equivalent dose is 56 Gy.

Melanoma

Radiotherapy has several uses in the treatment of melanoma. It can be used as adjuvant therapy following the surgical resection of a primary tumor or lymph node metastases, as treatment for regional lymph nodes in patients with a high risk of subclinical involvement, as palliative treatment of distant metastases or local recurrences, and very occasionally, as radical treatment of primary tumors.

According to a recent study, radiotherapy is used in just 1% to 15% of patients with melanoma, whereas the optimal utilization rate is estimated to be 23%.[62]

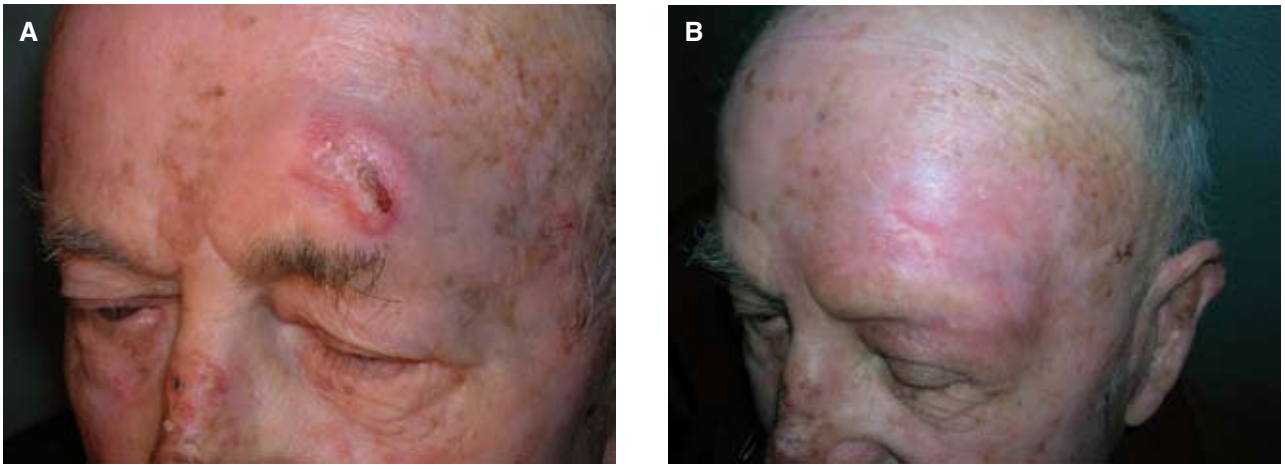


Figure 5. Squamous cell carcinoma in the upper eyebrow region (T4N0M0). B, Complete remission 2 months after completion of treatment with electron beam therapy (linear accelerator).

In vitro studies have confirmed the general belief that melanoma is radioresistant. The fact that melanoma cells appear to have an enormous capacity to recover from radiation-induced sublethal damage suggests that hypofractionated regimens (high doses per session) would offer therapeutic benefits. Several fractionation schedules can be used, and the recommended dose per session is in the range of 3 to 8 Gy.

Adjuvant Radiotherapy of Primary Lesions and Regional Lymph Nodes

Several factors are associated with an increased risk of tumor recurrence. A tumor depth of ≥4 mm, for example, has been associated with recurrence rates of between 6% and 14%. The corresponding rates are 5% to 17% for primary lesions in the head and neck region, 10% to 17% for primary lesions with ulceration, 14% to 16% for primary lesions with satellitosis, and 23% to 48% for desmoplastic melanomas.[63-65] Based on these findings, the indications for adjuvant radiotherapy following the resection of a primary tumor are desmoplastic melanoma, a tumor depth of >4 mm with ulceration or satellite lesions, and positive resection margins; radiotherapy can also be used as primary or adjuvant therapy following the resection of recurrent tumors.[64]

Therapeutic lymph node dissection has been reported to achieve control rates of 85% in patients with subclinical lymph node involvement.[64] Extracapsular lymph node involvement is associated with a 30% to 50% risk of lymph node recurrence. Other risk factors for recurrence are the involvement or 4 or more lymph nodes, a lymph node size of >3 cm, cervical lymph node involvement, and lymph node recurrence following dissection.[64,66,67]

Stevens et al[65] used an adjuvant hypofractionated regimen to irradiate the primary tumor site in 35 patients and diseased lymph nodes in 139 patients with risk factors for local recurrence. The recurrence rate was 11% for patients that underwent resection and radiotherapy and 50% for those that underwent surgery only. In a study conducted by the MD Anderson Cancer Center, the authors reported a local control rate of 87% for axillary lymph node metastasis following adjuvant radiotherapy in patients with 1 or more risk factors for recurrence.[68] The 5-year mild to moderate arm edema rate was 43%. Caution is recommended when indicating adjuvant radiotherapy in patients who have undergone inguinal lymph node dissection. It has been proposed that this treatment should be reserved for patients with 2 or more risk factors.[69] More conservative fractionation schedules (50 Gy at 2-2.5 Gy per session) may be adequate for inguinal or axillary irradiation as they reduce the risk of lymphedema and neuropathy.[70]

Elective Radiation of Clinically Negative Regional Lymph Nodes

The risk of subclinical regional lymph node involvement is directly related to the depth of the primary tumor, with a risk of less than 5% for a depth of less than 0.75 mm, of 10% for a depth of 0.76 to 1.50 mm, of 20% for a depth of 1.51 to 4 mm, and of 30% to 50% for a depth of >4 mm.[62] Bonnen et al[71] reported a local control rate of 89% at 5 and 10 years after the elective radiation of lymph node metastasis from head and neck melanoma tumors at a depth of ≥1.50 mm. In another study, local control rates of 82% to 95% were achieved with adjuvant radiotherapy in patients with a high risk of lymph node recurrence; the corresponding rate in patients treated with surgery only was 50%.[66]

Radical Primary Radiotherapy

This is a treatment option for inoperable patients.

Palliative Radiation Therapy

Palliative radiation therapy is indicated in the treatment of patients with melanoma and either unresectable local disease or metastatic disease (brain and bone metastasis, cutaneous and subcutaneous metastasis, metastatic medullar compression, etc).

Merkel Cell Carcinoma

Local recurrence rates of over 50% have led many investigators to recommend systematic adjuvant radiotherapy following the surgical treatment of Merkel cell carcinoma.[72,73] Wide treatment margins (measuring 3 to 5 cm) are defined due to the risk of in-transit metastasis and recurrence at the surgical margin, and both the primary site (tumor bed and surgical scar) and drainage lymph nodes are irradiated following surgery. The recommended radiation doses are similar to those used in squamous cell carcinoma: 50 to 60 Gy for subclinical disease and negative resection margins at the primary site, 60 to 66 Gy for microscopically positive margins, and 66 to 70 Gy for macroscopic disease. The corresponding lymph node dose recommendations are 46 to 50 Gy for subclinical disease (prophylactic) and 56 to 60 Gy for macroscopic lymph node disease[72,74] using a conventional schedule of 2 Gy per session 5 times a week.

A recent study by Allen et al[75] changed the routine use of adjuvant radiation therapy after surgery for Merkel cell carcinoma. The authors reviewed 251 cases treated at the

Memorial Sloan-Kettering Cancer Center over 32 years. Local tumor recurrence affected just 8% of patients with margin-negative resection of Merkel cell carcinoma and just 14% of those that underwent lymph node dissection, even without adjuvant radiotherapy. Five-year survival was 64%, and the authors found tumor stage at diagnosis rather than adjuvant radiotherapy to be a predictor of survival. On the basis of their findings, they recommended postoperative adjuvant radiotherapy only for patients with a high risk of local recurrence or for patients with positive resection margins, multiple lymph node involvement, or extracapsular lymph node involvement. The treatment of choice in patients who are considered inoperable for medical or surgical reasons is radical radiotherapy.

In a study of patients with stage I Merkel cell carcinoma treated with Mohs surgery, Boyer et al[76] studied local control rates in 20 patients who received local adjuvant radiation following surgery and 25 patients who underwent surgery only. All of the patients had disease-free resection margins. No significant differences were found between the groups for overall survival, recurrence-free survival, or disease-free survival. The authors recommend adjuvant radiotherapy after Mohs surgery in patients with incomplete resection or in patients in whom complete histologic margin control is not possible. Adjuvant radiation therapy should be considered for extensive or recurrent tumors.

Dermatofibrosarcoma Protuberans

Postoperative radiotherapy in patients with close or positive margins is recommended as the risk of recurrence is greater than 50%. The recommended radiation dose for microscopic disease is 60 to 66 Gy with daily doses of 2 Gy.[77] In patients with residual macroscopic disease, the recommended dose is 64 to 74 Gy.

Adjuvant radiotherapy is indicated for high-grade lesions regardless of the state of surgical margins.

Finally, preoperative radiotherapy is indicated as an alternative to extensive surgery with a risk of functional and cosmetic sequelae. Recommendations include delivering a dose of 50 Gy to the tumor, defining margins of 3 to 5 cm, and performing surgery at 4 to 6 weeks.

Conflicts of Interest

The authors declare no conflicts of interest.

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