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Radiation Therapy and Skin Cancer

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1. Introduction

Although radiation therapy (RT) can be very beneficial in a number of cutaneous malignancies, it tends to be a relatively underutilized therapy for a number of reasons. The hesitancy on the part of dermatologists to recommend RT is driven by a number of issues. First and foremost is perception inherent in dermatology training programs. All dermatologists in training encounter patients harmed by the historic overutilization of RT in the past, both by dermatologists themselves and radiation oncologists for non-malignant inflammatory diseases such as eczema, acne, and even fungal infections. Many patients treated in their youth with Grenz rays by dermatologists have gone on to develop multiple cutaneous malignancies later in life. As the role of ultraviolet light in carcinogenesis has come into focus, it can be intellectually awkward for dermatologists to discourage patients from excessive exposure to ultraviolet light and then recommend radiation therapy, especially in the younger population due to perceptions of the consequential increased risk for the latent development of further skin cancers. Dermatologists may focus too much on the carcinogenic consequences of RT (which are statistically quite modest) at the expense of the therapeutic benefits of RT. Another perceptual issue is radiated sites can be characterized by atrophy and telangiectasia which are cosmetically undesirable. Finally, familiarity with standard treatments within the bailiwick of dermatology training (excisional and Mohs micrographic surgery, laser surgery, cryosurgery, curettage and electrodessication, and medical therapies such as topical 5-fluorouracil and imiquimod cream to name a few), are naturally going to be considered first by a dermatologist who is well-versed in these therapies but is relatively unfamiliar with state of the art approaches currently utilized by radiation oncologists.

For these and other reasons, RT is a mostly underutilized treatment modality for many varieties of skin cancer and can have both high cure rates with excellent cosmetic outcomes. This chapter will address the most commonly encountered cutaneous malignancies where RT could be considered as either a first line or adjuvant treatment with acceptable side effect profiles. It remains the obligation of dermatology and radiation oncology training programs to better communicate and discuss the issues surrounding the indications for and selection of RT for skin cancers.

2. Basal cell carcinoma

Basal cell carcinoma (BCC) is, by far, the most common of all cancer types in Caucasians with increased rates directly tied to latitudes approaching the equator (Fears & Scotto, 1983).

Although metastases are very rare with BCC, the tumors are often in cosmetically sensitive areas of the face, scalp, and neck, and represent a major cause of morbidity and take out a major chunk of the health care expenditure pie. The annual cost of treating BCC and squamous cell carcinoma (SCC) in the Medicare population in the United States is estimated to be above $400 million (Liu & Chen, 2000; Mudigonda et al., 2010).

2.1 Epidemiology

There were an estimated 2 million cases of non-melanoma skin cancer diagnosed in the United States in 2010 (Edwards, 2010) and of those, 75-80% are BCC (Lang & Maize, 2005). The incidence of BCC continues to rise worldwide in the Caucasian population and is thought to be mainly a consequence of increased exposure to ultraviolet light.

2.2 Etiology

Ultraviolet light is the causative factor in the majority of BCC and risk is inversely related to inherent melanin content in the skin which serves a protective function. It is uncommon for blacks to get BCC, but if blacks suffer from albinism where the melanocytes fail to manufacture melanin, the risk for BCC increases substantially (Alexander & Henschke, 1981). Multiple BCCs can be seen in a few scenarios such as patients undergoing RT for acne or for other inflammatory conditions in their youth. Doses as low as 450 rads have been associated with the formation of BCC, and in some patients, very high numbers of tumors (Everall & Dowd, 1978). Ultraviolet light therapy given by dermatologists for inflammatory conditions such as psoriasis has also long been known to increase BCC risk (Halprin, 1980; Roenigk et al., 1981; Stern et al., 1979).

2.3 Clinical presentation

The three most commonly encountered subtypes of BCC are the nodular, superficial, and morpheaform variants. The nodular BCC most commonly presents as a nodule that resembles a drop of paraffin wax riddled with telangiectasia. Sometimes the center will begin to necrose and a central ulcer/eschar develops with a surrounding rolled edge (See Figure 1a). The superficial BCC is completely different and presents as a red scaling macule

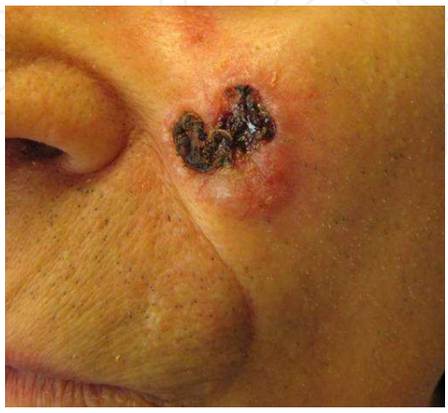


Fig. 1a. Basal cell carcinoma with paraffin wax like opalescence, telangiectasia, and ulceration

that often features notching at the border. Clinically the superficial BCC can be confused with actinic keratosis, nummular eczema, and even tinea (ring-worm). The morpheaform BCC is different still and often is scar-like and depressed compared to the surrounding skin, similar to a compressed snowshoe print. The surface is often shiny as the pores are frequently obliterated by the tumor.

2.4 Histology

The nodular BCC will have a pattern of palisading basophilic basal cells that extend off of the dermoepidermal junction and expand into the dermis. At the leading edge of the expansile tumor mass there is often a thin layer of degradation of the matrix leaving a retraction artifact between the tumor and the surrounding dermis. The tumor slowly dissolves the collagen as it glacially makes its way through the dermis (See Figure 1b). The superficial BCC is similar but has only small buds of the palisading basal cells extending off of the epidermis and lacks the deeper dermal infiltration. The morpheaform tumors arise in a scarred and fibrotic matrix and the basal cells are grouped into numerous thin and filamentous strands surrounded by sclerosis, giving an overall pattern similar to paisley. Since such tumors are much more filamentous and embedded in a sclerotic stroma, they are much less amenable to removal with a curette.

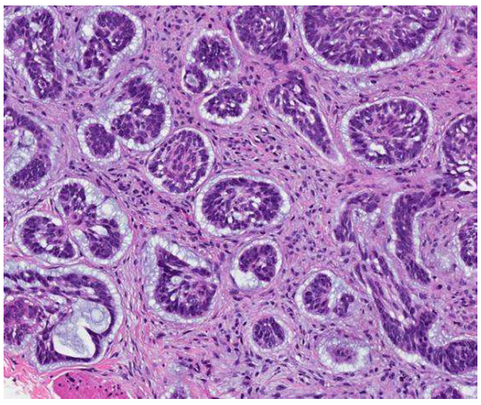


Fig. 1b. Histology of basal cell carcinoma

2.5 Treatment

The majority of BCCs are treated with curettage and electrodessication (CE). CE is not considered for morpheaform tumors, recurrent tumors, large tumors (> 2 cm) or tumors in thickly hair-bearing areas such as the scalp due to lower success rates. Simple excision is also a viable treatment option with cure rates similar to CE (Werlinger et al., 2002). Of all treatment modalities applied to BCC, Mohs micrographic surgery (MMS) has the highest documented cure rates (approximately 99% for most tumors) compared to 90-93 % cure rates for other modalities (Rowe et al., 1989). Pioneered by the late Fredrick Mohs, M.D. of the University of Wisconsin, MMS involves a *staged* excisional approach where the visible tumor is removed and then submitted for fresh tissue frozen sections. Areas of tumor positivity are recorded by the Mohs surgeon who then returns to the patient and removes additional tissue confined to specific tumor roots. This process is repeated until histologically negative margins are verified, and only then is the defect surgically repaired.

The great strength of this procedure is the reduction of the removal of uninvolved tissue to a bare minimum (as opposed to a wide local excision), combined with very high cure rates.

The main drawbacks of MMS are that the surgeries can be very morbid, especially when key anatomic structures are partially or completely removed as part of the surgery in areas on the nose, eyelids, ears, and lips. Although there have been ingenious advances in reconstructive surgery, the Mohs surgeon and facial and plastic reconstructive surgeons are left facing many surgical defects where the reconstructive options are limited. In such cases, radiation therapy can be a very desirable alternative to radical surgical excision.

2.6 Radiation therapy

Radiation therapy (RT) is not used as frequently as in the past, but it remains a very important part of the armamentarium for treating BCC. The chance of success is directly related to the clinician's ability to delineate tumor margins so the lesion is not undertreated. It has been suggested that in tumors with ambiguous borders, scouting biopsies be performed prior to embarking on RT to better define the required field (Lang, 2005). With respect to primary therapy, RT has the great advantage of avoiding reconstructive surgery in critical sites around the lacrimal system and on the nose and ears. (Chahbazian 1984; Leshin et al., 1993; Morrison et al., 1997). Many patients with BCC are poor surgical candidates due to advanced age and co-morbidities, and surgery becomes impractical. Some BCCs are not resectable even in healthy patients and RT is a viable alternative to surgery and, as will be discussed, is curative in most cases (about 95%). In some circumstances, RT may not be curative but palliation is an important consideration for large and complicated tumors. (RD, 1985).

RT has been discouraged in young patients in a wide range of reports (Brady, 1987; Braun-Falco, 1976; Chahbazian, 1980, 1984; Gladstein, 1978; Thissen, 1999), as there are concerns of the latent eruptions of cancer in the irradiated site as well as the tendency for treated sites to develop atrophy and telangiectasias over time that compromise the cosmetic appearance. As predicted, the size and extent of tumor will determine the success rate and long-term cosmetic result. RT has also been discouraged for morpheaform tumors. (Brady et al., 1987; Braun-Falco et al., 1976; Chahbazian, 1980, 1984; Dubin, 1983; Gladstein et al., 1978). There has also been reluctance to treat patients with the basal cell nevus syndrome who harbor a genetic defect in the PTCH tumor suppressor gene where RT may create additional DNA damage, creating higher risk for additional tumor formation. (Gorlin, 1987).

Table 1 is included by permission of the National Comprehensive Cancer Network (NCCN Guidelines®, 2011) with the following clarifications. Because of the wider beam penumbra, wider field margins are necessary when using electron beam than with orthovoltage X-rays. If lead skin collimation is used, tighter field margins can be used with electron beam adjacent to critical structures such as the lacrimal system. When using electron beam, bolus is necessary to achieve adequate surface dose. An electron beam energy should be chosen which achieves adequate surface dose and encompasses the deep margin of the tumor by at least the distal 90% line. Electron beam doses are specified at 90% of the maximal depth dose (Dmax). Orthovoltage X-ray doses are specified at Dmax (skin surface) to account for the approximately 10% higher biologic effectiveness between the two modalities of radiation.

Tumor Diameter	Margins	Dose (Gy)	# of Fractions
< 2 cm	1 - 1.5 cm	64	32 over 6 - 6.4 weeks
		55	20 over 4 weeks
		50	15 over 3 weeks
		35	5 over 5 days
≥ 2 cm	1.5 - 2cm	66	33 over 6 – 6.6 weeks
			55 over 4 weeks
Postoperative adjuvant		50	20 over 4 weeks
		60	30 over 6 weeks

Table 1. Dose Recommendations for Primary BCC and SCC

When the proper patient is selected and RT is expertly executed, response rates are excellent. The five-year complete response rates have been reported to range from 90 to 95%. A study looking at 862 primary BCCs treated with RT alone had a five-year complete response rate of 92.6%. (Silverman et al., 1992). Increasing diameter was associated with recurrence risk with 95.6% cure rates for tumors < 10 mm on the head, but cure rates of 90.5% if the tumors were > 10 mm. (Silverman et al., 1992). Long-term cosmetic outcomes were evaluated in this study and were thought to be satisfactory in 63% of RT-treated patients, 84% for patients who had surgery, and 91% with those treated with curettage and electrodessication. (Silverman et al., 1992). The data on the cosmetic outcome supports the notion that RT ought not to be a first line therapy for young patients if other options are available.

The general consensus in the literature appears to support the notion that tumors < 10 mm can be effectively treated with one dose of radiation. Mendenhall et al. recommend a single dose of 20 Gy, typically reserved only for when late cosmesis is not important and travel for the patient is exceedingly difficult. (Mendenhall et al. 1994). However, fractionation is recommended for tumors > 10 mm due to the improvement in the therapeutic ratio, allowing for less harm to surrounding normal tissue despite a larger biologically effective dose to the tumor.(Lang & Maize, 2005). Fractionation is particularly important for tumors overlying cartilage such as the nose and ears, or over bone. Additional considerations when choosing the extent of fractionation include patient convenience and performance status. For lesions < 3 cm where cosmesis is unimportant, 40 Gy in 8 fractions and 30 Gy in 5 fractions may be considered (Morrison et al., 1993).

The treatment of recurrent tumors with RT is not as effective as it is for primary tumors, which is also true for (MMS). In a study of 221 recurrent tumors that were subsequently treated with RT, the re-recurrence rate was 9.5%. (Silverman et al., 1992). In a second study treating 61 recurrent BCCs with RT the 5-year estimated Kaplan-Meier re-recurrence rate

was 4% for tumors < 10 mm and 19% for tumors > 10 mm with a cost that was roughly equivalent to MMS. (Wilder et al., 1991). These data were further stratified by stage where Kaplan-Meier 5-year predicted recurrence rates for stage I/II tumors (tumors of any size but confined to the skin) was 7% compared to a 58% predicted recurrence rate for tumors that were stage III/IV (tumors that invaded underlying bone, muscle, or cartilage)(Wilder et al. 1991). The authors emphasize that *tumor stage* (depth) is much more important than actual tumor size (diameter) in predicting responses to RT.

In summary, RT can be a very effective treatment for BCC and even recurrent BCC, but patient selection is critical as is the cooperation between the Mohs surgeon and the radiation oncologist in making every effort possible in delineating tumor margins in order to inform decisions about field sizes. This may include several scouting biopsies in order to estimate tumor perimeters. RT is particularly well-suited for the elderly or frail patient who is a poor surgical candidate but should be used with great caution in younger patients who may have a poor long-term cosmetic outcome. RT gives the great advantage of avoiding surgical morbidity to critical sites on the nose, eyelids, ears and lips where reconstructive options are limited. Since RT is frequently fractionated, some patients may balk at the need to make several trips to a medical center for treatment, but others jump at the chance to avoid an invasive surgical approach.

3. Squamous cell carcinoma

Squamous cell carcinoma (SCC) is the second most common cutaneous malignancy behind BCC and also occurs in chronically sun-exposed sites, particularly the head and neck. Unlike BCC, SCC does have significant metastatic potential and with the advent of solid organ transplantation, has become a significant risk for morbidity and mortality in that population. SCC is also more frequently associated with underlying states of chronic inflammation such as burn scars, chronic ulcers, chronic thermal injury, and exposure to chemical carcinogens such as arsenic and polycyclic hydrocarbons.

SCC begins with the squamous cells in the epidermis which are situated directly above the basement membrane where the basal cells are located in the stratum basale (See Figure 2). Historically, the layer of the epidermis containing the squamous cells is called the stratum spinosum, which takes its name from the observation under high power light microscopy of desmosomes emanating off of the squamous cells like "spines." Also known as the keratinocytes, the squamous cells undergo an abrupt transition in the stratum granulosum of the epidermis where the intracellular keratin filaments clump, the cell undergoes programmed death, and a keratogenous shell remains with intercellular wax esters acting like "mortar" between the keratinocyte "bricks" forming the watertight barrier of the outer layer of the skin, the stratum corneum. Because of the abundance of keratin protein in squamous cells, in general, SCC is clinically much more scaly and crusted than BCC.

3.1 Incidence and epidemiology

SCC accounts for about 10-20% of all skin cancers (Nguyen, 2005), with an incidence of approximately 700,000 cases per year in the United States with 2500 expected deaths in 2010.(Foundation, 2011). 80% of SCC occurs on sun-exposed sites such as the head and neck, and upper extremities. (Nguyen, 2005). Although BCC outnumbers SCC by 4:1, SCC is

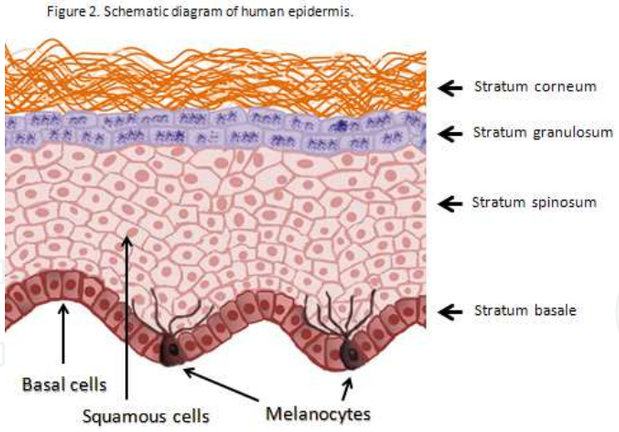


Fig. 2. Schematic diagram of human epidermis

responsible for the vast majority of non-melanoma deaths. In the general population, the rates of SCC have shown a doubling of the incidence over the last 40 years. (Stern, 1978). SCC is becoming a more common problem among solid organ transplant recipients and in patients with lymphoproliferative malignancies, presumably due to decreased immunosurveillance. A renal transplant recipient has an increased risk of developing SCC in the first year of 7%, 45% risk after the first 11 years following transplant, and 70% risk after 20 years. (Bouwes Bavinck et al., 1996). The situation is worse for heart transplant recipients who have a 2-3 times greater risk of SCC than do renal transplant patients.

Risk factors for the development of SCC include fair-skinned patients with risk associated with increasing rates of chronic cumulative UV exposure, living in areas of decreasing latitude, increased altitude, prior history of non-melanoma skin cancer, male gender (men are 2-3 times more affected than females), and age > 50. (Nguyen, 2005).

3.2 Etiology

The majority of SCC are caused by mutations induced by ultraviolet light exposure, most notably in the tumor suppressor gene p53. (Sarasin & Giglia-Mari, 2002). A smaller percentage of SCC are not related to UV injury, but rather will occur as a result of sites of chronic skin inflammation which can result from a number of causes such as chronic inflammatory skin diseases, particularly non-healing ulcers. Traumatic insult to the skin such as scar tissue from cuts or thermal or chemical burns has also been associated with SCC. Ionizing radiation as mentioned in the introduction is clearly associated with increased SCC risk as is chronic lymphedema.

Also implicated in the formation of SCC is exposure to chemical carcinogens. Polycyclic aromatic hydrocarbons such as soot, pitch, tar, oil shale, and mineral oil have all been documented associations with SCC. Arsenic has long been appreciated as having a causal link with SCC. (Baca & Dzubow, 1998).

3.3 Clinical presentation

Because squamous cells produce keratin protein which is a key feature in the barrier function of the skin, well-differentiated SCC will be associated with a degree of

hyperkeratosis with the clinical correlation of scale (See Figure 3a). As SCC becomes less well-differentiated, they often lose the ability to produce keratin with the clinical correlation of loss of scale and the tumors take on a more erosive appearance not unlike a stewed tomato. The distribution of SCC, as anticipated, favors chronically exposed sites such as the head and neck where 70% of SCC are found and another 15% occur on the upper extremities. (Nguyen, 2005). SCC frequently occurs in the setting of stigmata of chronic sun exposure such as multiple actinic keratosis (AK), which are small patches that are usually red in color and have a slightly roughened surface similar to fine grained sand paper. SCC of the lip has long been recognized as being generally more aggressive, with higher rates of metastases than the other head and neck locations, and is more likely found on the lower lip. (Dinehart & Pollack, 1989). Cigarette and pipe smoking have also been associated with increased rates of lip SCC. (Pentenero et al., 2011).

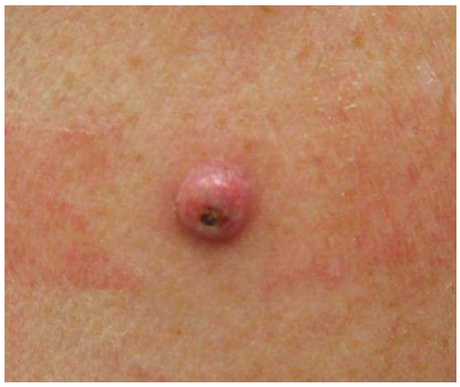


Fig. 3a. Squamous cell carcinoma

Verrucous carcinoma is a variant of SCC that clinically presents as a warty growth that may simulate the surface of a cauliflower. It may occur on the digits, oral mucosa, feet, or the anogenital region where it is known by the eponym "Buschke-Lowenstein tumor." (Schwartz, 1995). Although such tumors may be locally disfiguring, they are less likely to metastasize compared to other SCC subtypes. (Nguyen, 2005).

Bowen's disease is a in situ variant of SCC that presents as an erythematous patch with thin superficial scaling and frequently has notching of the borders which helps to distinguish it from nummular eczema, tinea corporis, or psoriasis. When Bowen's disease occurs on the penis, it has been known in the past as erythroplasia of Querat (Aynaud et al., 1994) although more recently, it has been suggested that the terms "Bowen's disease" and "erythroplasia of Querat" should not be used for lesions in the anogenital region and the preferred terms are vulval intraepithelial neoplasia for females and penile intraepithelial neoplasia for males(Wilkinson, 1992). Although an in situ tumor, Bowen's disease can progress to become an invasive SCC, particularly when it occurs at genital sites.

Although metastases from SCC are statistically much less likely than with melanoma, SCC can metastasize with fatal consequences. Regional metastases have an overall 5-year survival of 25% (Nguyen, 2005) and are a particular problem on the head and neck when SCC invades the perineurium of cranial nerves and gains access to the brain via foramina in the cranium. SCC also spreads via lymphatic channels to involve regional lymph nodes, and from there can gain access to the blood vessels with consequential distant metastases to

internal organs. The overall risk for metastases ranges between 2-6% (Nguyen, 2005), but may be associated with factors such as anatomic location, whether the tumor is primary or a recurrence after aggressive therapy, differentiation (well- or poorly-differentiated histologically), the presence of perineural invasion and the size of the diameter of the involved nerve, and the underlying immune status of the patient. Of head and neck sites, the ears and the lips confer higher risk for metastases at 8.8% and 13.7% respectively. (Nguyen, 2005; Ponten, 2003). The disparity in metastatic risk is dramatically increased between *primary* SCC (5.2% risk) to a 30.3% risk for *recurrent* tumors. (Nguyen, 2005). Increasing *size* also confers increasing risk where SCC <2 cm has a metastatic risk of 9.1% compared to 30.3% for tumors > 2 cm. (Nguyen, 2005). Perineural invasion is difficult to quantify but there is some suggestion and it seems logical that increasing diameter of the involved nerve is associated with increased risk. (Jambusaria-Pahlajani, 2010).

3.4 Histology

The histologic appearance of SCC will show keratinocyte hyperplasia and anaplasia, often with areas of dyskeratosis where keratin pearls will appear randomly in islands of squamous cells (See Figure 3b). Poorly-differentiated SCCs will lose the keratin production with a corresponding increase in the anaplastic appearance of the squamous cells. The pathologist may characterize the SCC as "well," "moderately," or "poorly" differentiated but often parses the terminology for intermediate states such as "well to moderately" or "moderate to poorly" differentiated. The poorly-differentiated SCCs warrant a high degree of vigilance since up to 17% of such tumors have been reported to metastasize compared to well-differentiated tumors with an estimated 0.6% risk. (Breuninger et al., 1990).

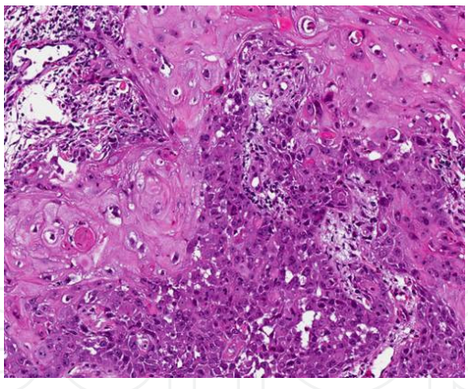


Fig. 3b. Histology of squamous cell carcinoma

3.5 Treatment options

When considering treatment options for SCC, approaches other than RT can be divided into three groups: topical therapies, destructive therapies, and surgical resection with margin control. The selection of a treatment modality will be greatly influenced by a number of variables that contribute to the physician's assessment of the perceived risk of metastases, the cosmetic and functional consequence of the treatment, and the general health status of the patient. RT can be effective as both a primary treatment as well as an adjuvant therapy for high-risk tumors.

When it comes to selecting RT for primary tumors, the first question to address is whether surgical excision with margin control is either feasible or practical since MMS has the highest reported cure rates for SCC compared to all other modalities. However, like all treatments for SCC, MMS cure rates begin to drop with increasing aggressive features such as tumor size, differentiation, discontinuity, perineural invasion, and a history of recurrence(s). Meta-analysis shows that MMS has 5-year recurrence rates for primary cutaneous SCC of 3.1% vs. 7.9% for other treatment options including CE, RT, and surgical excision. (Rowe et al., 1992). When it comes to high-risk tumors, MMS trumps other modalities as well for SCC of the lip, 2.3% (Mohs) *vs.* 10.5% (non-Mohs), on the ear, 5.3% (Mohs) *vs.* 18.7% (non-Mohs), and recurrent SCC 10.0% (Mohs) *vs.* 23.3% (non-Mohs). (Rowe et al., 1992).

In the clinical setting, circumstances arise where either MMS or surgical excision is simply not realistic and RT offers a reasonable alternative. The approximate overall 5-year cure rate for RT for primary SCC is on the order of 90%. (Rowe et al., 1992). There is great hesitancy on the part of many dermatologists to refer patients younger than 60 years of age due to perceptions of long-term cosmetic consequences of RT as previously mentioned, coupled with fears of increased risk of future malignancy in the treatment site. Although RT is associated with a *statistically* increased risk of secondary malignancies, one has to judge the *clinical* significance of the elevated risk before discounting RT in younger patients. Meadows et al. evaluated the risk of secondary neoplasms amongst survivors of childhood cancer from a large, United States, population-based registry. (Meadows et al., 2009). With 30 year follow-up, they demonstrated that the cumulative incidence of non-melanoma skin cancers in children who received RT was 4%, whereas the incidence in non-irradiated patients was 1%. So although the relative risk is high, the absolute excess risk for these non-lethal cancers is arguably low. With regard to other secondary malignancies, the cumulative incidence of secondary cancers over 30 years was 6% in the irradiated children, and 3% in the non-irradiated children.

The discussion of the treatment for SCC in the NCCN website is very candid about diversity of opinions about the role of RT for primary SCC across academic institutions, and more specifically between surgeons and radiation oncologists, stating that the radiation oncologists on the panel wanted to suggest that RT be considered as a first line therapy, whereas the surgeons did not. (NCCNN, 2011). The discussion was based on a large review of published data. (Avila et al., 1977; Collin, 1976; Fischbach et al., 1980; Fitzpatrick, 1995; Johnson et al., 1992; Lovett et al., 1990; Martin et al., 1970; Mazeron et al., 1988; Mendenhall et al., 1987; Petrovich et al., 1987a, 1987b, 1988; Rowe et al., 1989a, 1989b, 1992; Silverman et al; 1991, 1992; Stoll et al, 1964; Traenkle et al., 1962).

3.5.1 RT as primary therapy for SCC

The National Comprehensive Cancer Network published guidelines for RT for primary SCC are reprinted with permission in Table 1. Within these guidelines are specific dosing recommendations for primary SCC and BCC that are stratified by tumors < 2 cm and tumors ≥ 2 cm. In general, control rates for SCC primarily treated with RT are excellent, but slightly less effective than for BCC. In a report by (Solon *et al*., 1997) the four-year control rate was 96% (426/444) for BCC and 92% (144/156) for SCC with RT as primary therapy. As is the case for BCC, size influences local control rates as demonstrated by (Lovett *et al*., 1990): control rates for tumors less than 1 cm were 97% (86/89) for BCC *vs* 91% (21/23) for SCC; tumors 1-5 cm in size

had control rates of 87% (116/133) for BCC *vs* 76% (39/51) for SCC; and for lesions larger than 5 cm local control was 87% (13/15) for BCC *vs* 56% (9/16) for SCC.

Anatomic site considerations are critical in selecting therapy for primary SCC. MMS has excellent cure rates but is very morbid at specific anatomic sites with the consequence of posing difficult and complicated reconstructive challenges. For instance, SCC of the eyelids can often be treated with RT with high cure rates thus avoiding difficult staged surgical repairs. Also, tumors around the lacrimal system treated with RT can preserve the drainage system (JS, 2005) which is often compromised by reconstructive surgery. It was previously thought that lesions over cartilage, such as the ear, should not be treated with RT due to the risk of chondronecrosis, but it is now known that such sites can be safely treated with fractionated RT. (JS, 2005).

Verrucous carcinoma is particularly radiosensitive and RT can reasonably be considered as a first line therapy. Anogenital SCC is not uncommon, and surgical approaches can be very morbid leading to permanent loss of function and disfigurement. For anal SCC, the standard of care for most T1 and all T2 lesions and above is definitive combined chemoradiotherapy, with surgery reserved only for recurrences. (Bartelink et al., 1997; Flam et al., 1996; UKCCCR, 1996). This therapy results in equivalent cure rates to radical surgery, but offers functional organ preservation.

The medical community has embraced chemoradiotherapy as the gold-standard curative-intent treatment for most advanced squamous cell carcinomas of the head and neck, esophagus, uterine-cervix, and anus, with the goal of functional organ preservation. However, for the more rare entity of penile cancer, surgery remains the most commonly performed treatment. Surgical approaches to SCC of the penis frequently result in distortions of the urethra with consequential disruptions of urine flow direction. Partial or complete penectomies are extremely morbid procedures often with devastating emotional and psychological consequences for the patient. (Sarin et al., 1997). The authors have a series of successfully treated SCC of the penis. As one example, a 49 year old man presented with verrucous carcinoma staged as T1a,N2,M0 (stage IIIB). He presented with conventional condylomas on the base of the penis with a cauliflower morphology, while on the penile shaft there were verrucous plaques with hyperkeratosis and fissuring (See Figure 4). Penectomy and radical inguinal surgery had been recommended, but the patient elected to undergo an organ-sparing approach. He was treated with a regimen that would be considered "standard" for an anal SCC: 5580 cGy to the penis, 4500 cGy to the inguinal and pelvic nodes using an intensity-modulated radiotherapy technique. RT was given with concurrent weekly cisplatinum at 40 mg/m^2.

RT can also be used for SCC that involves the glans penis and encroaches on or involves the urethra where surgery can cause permanent disfiguration. Because penile cancer is a rare entity, no prospectively performed trials with RT exist. However, numerous retrospective studies using interstitial brachytherapy, external beam radiotherapy, or combinations have been reported and are summarized in Table 2. (Sarin et al., 1997) Of note, these studies did not combine chemotherapy with RT and demonstrate local control rates in the 57% to 85% range with RT alone with excellent functional and cosmetic results. It is important to note that the local failures were successfully salvaged with RT, leading to ultimate control rates of 90% to 97%. The most common functional deficit reported after RT is urethral stricture, reported in 9-41% of subjects. (Sarin, 2002).

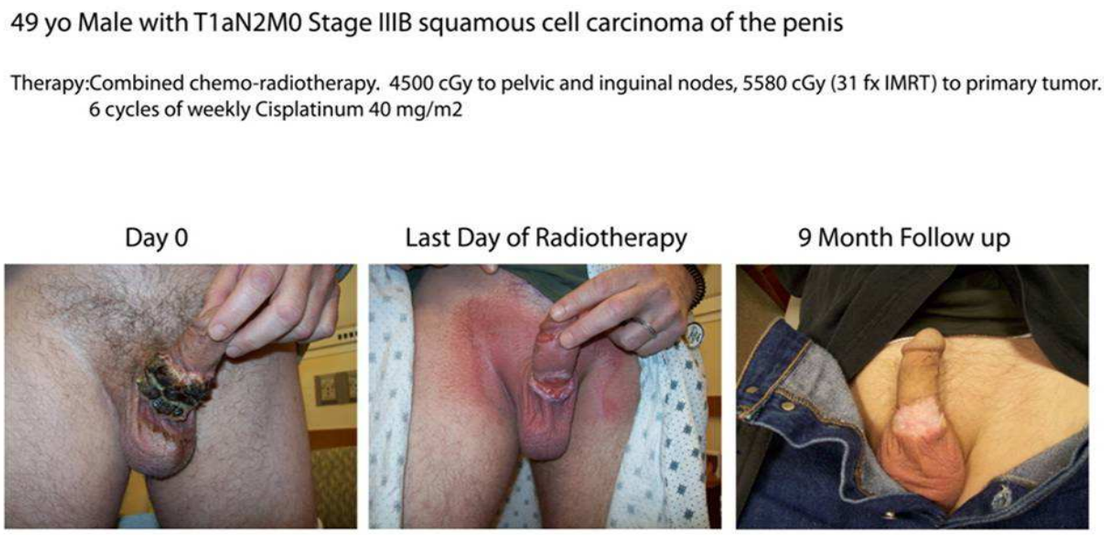


Fig. 4. Verrucous carcinoma of the penis, pre- and post- treatment

Study	Treatment	Local Control		Penectomy for necrosis	Urethral stricture
		Initial	Post salvage		
Rozan *et al* French multi-center 12 years	Implant 63 Gy (185 men) Others (75 men)	85%	94%	7%	30%
Delannes *et al* Toulouse, France 7 years	Implants- 60 Gy (51 patients)	82%	94%	16%	41%
Ravi *et al* Adyar 12 years	EBRT - 50 to 60 Gy (128 patients) Brachy – 60 to 70 Gy (28 patients)	65%	97%	6%	24%
Sarin *et al* Royal Marsden, UK. 5 years	EBRT – 60 Gy (56 patients) Implants – 60 Gy (13 patients)	57%	90%	3%	14%
Chaudhary *et al* TMH 2 years	Ir-192 Implant – 50 Gy (23 patients)	78%	96%	None	9%

Table 2. Radiotherapy for penile cancer (Data compiled in: Treatment Options for Urological Cancer, 2002)

3.5.2 RT as adjuvant therapy for SCC

For patients that have had the SCC removed surgically but are thought to be at high risk for local recurrence due to perineural invasion or aggressive histologic patterns, post-operative adjuvant RT should be considered. This is particularly true where perineural invasion is present despite negative margins on histology, as the patient is known to have a substantial

increased risk of local recurrence (Nyguyen, 2005). (See Table 1). RT for SCC showed 5-year actuarial local control of 0.54 for primary SCC, 0.0 for recurrent SCC, and 0.42 for nodal metastases. (Shim & Wilder, 1991).

3.5.3 RT for regional lymph node involvement

Regional disease includes SCC that has spread to regional lymph node basins and is divided into two treatment groups: those patients who have undergone completion lymph node dissection and are deemed at high risk for local recurrence, and those patients who did not. The NCCN guidelines committee suggests that all doses be delivered at 2 Gy per fraction using the shrinking field technique. This means the highest-risk areas should be prescribed the dose specified in Table 3, but lower doses may be prescribed for elective nodal region at less of a risk for relapse. For tumors after lymph node dissection, patients are stratified to those having extracapsular extension (ECE) and those who do not, and dosages are stratified by site: head and neck vs. axilla and groin (See Table 3).

Regional Disease	Dose (Gy)	Duration
After lymph node dissection		
Head and neck; with ECE[1]:	60-66	6- 6.6 weeks
Head and neck; without ECE:	56	5.6 weeks
Axilla, groin; with ECE:	60	6 weeks
Axilla, groin; without ECE:	54	5.4 weeks
No lymph node dissection		
Clinically (-) but at risk for subclinical disease	50	5 weeks
Clinically evident adenopathy: head and neck:	66 - 70	6.6 – 7 weeks
Clinically evident adenopathy: axilla, groin:	66	6.6 weeks
[1]ECE = extracapsular extension		

Table 3. Dose Recommendations for Squamous Cell Carcinoma: Regional Disease (2 Gy per fraction with shrinking field technique). Used by permission of the National Comprehensive Cancer Network

Although the above nodal dose guidelines represent level II consensus guidelines from the NCCN skin panel, it is noteworthy that the doses used to control nodal metastases in anal squamous cell cancers are lower (usually in the 45Gy to 56Gy range) when given in the context of chemotherapy. This could be due to the potent radiosensitizing effect of chemotherapy or an intrinsic radiosensitivity of anal squamous cell primaries relative to other locations.

4. Melanoma

Melanoma is the third most common skin cancer but is responsible for the majority of skin cancer deaths in the United States. The majority of melanomas present either as an unusual

appearing nevus relative to the other nevi on the body, or occur as a change in an existing nevus. Melanoma begins with the melanocyte, the pigment-producing cell of the epidermis which is derived from the neural crest during embryology (See Figure 2). The virulence of melanoma may be in part related to its origin, where it appears on the stage very early during embryogenesis and may have the cassette of genetic capabilities for migration not as common in basal cells and squamous cells that appear much later as the fetus develops. For whatever reason, melanoma has a high propensity for metastasis which is directly related to the depth of invasion measured in millimeters from the granular layer to the deepest part of the tumor by a calibrated ocular micrometer, and is referred to as the Breslow depth.(Breslow, 1970). For example, a melanoma with a Breslow depth less than 1 millimeter without other adverse features predicts a 5-year survival of about 95%, whereas a melanoma 4 millimeters in depth without other adverse features has an associated survival of about 65%. If ulceration is present in the primary tumor, survival for a 4 millimeter melanoma drops to about 50% at 5 years. (Balch et al., 2009).

4.1 Epidemiology

It is estimated that in 2010 there were 68,130 new cases of invasive melanoma in the U.S., with 8700 deaths (Jemal et al., 2010). The incidence of melanoma continues to rise as demonstrated by the Surveillance, Epidemiology and End Results (SEER) data, which has shown an increase in incidence in the United States from 6.7 cases per 100,000 in 1973 to 20.4 cases per 100,000 in 1996 in males, and from 5.9 cases per 100,000 to 14.3 cases per 100,000 cases in females. (Berwick, 2003; Surveillance, 2002). Although melanoma can occur in black patients, it is much more common in Caucasian patients with the highest rates of incidence in Australia (40.5/100,000), New Zealand (36.7/100,000), Norway (14.1/100,000) and the United State (13.3/100,000) for males. (Berwick, 2003; Ferlay et al., 2001).

4.2 Etiology

Melanoma appears to be a consequence of both genetic factors and environmental factors, in particular exposure to ultraviolet light. Well-known risk factors for melanoma include a personal or family history of melanoma, UV exposure, childhood sunburns, a high number of nevi, fair skin, blue eyes, easy freckling, higher socioeconomic status, and living at equatorial latitudes, to name a few. (Nestle, 2003). The majority of melanoma cases are spontaneous, but it is estimated that 6% to 14% of melanomas occur in family groups. (Ang et al., 1998). The gene most frequently involved in melanoma resides on chromosome 9p21 and is known as CDKN2A, whose gene product (p16) acts a tumor suppressor. (Pollock et al., 2003).

4.3 Clinical presentation

Melanoma can be roughly divided into various categories that have differing biological and genetic characteristics with varying degrees of causation by sun-exposure. For example, most melanomas appear on intermittently-exposed sites such as the torso. Other subtypes occur in chronically-exposed sites such as the head and neck, non-sun-exposed sites such as the palms, soles, genital/mucosal surfaces and ocular melanoma form their own entity. (Whiteman, et al., 2011).

In general, melanoma will present as a pigmented lesion that visibly changes over time, usually in terms of size and/or color (See Figure 5a). A very useful feature termed the “ugly

duckling" sign (Grob & Bonerandi, 1998) connotes the disparity in the appearance of the melanoma compared to surrounding nevi. We have found the "ugly duckling" sign to be of particular effectiveness in identifying melanomas in our high-risk patient group in our mole-mapping clinic at our institution, where total body photography is used to track nevi longitudinally for any signs of change that might herald malignant transformation. (Goodson et al., 2010).

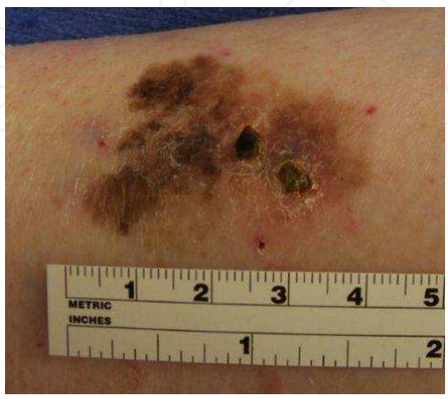


Fig. 5a. Superficial spreading melanoma with border irregularity and color variation.

4.4 Histology

Entire book chapters and even books have been dedicated to the problem of reproducibly making the distinction between melanoma and severely atypical nevi that are not melanoma under the light microscope. For the purposes of this chapter, the hallmark histologic features of melanoma include the proliferation of atypical melanocytes with *lack of maturation* of the melanocytes with depth, (See Figure 5b.) The presence of ulceration, mitotic figures, and angiolymphatic invasion are negative prognostic features. (Nestle, 2003).

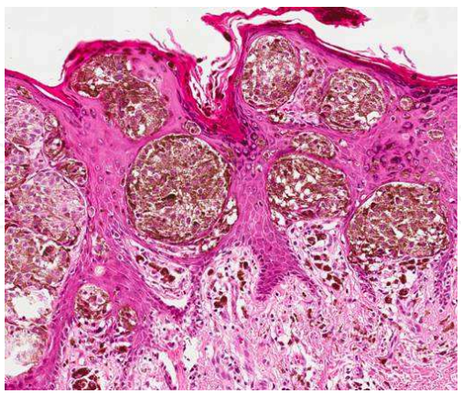


Fig. 5b. Histology of superficial spreading melanoma

4.5 Treatment

Melanoma is, by and large, considered a surgical disease. The role of RT for melanoma can be summarized as the occasional use as primary treatment for lentigo maligna (LM) or

unresectable primary tumors and in the adjuvant setting to improve local control or palliation.

4.5.1 Radiation as first-line therapy for melanoma

Lentigo maligna (LM) is a subtype of melanoma that occurs in chronically sun-exposed sites, usually on the head and neck, and is subdivided into lentigo maligna (LM), which is an in situ tumor, and lentigo maligna melanoma (LMM) which connotes histologic invasion. When invasion is present, the recommended treatment is surgical resection. (NCPGION, 2011). However, in situ tumors pose no immediate threat of metastases to the patient and are treated to prevent the future potential for invasion. The actual risk of invasion is unknown but has been predicted to occur at a rate of 2.2%at 45 years and 4.7% at 65 years. (Weinstock & Sober, 1987). In such cases, RT can be considered as a primary therapy for LM, because surgical excisions commonly result in very large defects with significant associated morbidity. (Johnson et al., 1997). When RT is used as primary therapy for LM (Grenz rays or soft X-rays using the Miesher technique), the cure rates range from 86 to 95%. (Farshad et al., 2002; Schmid-Wendtner et al., 2000; Tsang et al., 1994). The largest published study to date included 150 patients with both LM and LMM and a mean follow-up of 8 years with a complete response rate of 93%. (Farshad et al., 2002). For LM, definitive RT achieved a crude local control rate of 95%, with a mean time to recurrence of 45.6 months. Four of the five recurrences were at the edge of the radiation field, so the authors recommended targeting a margin of at least 10 mm around the visible lesion. (Farshad et al., 2002).

4.5.2 RT in the adjuvant setting for local or regional disease

Adjuvant RT is recommended for consideration in the NCCN guidelines under several circumstances: primary disease at risk for local recurrence, regional disease, and metastatic disease. (NCPGiON, 2011). As for primary disease, adjuvant radiation is often considered for the desmoplastic subtype of melanoma (DNM), a spindle cell variant of melanoma that is frequently associated with perineural invasion and is prone to local recurrences. (Vongtama et al., 2003). RT can be considered post-operatively when extensive neurotropism is present, since this will put the patient at an increased risk of a local recurrence (See Table 4). (Chen et al., 2006). RT was also recommended for patients with inadequate margins, which occurred predominately in the head and neck region in this series.

Regional disease includes large primary tumors > 3 centimeters in diameter as well as those cases where there are in transit or satellite metastases around the primary tumor where it is not practical to resect them with the primary tumor (See Table 4). However, even with radiation, patients with satellitosis are at risk for a recurrence in the radiated field. (Chang et al., 2006). Dosing must be tailored to specific sites and sizes of radiation fields. The head and neck area can be treated with orthovoltage or low-energy electrons with bolus in doses ranging from 24 to 36 Gy in four to six fractions. The larger the area, > 50 cm^2, the greater the need for more fractions, especially on the distal lower extremity. It has been recommended that a large surface on the trunk can tolerate 36 Gy in 12 fractions, however, a similar sized field on the lower limbs should be treated with 50 Gy in 25 fractions over 5 weeks. (Ainslie & McKay, 2003).

PRIMARY DISEASE
• Adjuvant treatment for selected patients with desmoplastic melanoma with extensive neurotropism
REGIONAL DISEASE
• Extracapsular extension • ≥4 involved nodes • Size ≥ 3 cm • Cervical **> Axillary > Inguinal Location • Recurrent disease after prior complete nodal dissection **For cervical nodes, consider RT if >2 nodes involved or nodes > 2cm in size
METASTATIC DISEASE
• Brain metastases (see NCCN Central Nervous System Cancers Guidelines) - Definitive or palliative stereotactic radiosurgery and/or whole brain radiation - Adjuvant radiation following resection of brain metastases • Other symptomatic or potentially symptomatic soft tissue and/or bone metastases

Table 4. Principles of Radiation Therapy for Melanoma (Reprinted by permission of the National Comprehensive Cancer Network)

For nodal melanoma that has been completely resected, adjuvant RT is considered where a high risk of local recurrence is anticipated (see Table 4). (NCPGiON, 2011). There are no published multi-center trials for RT in this setting, and published data are from single institutions. Most studies demonstrate improved regional control compared to surgery alone. (Ang et al., 1994; Burmeister et al., 1995; Corry et al., 1999; O'Brien et al., 1997; Stevens et al., 2000; Strom & Ross, 1995). The largest retrospective review investigating the role of RT included 615 patients meeting high-risk criteria for relapse. (Agrawal et al., 2009). At a median follow-up of 5 years, regional recurrence occurred in only 10.2% of the radiated patients versus 40.6% of the non-radiated patients. Of note, RT significantly increased treatment-related morbidity (5-year rate of 20% versus 13%, p=0.004), particularly with regards to *lymphedema*. The consensus opinion appears to be that overall survival is not greatly improved with adjuvant RT because four randomized trials involving complete surgical removal of subclinical lymph node involvement with elective lymph node dissections did not significantly improve survival. (Ainslie & McKay, 2003; Balch et al., 2000; Cascinelli et al., 1998; Sim et al., 1986; Veronesi et al., 1982). Retrospective data has not shown one regimen is more efficacious or safe than another, but delivering radiation over a longer time period might decrease the risk of side effects. (Chang et al., 2006). Several published series warn about the concomitant use of RT and interferon-alpha where increased regional toxicity has been observed. (Buckner et al., 2001; Damle et al., 1999; Hazard et al., 2002; Holsti et al., 1987; Stock et al. 1997).

When local, regional, or metastatic melanoma is not completely resected or is deemed unresectable, palliative RT should be considered. Although randomized trials have not shown any superiority of hypofractionated regimens over standard fractionation, a biologically effective dose >39 Gy_{10} (i.e. a regimen stronger than 30 Gy in 10 fractions) is recommended (See Table 4). (Ainslie & McKay, 2003; Olivier et al., 2007; Overgaard et al. 1985; Sause et al., 1991). Radiation effectively improves patient quality of life, as significant

symptom relief is achieved for 68% to 84% of patients. (Konefal et al., 1988; Olivier et al., 2007). Reports for clinical complete response (CR) rates range from 17 to 69%, with 49 to 97% achieving either a partial response (PR) or CR. (Overgaard et al., 1985; Sause et al., 1991; Seegenschmiedt et al., 1999).

4.5.3 RT in the setting of metastatic disease

As for metastatic disease, RT is recommended for brain metastases as either definitive stereotactic radiosurgery (SRS) or whole-brain radiotherapy (WBRT) for palliation. RT is also considered post-operatively in cases where a brain metastasis has either been resected or treated with SRS. (Fogarty et al., 2011). For patients with multiple metastatic melanoma lesions in the brain, WBRT is the most frequently utilized form of palliation. In a summary of a large number of series, WBRT provided symptomatic improvement in over two-thirds of patients, however, the medial survival is only 3.5 months. (Morton et al., 2003). A cautionary note is important to consider in the rare cases where patients have prolonged survival and can experience brain atrophy and consequential dementia. Striking functional decline was documented in 30% of women undergoing prophylactic brain irradiation in metastatic breast cancer. (Huang et al., 2009). In another study, brain atrophy developed in 30% of 92 patients undergoing WBRT, although the authors state that this was not necessarily accompanied by decreases in mini-mental status examination scores. (Shibamoto et al., 2008). It should be noted that over 90% of patients with brain metastases have been found to have some level of neurocognitive dysfunction before radiation. (Meyers et al., 2004). Although long-term survival is unlikely following WBRT for melanoma, it is advisable to inform patients and family members of the risk for post-treatment dementia.

For solitary metastatic lesions in the brain, surgical resection (potentially followed by radiation) or SRS should be considered. In two radomized trials for solitary melanoma metastases in the brain, surgical resection followed by WBRT led to better palliation and prolonged disease-free survival than surgery alone. However, overall survival was only increased in one of the two studies (18-month vs. 6-month medial survival; $P = 0.002$). (Hagen et al., 1990; Skibber et al., 1996).

SRS is becoming an increasingly-used alternative to craniotomy/surgical resection in patients with a small number (generally ≤ 4) of brain metastases, each measuring ≤ 4 cm. (Breneman et al., 1997; Chen et al., 2000; Samlowski et al., 2007). SRS may be a way to quickly address brain metastases to allow for intracranial control, perhaps buying time until more systemic options become available. In general, SRS alone or followed by WBRT yield results similar to surgical resection followed by WBRT. Again, the addition of WBRT after surgery or SRS improves disease-free survival but not necessarily overall survival. (Bafaloukos & Gogas, 2004).

5. Merkel cell carcinoma

Also known as primary neuroendocrine carcinoma of the skin, Merkel cell carcinoma (MCC) has the dubious distinction of being the most deadly of the skin cancers, including melanoma. Despite its virulence, MCC has not achieved the notoriety of melanoma due to its rarity.

5.1 Epidemiology

In the United States, MCC accounts for much less than 1% of all cutaneous malignancies and is estimated to occur at 0.24 tumors per 100,000 person-years compared to 17.0 tumors per 100,000 person-years for melanoma. (Agelli & Clegg, 2003). Overall survival rates are estimated to be 87% (1 year) and 49% (5 years) and a cause-specific survival rate of 62% at five years. (Lewis et al., 2006).

5.2 Etiology

The Merkel cell polyoma virus is detected in 43% to 100% of MCC tissue (Feng et al., 2008; Rollison et al., 2010), but its exact role in the pathogenesis of MCC remains to be sorted out. (Group, 2009). Because MCC tends to occur in a distribution similar to BCC and SCC, ultraviolet light has been suspected as playing a causative role, perhaps in conjuction with polyoma virus infection, but the exact etiology remains elusive.

5.3 Clinical presentation

MCC does not have a distinct and characteristic clinical presentation and is frequently mistaken for both benign and malignant neoplasms, but does have a predilection for sun-exposed sites on the head and neck, sun-exposed extremities and is most commonly seen in elderly Caucasians (See Figure 6a). Clinical signs of regional lymph node involvement is seen in 11-15%, while 50-70% of patients will eventually develop regional nodal metastases. (Hitchcock et al., 1988). Local recurrence rates are very high: 25-30%. Up to 50% of patients develop distant metastases with the most common sites being the liver, bone, brain, lung, skin, and distant lymph nodes. (Akhtar et al., 2000; Gillenwater et al., 2001; Medina-Franco et al., 2001; Taylor & Heilman, 2005).

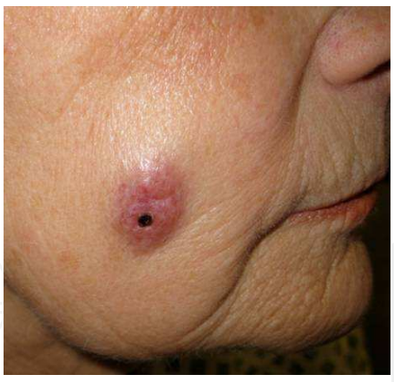


Fig. 6a. Merkel cell carcinoma, with bunch biopsy site in center of tumor

The most important prognostic feature of MCC is the stage followed by tumor size. (Akhtar et al., 2000; Allen et al., 1999; Haag et al., 1995; Kokoska et al., 1997; Medina-Franco et al., 2001; Ott et al., 1999; Ratner et al., 1993; Skelton et al., 1997). The American Joint Committee on Cancer (AJCC) staging system divides the presentation of MCC into local, regional, and disseminated disease. (Edge et al., 2009). 60%-70% of patients present with local disease only (Stage I) and have with an estimated 3-year survival of 55-73%, while up to 40% of patients present with regional node involvement (Stage II) with a 33% 3-year survival estimate. (Yiengpruksawan et al., 1991).

5.4 Histology

The histopathology of MCC may mimic other types of malignancies, particularly basal cell carcinoma. Under light microscopy, the appearance is one of monotonous aggregates of small basophilic cells that are closely packed with a large nuclear:cytoplasmic ratio (See Figure 6b). A high mitotic rate and vesicular nuclei are common. The neoplasm is mostly dermal and is usually separated from the epidermis by a thin layer of uninvolved dermis called the "Grenz zone." Histologically, the closest simulant to MCC is metastatic small cell carcinoma of the lung. The distinction between those two diagnoses can usually be made with immunohistochemistry, since MCC reacts with the immunostain for cytokeratin 20 (CK20) in 89-100% of tumors but does not react with thyroid transcription factor 1(TTF-1) which is expressed in small cell lung cancer but not MCC. (Cheuk et al., 2001; Hanly et al., 2000; Scott & Helm, 1999).

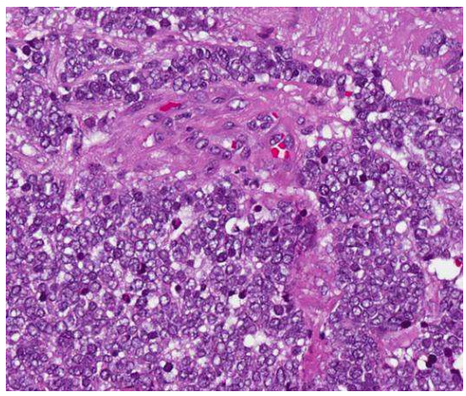


Fig. 6b. Histology of Merkel cell carcinoma

5.5 Treatment

Like melanoma, MCC is a disease best treated surgically. The National Comprehensive Cancer Network™ (NCCN) panel has acknowledged substantial variability in treatment recommendations among physicians representing multiple institutions across the United States, therefore, the treatment recommendations by the NCCN are broad to include disparate attitudes between institutions hampered by the lack of randomized controlled studies to draw upon. (NCPGiON, 2011). In general, a wide local excision is recommended for the primary site with the option of adding a sentinel lymph node biopsy. Postoperative radiation to the primary site is routinely performed at some institutions, whereas others add RT only if the surgical margins are close or positive. The same philosophy applies to regional lymph node basins where some institutions will routinely irradiate regional lymph node basins regardless of sentinel lymph node status, while others reserve postoperative RT for basins with positive nodes, and in some cases, only if the nodes demonstrated extracapsular spread.

The difficulty in making firm treatment recommendations for RT sits firmly in the paucity of prospective randomized data from which to make informed clinical decisions. Despite the fact that the benefits of RT in MCC are mixed in the literature, there is published evidence that postoperative radiation can help to minimize locoregional recurrences but not necessarily improve overall survival. A meta-analysis compared surgery alone compared to surgery

followed by RT to the surgical site showing a lower risk of local and regional recurrences but a difference in overall survival did not reach statistical significance. (Lewis et al., 2006). In a series of 82 patients, both relapse-free survival and overall survival were improved with RT to the primary site or the regional lymph node basins (Jabbour et al., 2007), therefore, the NCCN panel includes RT as an option for all stages of MCC. Further support for adjuvant RT comes from a SEER analysis of 1,665 patients, which showed RT was associated with improved survival for all size tumors, especially for those >2 cm. (Mojica et al., 2007).

There are occasions where RT is an acceptable first line therapy for primary tumors, particularly when the tumors are large, have satellite metastases, deemed unresectable, or the patient is a poor surgical candidate. Because MCC tends to occur in an elderly patient cohort, surgical morbidity is often a significant consideration when designing a treatment strategy. In a retrospective series of 43 patients, RT was used as monotherapy and had a reported in-field tumor control rate of 75%. (Veness et al., 2010). Additionally, radiation may be useful for palliation when surgical resection is not feasible for either primary or secondary lesions.

Primary Site	Dose (Gy)
• Negative resection margins	50 - 56
• Microscopic (+) resection margins	56 - 60
• Gross (+) resection margins or unresectable	60- 66
Nodal Bed	
• **No SLNB or LN Dissection**	
➢ Clinically (-) but at risk for subclinical disease	46 - 50
➢ Clinically evident lymphadenopathy	60 - 66
• **After SLNB without LN dissection**	
➢ Negative SLNB: axilla or groin	RT not indicated
➢ Negative SLNB: head and neck, it at risk for false negative biopsy	46 - 50
➢ Microscopic N+ on SLNB: axilla or groin	50 - 54
➢ Microscopic N+ on SLNB: head and neck	50 -60
• **After LN Dissection**	
➢ Lymph node dissection: axilla or groin	50 - 54
➢ Lymph node dissection: head and neck	50 - 60

Table 5. Dose Recommendations for Merkel Cell Carcinoma (2 Gy per fraction with shrinking field technique)

Table 5 with recommended dosages for RT for MCC is reprinted by the permission of the National Comprehensive Cancer Network™ with the following qualifying comments. When MCC on the extremities and torso has been treated with wide local excision (WLE) with negative margins and negative sentinel lymph node biopsy (SLNB), RT is usually reserved

for the primary site only (but not given at all institutions). If a SLNB is not performed, RT to the nodal basins can be considered. For head and neck MCC, the risk of falsely negative SLNB is higher and two scenarios may exist: first, if the SLNB is negative, consideration can be given to irradiate the primary site +/- the nodal beds or observe; second, if the WLE is performed without SLNB, consideration should be given to irradiate the primary site +/- nodal beds with the in-transit lymphatics if feasible.

As for the authors, the decisions made regarding the use of RT as either a primary therapy or adjunctive therapy for resected MCC occur after presentation of each individual case in a multidisciplinary tumor conference setting. The multidisciplinary conference has the advantage of including the input of the radiation oncologists, pathologists, surgeons, medical oncologists, and dermatologists. The details of each specific case with regards to staging, tumor histology characteristics, general state of health of the patient, etc. are all factored into tailoring a treatment algorithm appropriate for a given patient and clinical scenario.

6. Cutaneous lymphoma

The cutaneous lymphomas are a subtype of extra-nodal non-Hodgkins lymphomas that are generally divided into three categories: cutaneous T-cell lymphomas, cutaneous B-cell lymphomas, and the natural killer cell (NK cell) lymphomas. As a group, the cutaneous lymphomas are considered as skin-associated lymphoid tissue (SALT) lymphomas. Although there are histologic correlates with the systemic lymphomas, the distinct clinical characteristics and clinical courses of the skin lymphomas requires that the clinician consider them as distinct entities when considering treatment options.

6.1 Cutaneous T-cell lymphoma

When most clinicians hear the term "cutaneous T-cell lymphoma" (CTCL), they are likely to bring images to mind of the two most well-known variants: mycosis fungoides (MF) and Sézary syndrome (SS). There are, in fact, a fascinating myriad of CTCL subtypes including MF, SS, anaplastic large cell lymphoma, subcutaneous panniculitis-like CTCL, granulomatous slack skin, and peripheral T-cell lymphoma to name a few of the most frequently-encountered variants. Both focal electron beam therapy and total body electron beam therapy can greatly reduce morbidity and may provide complete cures in many cases.

6.1.1 History

The term "mycosis fungoides" is an unfortunate appellation that has been a source of confusion since the term was coined by the French physician Alibert, who first described the condition in 1806 in a single patient with tumor stage MF presenting with large fleshy protuberances on the head and neck that indeed resembled mushrooms, hence the name, "*mycosis fungoides.*" (JLM, 1806). The report occurred long before fungus was known to cause disease in the skin and was rather a descriptive term that continues to confuse both patients and physicians alike, who naturally associate the diagnosis with an underlying fungal infection. MF is an extra-nodal cutaneous lymphoma predominantly comprised of CD4+ T-cells.

The second most well-known variant is Sézary syndrome (SS), which can be thought of as the leukemic variant of MF where there are a high number of circulating enlarged malignant lymphocytes called "Sézary cells," as described by Sézary in 1936 in a patient with what came to be known as the classic triad of erythroderma (globally inflamed red skin), lymphadenopathy, and more than 10% of the circulating white blood cells have a Sézary cell morphology under light microscopy. (Sezary, 1938). The principles of radiotherapy will be similar for MF, SS, and the various subgroups, therefore, MF and SS will be used as representative diseases for modeling therapy in this chapter.

6.1.2 Epidemiology

In the United States, CTCL is considered a rare disorder. A review data from 13 population-based cancer registries of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute was reviewed from 1973 to 2002 and an incidence of 6.4 cases per million was observed. (Criscione & Weinstock, 2007). An increasing incidence was observed over that observation period but the reason for the increased incidence is unknown. CTCL is most certainly underreported. The majority of cases of MF are low-grade and are treated locally by dermatologists and not referred to cancer treatment centers and consequently, not entered into tumor registries. Also, many cases of early stage MF are not actually diagnosed accurately since MF can easily simulate either psoriasis or eczema and confirming biopsies are never performed, so the diagnosis is never entered into tumor registries.

6.1.3 Clinical presentation

MF has a distinct clinical presentation that classically begins as erythematous patches that can eventually progress to thicker plaques, and then to raised tumors on the skin (See Figure 7a). This progressive nature of the skin involvement is captured in the staging schema with T1 being patches and plaques covering less than 10% of the total skin surface, T2 for > 10% of the surface, T3 for tumors, and T4 for erythroderma or red inflamed skin globally distributed. The distribution of MF lesions is, in general, very reproducible with the patches predominantly located in sun-protected areas in a "bathing-suit" distribution. This implies involvement of the axilla, mid-axillary line, torso, buttocks, and groins. The fact that ultraviolet light is frequently very effective in treating MF may explain why the disease is much less frequently observed in sun-exposed sites. For patch-stage patients, the lesions are curiously positioned in the middle ground between psoriasis plaques and patches of atopic dermatitis (eczema), where the former are very well-demarcated while the later have much less defined borders.

SS presents with an entirely different clinical picture where the patients present with widespread erythema and scaling, and frequently have difficulty maintaining a comfortable body temperature due to the massive loss of heat through the dilated capillaries diffusely in the skin. Patients with SS frequently have severe pruritus accompanied by fissures and erosions that often get infected, and indeed the main cause of death for both MF and SS is sepsis from a skin source. SS patients classically present with palpable lymphadenopathy.

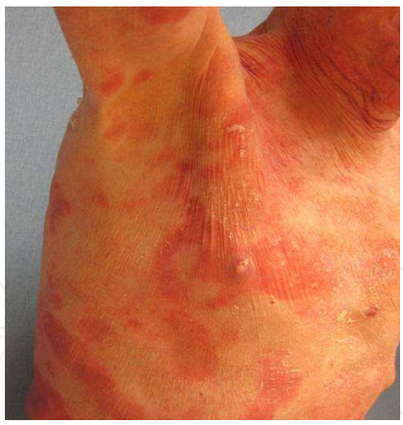


Fig. 7a. Cutaneous T-cell lymphoma (mycosis fungoides)

6.1.4 Histology

The biopsy of classic early stage MF has the distinct feature of swarms of atypical lymphocytes in the upper dermis that home to the epidermis like moths to a street lamp (epidermotropism). The epidermis is peppered with atypical lymphocytes occurring singly and in clusters of T-cell aggregates eponymously called "Pautrier microabscess" (See Figure 7b). (LM, 1937). Problematically, MF is a slowly evolving disease and it may take many years before a skin biopsy displays distinctive diagnostic features. In such ambiguous cases, skin specimens are submitted for clonality testing by looking for overexpression of a singular T-cell receptor on the surface of the CD4+ cells. As the disease progresses from patches and plaques to tumors, the epidermotropism is lost and densely packed aggregates of atypical lymphocytes are seen occupying the superficial and deep dermis without epidermal involvement.

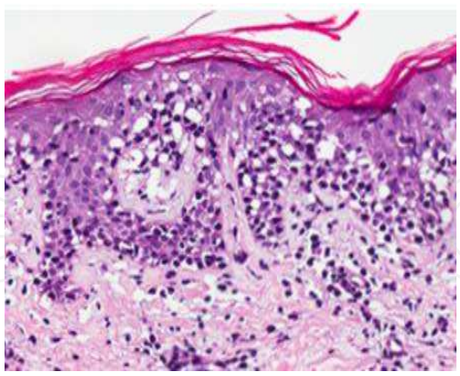


Fig. 7b. Histology of cutaneous T-cell lymphoma, mycosis fungoides subtype

The histology of SS is even more problematic since the classic features of MF are only seen about half of the time, whereas the remaining cases may be impossible for the dermatopathologist to distinguish from generic "dermatitis" where the influx of lymphocytes is so extreme that the distinguishing features of the Pautrier microabscesses are lost. In such cases, flow cytometry of the peripheral blood can be very helpful and cell sorting easily detects an aberrant overexpression of a T-cell clone.

6.1.5 Staging

In general terms, T1 disease includes patients with less than 10% of the skin involved and the five-year survival is not statistically different than that for the control population. (Kim et al., 1996). Patients with T2 disease (> 10% of the skin surface involved) do have an increased mortality with 15% eventually dying from their disease. (Kim et al., 1999). Approximately half of all patients with T3 disease (skin tumors) or T4 disease (erythroderma) die of their disease. (Kim et al., 2003).

6.1.6 Treatment

The majority of patients presenting with MF are treated with skin-based therapies, most frequently ultraviolet light in the form of narrow band UVB or PUVA which is UVA combined with the orally ingested photosensitizer "psoralens" (psoralens + UVA = PUVA). Topical agents include topical chemotherapeutic agents such as nitrogen mustard and carmustine, and a topical retinoid, bexarotene. When these skin-based topical therapies are ineffective, systemic therapies that can be considered include interferon –alpha 2b given as subcutaneous injections (Olsen & Bunn, 1995) and is often combined with a skin-based therapy such as ultraviolet light. Another alternative is oral bexarotene (Olsen & Bunn, 1995), which can also be combined with light therapy. Newer agents include the histone deacetylase inhibitors vorinostat (oral) (Kavanaugh et al., 2010) or romidepsin (intravenous). (Bertino & Otterson, 2011). Denileukin difititox is a fusion protein of interleukin-2 with a diphtheria toxin moiety that acts as a Trojan horse of sorts. The fusion protein is bound to the surface of the T-cell by its IL-2 receptor and the drug is internalized and the diphtheria toxin provokes apoptosis. (Duvic & Cather, 2000).

6.1.7 Radiation therapy for CTCL

Radiation therapy plays a critical role in the treatment of MF and is considered in three scenarios: curative treatment for uni- or paucy lesional MF, intent to achieve a complete response with total skin electron beam therapy (TSEBT), or local palliation with external beam radiation therapy (EBRT).

MF is radiosensitive compared to other skin cancers and doses as low as 2000-3000 cGy can yield high rates of durable remissions. For localized cases of stage I MF, electron beam is the most common radiotherapeutic modality, however, kilovoltage X-rays also have rapid dose fall off and hence work well in this application. Various different electron beam energies can be selected to appropriately treat the lesions. Due to the skin-sparing aspects of electron beam, the use of tissue equivalent bolus material to achieve full dose at the skin surface is standard. Micaily *et al.* reported on 18 patients with unilesional MF treated with electron beam at 30.6 Gy. (Micaily et al., 1998). The complete response rate was 100% and 2 patients failed out of field. The relapse free survival and overall survival rates were 86% and 100%, respectively. Wilson and colleagues reported on 21 patients treated with a median dose of 20 Gy for stage IA MF.(Wilson et al., 1998). Local control was 75% at 10 years, and 85% for patients with unilesional disease. For patients that received >20 Gy, disease free survival was 91%. Dose recommendations are provided in Table 6.

TSEBT is often considered for plaque (T2) and tumor (T3) cases due to the more guarded prognosis than T1 patients (10% of the skin involved). Because the response rates are so

good for skin-directed therapies, TSEBT is not commonly used for T1 cases. TSEBT is a specialized technique for radiotherapy departments and is not widely available. The typical dose is 36 Gy in 36 fractions given 4 times weekly for 9 weeks. There are 6 body positions with two gantry positions for each body position. Selective electron boosts are administered to areas that do not receive adequate dose: the scalp, perineum and soles of feet. Also selective blocking is performed to prevent excessive toxicity to the eyes, hands, feet and nails.

In a Stanford study, a total of 180 patients with MF were treated with total skin electron-beam therapy (TSEBT) with or without topical nitrogen mustard. (Navi et al., 2011). The overall response rate was 100% while 60% of patients achieved a complete response (75% with T2 and 47% with T3) and the overall survival was 59% (T2) and 40% (T3). Those patients with incomplete responses or relapse had a 100% overall response rate with a second round of TSEBT. The response durations in this study were 29 months for T2 disease and 9 months for T3 disease (P = 0.006). Attempts have been made to prolong the response rates after TSEBT; however, combined PUVA (Quiros et al., 1997), nitrogen mustard (Navi et al., 2011), and interferon-alpha 2b (Roberge et al., 2007) did not statistically prolong relapse time.

Toxicities associated with TSEBT can be severe. Acute toxicities (defined as those during treatment and within 3 months of completion) include erythema, moist and dry desquamation, and pain. Given the severity of erythema and the resultant pain and discomfort, it is common to give a treatment break for a week or more during TSEBT. Late toxicities include generalized erythema (which can make it difficult for the clinician to separate from recurrence), telangiectasia, xerosis, secondary malignancies, and temporary and sometimes permanent loss of hair follicles, sweat glands, and nails. (KB, 2005). In our experience, hair loss is the main complaint from the patient, and is particularly distressing for females.

EBRT is very useful as a palliative treatment for recurrent MF when isolated tumors are present. MF is relatively radiosensitive compared to other skin cancers and doses as low as 400 cGy in 2 fractions can be very effective. Tumoritis has been known to occur with low doses of RT. This is secondary to prompt apoptosis resulting in rapid desquamation of the tumor site itself with relative sparing of the normal surrounding skin. Advanced MF lesions frequently ulcerate with RT and local wound care is essential to reduce the risk of infection. It is important to be prudent and patient and treat deep lesions with low, palliative doses (2 Gy x 2 or 3 Gy x 2).

6.2 Cutaneous B-Cell Lymphoma (CBCL)

The cutaneous B-cell lymphomas (CBCL) are less common than are the cutaneous T-cell lymphomas and represent between 18.8% and 26.4% of all cutaneous lymphomas. (Fink-Puches et al., 2002; Willemze et al., 1997). As opposed to most CTCL, CBCL presents as either solitary or paucilesional nodules on the skin with a red to violaceous color without any surface change such as scaling. The vast majority of CBCL are very low-grade malignancies with an excellent prognosis. It is important to make a distinction between primary cutaneous B-cell lymphomas which appear to arise in and stay in the skin as opposed to secondary cutaneous B-cell lymphoma where the skin is a secondary organ of involvement from a systemic lymphoma. Clinically the primary and secondary cutaneous B-cell lymphomas can be indistinguishable, therefore, a search for a systemic lymphoma is

undertaken before the diagnosis of primary CBCL is confidently made. Radiotherapy is the mainstay of treatment for the majority of CBCL cases.

6.2.1 Epidemiology

Due to the rarity of CBCL, the actual incidence is difficult to determine, although there is a curious range in incidence across geographical areas. CBCL has been reported to comprise 4.5% of all cutaneous lymphomas in the United States (Zackheim et al., 2000) to 26.4% of cases in Austria. (Fink-Puches et al., 2002). The varying regional incidence of CBCL is likely due to do differences in how CBCL is classified and entered into tumor registries. However, there is also good evidence that etiologic factors may well contribute to regional disparities in incidence. For example, it has been reported for many years now that infection with *Borrelia burgdorferi* has been linked with CBCL in Europe but a similar link has not been demonstrated in the U.S. (Cerroni et al., 1997; Goodlad et al., 2000).

6.2.2 Etiology

The hypothesis linking an underlying infection to CBCL is the notion that chronic antigenic stimulation may eventually lead to the selection of B-cell subclones over time. A similar hypothesis has been proposed for the development of small bowel lymphoma in patients with chronic bowel inflammation with celiac sprue or the development of MALT (mucosa associated lymphoid tissue) lymphomas arising in the gastric mucosa of patients with chronic *Helicobactor pylori* infection. (Fischbach et al., 2005). The reality is that the majority of cases of CBCL arise spontaneously and multiple attempts to pinpoint a specific cause have been unsuccessful. Putative etiologic agents include *Borrelia spp.,* Epstein-Barr virus, or human herpes viruses. (Nagore et al., 2000; Zochling et al., 1998). Interestingly, there are cases of presumed benign reactive lymphoid hyperplasia (pseudolymphoma) simulating CBCL that have occurred secondary to drugs, vaccinations, arthropod bites, or chronic folliculitis. (Bergman, 2010). The question as to whether pseudolymphomas can progress to true CBCL has not been definitively answered, although it seems logical that with chronic antigenic stimulation, the ultimate selection of a B-cell clone remains a possibility.

6.2.3 Clinical presentation

There are many variants of CBCL, but the three entities discussed in this chapter are the two most common forms with indolent behavior (cutaneous follicle center cell lymphoma and cutaneous marginal zone lymphoma) and a more aggressive variant, large B-cell lymphoma of the leg as described in the European Organization for the Treatment of Cancer (EORTC) classification scheme. (Willemze et al., 1997).

Primary cutaneous follicle center cell lymphoma (FCCL) and primary cutaneous marginal zone lymphoma (MZL) are frequently indistinguishable clinically and can only be separated histologically. Both usually present as either solitary or grouped red to plum-colored nodules that have a smooth surface without the scaling common to CTCL (See Figure 8a.). Compared to CTCL, the color tends to shift slightly on the spectrum from red to purple. The nodules are generally non-tender and are usually distributed on the head and neck or the torso. It is more uncommon to see lesions on the extremities. The prognosis for both entities is excellent.

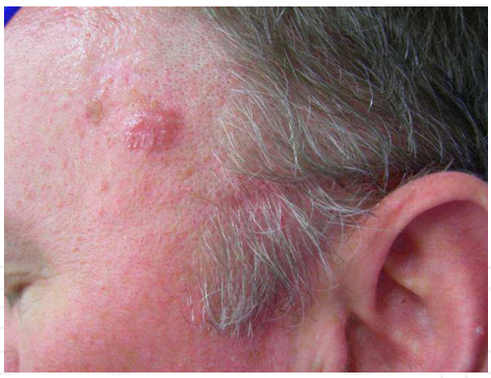


Fig. 8a. Cutaneous B-cell lymphoma

Large B-cell lymphoma of the leg (LBCLL) is one of the dermatologic diseases with a striking predilection for a specific anatomic site. The patients are almost uniformly elderly with a female to male predominance and the presentation is one of plum-shaped and plum-colored nodules usually confined to one leg, most commonly below the knee. (Kerl & Cerroni, 1996; Vermeer et al., 1996). As the name implies, the B-cells show a striking large cell morphology compared to the relatively small-sized B-cells in FCCL and MZL. Unlike the other cutaneous B-cell lymphomas, it is common for nodules in LBCLL to ulcerate and lesions are usually grouped and multiple as opposed to solitary. The prognosis is much more guarded in LBCLL, with an estimated 5-year survival at about 50%. (Fink-Puches et al., 2002; Willemze, 1997). There are other systemic large B-cell lymphomas that can secondarily involve the skin of the leg, therefore, a search for an underlying systemic lymphoma is essential in these patients. (Cerroni, 2003).

6.2.4 Pathology

Follicle Center Cell Lymphoma (FCCL):

Skin biopsies of FCCL have a fascinating appearance under light microscopy: a dermal infiltrate is comprised of lymphocytes simulating the germinal centers/follicles seen in lymph nodes (See Figure 8b). In about 25% of cases, the follicular architecture resembling the lymph node is classic, while the majority of cases will have less well-formed follicular

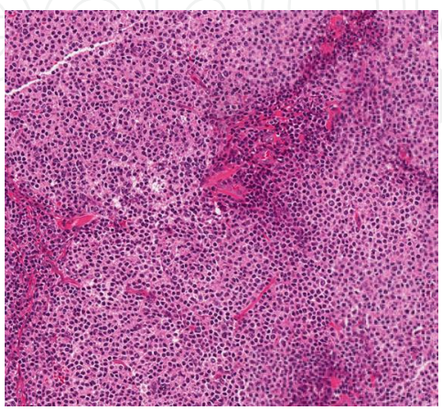


Fig. 8b. Histology of cutaneous B-cell lymphoma, follicle center cell type.

architecture. (Cerroni et al., 2000). There is often an admixture of other inflammatory cells, including T-cells, histiocytes, eosinophils, and plasma cells. The B-cells express the B-cell markers CD-20 and CD-79a, but unlike nodal lymphomas, do not express the Bcl-2 protein. (Cerroni et al., 1994; Cerroni & Kerl, 1994). The tumors stain positively for kappa or lambda light chains but may or may not have an identifiable restriction of one light chain favoring another. Not present in FCCL is the 14;18 translocation normally found in nodal follicular lymphomas, and when present, should alert the clinician to search for an underlying systemic lymphoma. (Cerroni et al., 1994; Delia et al., 1989).

Marginal Zone Lymphoma (MZL):

The infiltrate in MZL is also dermal-based with sparing of the epidermis, but the follicular architecture is much less well-defined. There is, however, an infiltrate surrounding the neoplasm with pale-staining cells with abundant pale cytoplasm referred to by hematopathologists as "marginal zone cells." These are centrocyte-like cells that are CD-20 and –CD-79a positive, and unlike FCCL, Bcl-2 protein is usually positive. The majority of cases of MZL with demonstrate light chain restriction with a predominance of one of the light chains over the other.

Large B-cell Lymphoma of the Leg (LBCLL):

In contrast to FCCL and MZL, the infiltrates of LBCLL will abut the epidermis and can often percolate into the epidermis and simulate the epidermotropism of CTCL. (Cerroni et al, 2009). The B-cells are larger and consist of immunoblasts, centroblasts, and large centrocytes. Cells express CD-20 and CD79a as expected but staining for the Bcl-2 protein is variable. Another pitfall may be the presence of CD30 positive large cells, which may simulate anaplastic large cell lymphoma derived from T-cells. In such cases, the CD30 does not have prognostic import as it does in anaplastic large cell lymphoma where its presence connotes a more favorable prognosis.

6.2.5 Treatment

Because most FCCL and MZL follow an indolent course, observation can be an acceptable practice with follow-up visits scheduled every six months or if new lesions arise. It has been our experience that many solitary lesions will actually involute with an incisional biopsy, which is to say that even if a small portion of the tumor is biopsied, the lesion may undergo spontaneous regression. In these cases it has been our practice to observe the lesion over time and treat only in cases of a local recurrence. In most cases, local RT is the first line treatment and provides high response rates coupled with excellent cosmesis and minimal morbidity.

Radiotherapy was evaluated in a meta-analysis study of 460 patients with FCCL and the complete response rate was 99% (457/460), with doses ranging from 20-54 Gy but in general averaging above 30 Gy. The relapse rate was 30%, but not defined as to whether these were in-field vs. extra-field recurrences. That same study included a meta-analysis of 132 patients with MZL treated with radiotherapy, and again showed a 99% complete response rate (130/132), with average dosages between 30-45 Gy and margins ranging from 1 to 5 cm. (Senff et al., 2008). The recurrence rate was 46%, but again not specified if these were in-field

recurrences or other site recurrences. We have examined our own experience for patients with cutaneous B cell lymphoma. We identified 38 cases treated. The overall survival for the entire study population at 5 and 10 years was 97% and 78%, respectively, whereas disease-specific overall survival has not shown any deaths in the FCCL and MZL subgroups. Among patients that relapsed, in-field control was achieved in 82% of patients. Patients treated with other local therapies had a significant higher rate of failure (p=0.01). (Tward et al., 2009).

Other treatment modalities included surgical excision for small solitary lesions, intralesional interferon-alpha, or intralesional or systemic rituximab therapy which is a monoclonal antibody to CD20. Due to ease of use and response rates, RT is the most commonly used first line treatment with doses recommended of 30 Gy with margins of 1 to 1.5 cm of uninvolved surrounding skin (See Table 6). (Senff et al., 2008).

Disease	Dose (Gy)	# of Fractions
MF (unilesional)	24-36	10-18
MF (TSEBT)	30-36	30-36
MF (palliative)	4-6	2-3
FCCL	30	15
MZL	30	15
FCCL or MZL (palliative)	4	2
LBCLL	30-40	15-20

Table 6. Dose Recommendations for Cutaneous Lymphomas

For LBCLL where the prognosis is much more guarded, the EORTC recommends that these cases be treated with multi-agent chemotherapy similar to treatment for diffuse large B-cell lymphoma. (Senff et al., 2008). Recommended is R-CHOP (rituximab plus cyclophosphamide, doxorubicin (Adriamycin), oncovin (Vincristine), and prednisone with or without adjuvant radiotherapy. Unfortunately, there are no controlled trials available to help make an informed decision in such cases. At our institution, the decision as to whether or not to add radiotherapy to R-CHOP is made in the setting of the Multidisciplinary Lymphoma Conference, and is based on the extent of the cutaneous disease.

7. Conclusion

Radiation therapy is an excellent treatment choice for a variety of skin cancers in a wide number of anatomic locations, which frequently offers high rates of cure with excellent cosmesis and provides patients an alternative to aggressive and often disfiguring surgery. RT also fills an important role as an adjunctive therapy when combined with other systemic agents with or without surgery, and should be included in the armamentarium of any multidisciplinary approach to skin cancer. Improved communication between academic training programs in dermatology and radiation oncology are needed to overcome historical biases that contribute to the underutilization of this very useful treatment modality.

8. References

Agelli, M. and L.X. Clegg, *Epidemiology of primary Merkel cell carcinoma in the United States.* J Am Acad Dermatol, 2003. 49(5): p. 832-41.

Agrawal, S., et al., *The benefits of adjuvant radiation therapy after therapeutic lymphadenectomy for clinically advanced, high-risk, lymph node-metastatic melanoma.* Cancer, 2009. 115(24): p. 5836-44.

Jill Ainslie, L.J.P., Michael J. McKay, *Radiotherapy for primary and regional melanoma*, in *Cutaneous Melanoma*

Akhtar, S., K.K. Oza, and J. Wright, *Merkel cell carcinoma: report of 10 cases and review of the literature.* J Am Acad Dermatol, 2000. 43(5 Pt 1): p. 755-67.

Alexander, G.A. and U.K. Henschke, *Advanced skin cancer in Tanzanian albinos: preliminary observations.* J Natl Med Assoc, 1981. 73(11): p. 1047-54

Allen, P.J., Z.F. Zhang, and D.G. Coit, *Surgical management of Merkel cell carcinoma.* Ann Surg, 1999. 229(1): p. 97-105.

Ang, C.G., et al., *Characteristics of familial and non-familial melanoma in Australia.* Melanoma Res, 1998. 8(5): p. 459-64.

Ang, K.K., et al., *Postoperative radiotherapy for cutaneous melanoma of the head and neck region.* Int J Radiat Oncol Biol Phys, 1994. 30(4): p. 795-8.

A.N.H. Charles M. Balch, Arthur J. Sober, Seng-jaw Soong, Editor 2003, Quality Medical Publishing, Inc.: St. Louis, Missouri. p. 449-471.

Avila, J., et al., *Carcinoma of the pinna.* Cancer, 1977. 40(6): p. 2891-5.

Aynaud, O., M. Ionesco, and R. Barrasso, *Penile intraepithelial neoplasia. Specific clinical features correlate with histologic and virologic findings.* Cancer, 1994. 74(6): p. 1762-7.

Baca HJ, B.S., Dzubow L, *Risk Factors*, in *Cutaneous Oncology: pathophysiology, diagnosis, and management*, M.M. Miller SJ, Editor 1998, Blackwell Science: Malden, MA. p. 382-390.

Bafaloukos, D. and H. Gogas, *The treatment of brain metastases in melanoma patients.* Cancer Treat Rev, 2004. 30(6): p. 515-20.

Balch, C.M., et al., *Long-term results of a multi-institutional randomized trial comparing prognostic factors and surgical results for intermediate thickness melanomas (1.0 to 4.0 mm). Intergroup Melanoma Surgical Trial.* Ann Surg Oncol, 2000. 7(2): p. 87-97.

Balch, C.M., et al., *Final version of 2009 AJCC melanoma staging and classification.* J Clin Oncol, 2009. 27(36): p. 6199-206.

Bartelink, H., et al., *Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups.* J Clin Oncol, 1997. 15(5): p. 2040-9.

Bergman, R., *Pseudolymphoma and cutaneous lymphoma: facts and controversies.* Clin Dermatol, 2010. 28(5): p. 568-74.

Bertino, E.M. and G.A. Otterson, *Romidepsin: a novel histone deacetylase inhibitor for cancer.* Expert Opin Investig Drugs, 2011. 20(8): p. 1151-8.

Berwick M, W.M., *Epidemiology: Current Trends*, in *Cutaneous Melanoma*, B.C.e. al, Editor 2003, Quality Medical Publishing, Inc: St. Louis, MO. p. 16-17.

Bouwes Bavinck, J.N., et al., *The risk of skin cancer in renal transplant recipients in Queensland, Australia. A follow-up study.* Transplantation, 1996. 61(5): p. 715-21.

Brady LW, B.S., Fitzpatrick PJ, *Skin Cancer*, in *Principles and Practice of Radiation Oncology*, B.L. Perez CA, Editor 1987, Lippincott: Philadelphia, PA. p. 377.

Braun-Falco O, L.S., Goldschmidt H, in *Dermatologic Radiotherapy*1976, Springer: New York, NY. p. 69.

Breneman, J.C., et al., *Stereotactic radiosurgery for the treatment of brain metastases. Results of a single institution series.* Cancer, 1997. 79(3): p. 551-7.

Breslow, A., *Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma.* Ann Surg, 1970. 172(5): p. 902-8.

Breuninger, H., B. Black, and G. Rassner, *Microstaging of squamous cell carcinomas.* Am J Clin Pathol, 1990. 94(5): p. 624-7.

Buckner, J.C., et al., *A phase III study of radiation therapy plus carmustine with or without recombinant interferon-alpha in the treatment of patients with newly diagnosed high-grade glioma.* Cancer, 2001. 92(2): p. 420-33.

Burmeister, B.H., et al., *Radiation therapy for nodal disease in malignant melanoma.* World J Surg, 1995. 19(3): p. 369-71.

Cascinelli, N., et al., *Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. WHO Melanoma Programme.* Lancet, 1998. 351(9105): p. 793-6.

Cerroni, L. and H. Kerl, *Aberrant bcl-2 protein expression provides a possible mechanism of neoplastic cell growth in cutaneous basal-cell carcinoma.* J Cutan Pathol, 1994. 21(5): p. 398-403.

Cerroni, L., et al., *bcl-2 protein expression and correlation with the interchromosomal 14;18 translocation in cutaneous lymphomas and pseudolymphomas.* J Invest Dermatol, 1994. 102(2): p. 231-5.

Cerroni, L., et al., *Infection by Borrelia burgdorferi and cutaneous B-cell lymphoma.* J Cutan Pathol, 1997. 24(8): p. 457-61.

Cerroni, L., et al., *Primary cutaneous follicle center cell lymphoma with follicular growth pattern.* Blood, 2000. 95(12): p. 3922-8.

Cerroni L, K.H., *B-cell lymphomas of the skin*, in *Dermatology*, J.J. Bolognia JL, Rapini RP, et al, Editor 2003, Mosby: London. p. 1907-1919.

Cerroni L, G.K., Kerl H, *Skin Lymphoma: The Illustrated Guide*, 2009, Wiley-Blackwell Oxford. p. 156-163.

Chahbazian CM, B.G., *Radiation therapy for carcinoma of the skin of the face and neck. Special considerations.* JAMA, 1980. 244: p. 1135-1137.

Chahbazian CM, B.G., *Skin cancer*, in *Modern Radiation Oncology Classic Literature and Current Management*, e. Gilbert HA, Editor 1984, Harper & Row: Philadelphia, PA. p. 158.

Chang, D.T., et al., *Adjuvant radiotherapy for cutaneous melanoma: comparing hypofractionation to conventional fractionation.* Int J Radiat Oncol Biol Phys, 2006. 66(4): p. 1051-5.

Chen, J.C., et al., *Stereotactic radiosurgery in the treatment of metastatic disease to the brain.* Neurosurgery, 2000. 47(2): p. 268-79; discussion 279-81.

Chen, J.Y., et al., *Desmoplastic neurotropic melanoma: a clinicopathologic analysis of 128 cases.* Cancer, 2008. 113(10): p. 2770-8.

Cheuk, W., et al., *Immunostaining for thyroid transcription factor 1 and cytokeratin 20 aids the distinction of small cell carcinoma from Merkel cell carcinoma, but not pulmonary from extrapulmonary small cell carcinomas.* Arch Pathol Lab Med, 2001. 125(2): p. 228-31.

Collin, J.R., *Basal cell carcinoma in the eyelid region.* Br J Ophthalmol, 1976. 60(12): p. 806-9.

Corry, J., et al., *Nodal radiation therapy for metastatic melanoma.* Int J Radiat Oncol Biol Phys, 1999. 44(5): p. 1065-9.

Criscione, V.D. and M.A. Weinstock, *Incidence of cutaneous T-cell lymphoma in the United States, 1973-2002.* Arch Dermatol, 2007. 143(7): p. 854-9.

Damle, S., et al., *Phase I-II study of 5-fluorouracil, recombinant interferon alpha2a, and cisplatin in combination with external beam radiation therapy followed by surgery in patients with locally advanced carcinoma of the esophagus.* Am J Clin Oncol, 1999. 22(4): p. 391-5.

Delia, D., et al., *Clonal immunoglobulin gene rearrangements and normal T-cell receptor, bcl-2, and c-myc genes in primary cutaneous B-cell lymphomas.* Cancer Res, 1989. 49(17): p. 4901-5.

Dinehart, S.M. and S.V. Pollack, *Metastases from squamous cell carcinoma of the skin and lip. An analysis of twenty-seven cases.* J Am Acad Dermatol, 1989. 21(2 Pt 1): p. 241-8.

Dubin N, K.A., *Multivariate risk score for recurrent cutaneous basal cell carcinomas.* Arch Dermatol, 1983. 119: p. 373-377.

Duvic, M. and J.C. Cather, *Emerging new therapies for cutaneous T-cell lymphoma.* Dermatol Clin, 2000. 18(1): p. 147-56.

Edge SB, C.M., Byrd DR, *Merkel Cell Carcinoma*, in *AJCC Cancer Staging Manual*, C.M. Edge SB, Byrd DR, Editor 2009, Springer-Verlag New York, LLC: New York.

Edwards, B.K., et al., *Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates.* Cancer, 2010. 116(3): p. 544-73.

Everall, J.D. and P.M. Dowd, *Influence of environmental factors excluding ultra violet radiation on the incidence of skin cancer.* Bull Cancer, 1978. 65(3): p. 241-7.

Farshad, A., et al., *A retrospective study of 150 patients with lentigo maligna and lentigo maligna melanoma and the efficacy of radiotherapy using Grenz or soft X-rays.* Br J Dermatol, 2002. 146(6): p. 1042-6.

Fears, T.R. and J. Scotto, *Estimating increases in skin cancer morbidity due to increases in ultraviolet radiation exposure.* Cancer Invest, 1983. 1(2): p. 119-26.

Feng, H., et al., *Clonal integration of a polyomavirus in human Merkel cell carcinoma.* Science, 2008. 319(5866): p. 1096-100.

Ferlay J, B.F., Pisani P, Parkin DM. *GLOBOCAN 2000. Cancer Incidence, Mortality and Prevalence Worldwide, version 1.0. IARC*. 2001; Available from: Limited version accessed at http://www.-dep.iarc.fr/globocan/globocan.html.

Fink-Puches, R., et al., *Primary cutaneous lymphomas: applicability of current classification schemes (European Organization for Research and Treatment of Cancer, World Health Organization) based on clinicopathologic features observed in a large group of patients.* Blood, 2002. 99(3): p. 800-5.

Fischbach, W., A.O. Chan, and B.C. Wong, *Helicobacter pylori and Gastric Malignancy.* Helicobacter, 2005. 10 Suppl 1: p. 34-9.

Fitzpatrick, P.J., *Organ and functional preservation in the management of cancers of the eye and eyelid.* Cancer Invest, 1995. 13(1): p. 66-74.

Flam, M., et al., *Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study.* J Clin Oncol, 1996. 14(9): p. 2527-39.

Fogarty, G., et al., *Whole brain radiotherapy after local treatment of brain metastases in melanoma patients--a randomised phase III trial.* BMC Cancer, 2011. 11: p. 142.

Foundation, S.C. *Skin Cancer Information, Squamous cell carcinoma*. 2011; Available from: http://www.skincancer.org/scc-treatment-options.html.

Gillenwater, A.M., et al., *Merkel cell carcinoma of the head and neck: effect of surgical excision and radiation on recurrence and survival.* Arch Otolaryngol Head Neck Surg, 2001. 127(2): p. 149-54.

Gladstein AH, K.A., Bart RS, *Radiotherapy of cutaneous malignancies*, in *Physical Modalities in Dermatologic Therapy. Radiotherapy, Electrosurgery, Phototherapy, Cryosurgery*, G. H, Editor 1978, Springer-Verlag: New York, NY. p. 95.

Goodlad, J.R., et al., *Primary cutaneous B-cell lymphoma and Borrelia burgdorferi infection in patients from the Highlands of Scotland.* Am J Surg Pathol, 2000. 24(9): p. 1279-85.

Goodson, A.G., et al., *Comparative analysis of total body and dermatoscopic photographic monitoring of nevi in similar patient populations at risk for cutaneous melanoma.* Dermatol Surg, 2010. 36(7): p. 1087-98.

Gorlin, R.J., *Nevoid basal-cell carcinoma syndrome.* Medicine (Baltimore), 1987. 66(2): p. 98-113.

Grob, J.J. and J.J. Bonerandi, *The 'ugly duckling' sign: identification of the common characteristics of nevi in an individual as a basis for melanoma screening.* Arch Dermatol, 1998. 134(1): p. 103-4.

Group, R.M.C.C., *Merkel cell carcinoma: recent progress and current priorities on etiology, pathogenesis, and clinical management.* J Clin Oncol, 2009. 27: p. 4021-4026.

Guidelines™), N.C.P.G.i.O.N. *Melanoma. Version 1.2012*. 2011; Available from: http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf.

Guidelines™), N.C.P.G.i.O.N. *Merkel Cell Carcinoma, Version 1.2012*. 2011; Available from: http://www.nccn.org/professionals/physician_gls/pdf/mcc.pdf.

Guidelines, N.C.C.N.N. *Squamous Cell Skin Cancers*. 2011 2011]; Version 2.2011:[Available from: http://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf.

Haag, M.L., L.F. Glass, and N.A. Fenske, *Merkel cell carcinoma. Diagnosis and treatment.* Dermatol Surg, 1995. 21(8): p. 669-83.

Hagen, N.A., et al., *The role of radiation therapy following resection of single brain metastasis from melanoma.* Neurology, 1990. 40(1): p. 158-60.

Halprin, K.M., *Psoriasis, skin cancer, and PUVA.* J Am Acad Dermatol, 1980. 2(5): p. 432-4.

Hanly, A.J., et al., *Analysis of thyroid transcription factor-1 and cytokeratin 20 separates merkel cell carcinoma from small cell carcinoma of lung.* J Cutan Pathol, 2000. 27(3): p. 118-20.

Hazard, L.J., W.T. Sause, and R.D. Noyes, *Combined adjuvant radiation and interferon-alpha 2B therapy in high-risk melanoma patients: the potential for increased radiation toxicity.* Int J Radiat Oncol Biol Phys, 2002. 52(3): p. 796-800.

Hitchcock, C.L., et al., *Neuroendocrine (Merkel cell) carcinoma of the skin. Its natural history, diagnosis, and treatment.* Ann Surg, 1988. 207(2): p. 201-7.

Holsti, L.R., et al., *Enhancement of radiation effects by alpha interferon in the treatment of small cell carcinoma of the lung.* Int J Radiat Oncol Biol Phys, 1987. 13(8): p. 1161-6.

Huang, F., et al., *Prophylactic cranial irradiation in advanced breast cancer: a case for caution.* Int J Radiat Oncol Biol Phys, 2009. 73(3): p. 752-8.

Jabbour, J., et al., *Merkel cell carcinoma: assessing the effect of wide local excision, lymph node dissection, and radiotherapy on recurrence and survival in early-stage disease--results from a review of 82 consecutive cases diagnosed between 1992 and 2004.* Ann Surg Oncol, 2007. 14(6): p. 1943-52.

Jambusaria-Pahlajani, A., et al., *Uncertainty in the perioperative management of high-risk cutaneous squamous cell carcinoma among Mohs surgeons.* Arch Dermatol, 2010. 146(11): p. 1225-31.

Jemal, A., et al., *Cancer statistics, 2010.* CA Cancer J Clin, 2010. 60(5): p. 277-300.

JLM, A. *Tableau de plan fongoide: Description des maladies de la peau observe a l'hopital St. Louis et exposition des meilleures methods suivies pour leur traitment*. in *Barior l'Aine et Files*. 1806. Paris, France.

Johnson, T.M., et al., *Squamous cell carcinoma of the skin (excluding lip and oral mucosa).* J Am Acad Dermatol, 1992. 26(3 Pt 2): p. 467-84.

Johnson, T.M., et al., *Usefulness of the staged excision for lentigo maligna and lentigo maligna melanoma: the "square" procedure.* J Am Acad Dermatol, 1997. 37(5 Pt 1): p. 758-64.

Kavanaugh, S.M., L.A. White, and J.M. Kolesar, *Vorinostat: A novel therapy for the treatment of cutaneous T-cell lymphoma.* Am J Health Syst Pharm, 2010. 67(10): p. 793-7.

KB, H., *Cutaneous T-cell lymphoma: mycosis fungoides and Sézary syndrome*, in *Cancer of the Skin*, R.D.e. al., Editor 2005, Elseiver. Inc.: Philadelphia, PA. p. 349-362.

Kerl, H. and L. Cerroni, *The morphologic spectrum of cutaneous B-cell lymphomas.* Arch Dermatol, 1996. 132(11): p. 1376-7.

Kim, Y.H., et al., *Clinical stage IA (limited patch and plaque) mycosis fungoides. A long-term outcome analysis.* Arch Dermatol, 1996. 132(11): p. 1309-13.

Kim, Y.H., et al., *Clinical characteristics and long-term outcome of patients with generalized patch and/or plaque (T2) mycosis fungoides.* Arch Dermatol, 1999. 135(1): p. 26-32.

Kim, Y.H., et al., *Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression.* Arch Dermatol, 2003. 139(7): p. 857-66.

Kokoska, E.R., et al., *Early aggressive treatment for Merkel cell carcinoma improves outcome.* Am J Surg, 1997. 174(6): p. 688-93.

Konefal, J.B., B. Emami, and M.V. Pilepich, *Analysis of dose fractionation in the palliation of metastases from malignant melanoma.* Cancer, 1988. 61(2): p. 243-6.

Lang, P.G., Maize, J.C., *Basal cell carcinoma*, in *Cancer of the Skin*, D.L. Rigel DS, Reitgen DS, Bystryn JC, Marks R, Editor 2005, Elsevier-Saunders: Philadelphia, PA. p. 101-132.

Leshin, B., et al., *Management of periocular basal cell carcinoma: Mohs' micrographic surgery versus radiotherapy.* Surv Ophthalmol, 1993. 38(2): p. 193-212.

Lewis, K.G., et al., *Adjuvant local irradiation for Merkel cell carcinoma.* Arch Dermatol, 2006. 142(6): p. 693-700.

Liu, Z. and J. Chen, *[The research advance of brain derived neurotrophic factor].* Sheng Wu Yi Xue Gong Cheng Xue Za Zhi, 2000. 17(4): p. 454-6, 460.

LM, P., *Erythrodermie quasi-généralisée, mais respectant des ilôts de peau saine, avec petites tumeurs à formule histologique de mycosis fongoide.* Bull Soc Derm Syphil, 1937. 44: p. 1307-1319.

Lovett, R.D., et al., *External irradiation of epithelial skin cancer.* Int J Radiat Oncol Biol Phys, 1990. 19(2): p. 235-42.

Martin H, S.E., Spiro RH, *Radiation-induced cancer of the head and neck.* Cancer, 1970(25): p. 61-71.

Mazeron, J.J., et al., *Radiation therapy of carcinomas of the skin of nose and nasal vestibule: a report of 1676 cases by the Groupe Europeen de Curietherapie.* Radiother Oncol, 1988. 13(3): p. 165-73.

Meadows, A.T., et al., *Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort.* J Clin Oncol, 2009. 27(14): p. 2356-62.

Medina-Franco, H., et al., *Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases.* Ann Surg Oncol, 2001. 8(3): p. 204-8.

Mendenhall, W.M., et al., *T2-T4 carcinoma of the skin of the head and neck treated with radical irradiation.* Int J Radiat Oncol Biol Phys, 1987. 13(7): p. 975-81.

Mendenhall, W.M., et al., *Carcinoma of the Skin*, in *Management of Head and Neck Cancer: A Multidisciplinary Approach*, R.R. Million and N.J. Cassisi, Editors. 1994, J.B. Lippincott Company: Philadelphia. p. 643-691.

Meyers, C.A., et al., *Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial.* J Clin Oncol, 2004. 22(1): p. 157-65.

Micaily, B., et al., *Radiotherapy for unilesional mycosis fungoides.* Int J Radiat Oncol Biol Phys, 1998. 42(2): p. 361-4.

Mojica, P., D. Smith, and J.D. Ellenhorn, *Adjuvant radiation therapy is associated with improved survival in Merkel cell carcinoma of the skin.* J Clin Oncol, 2007. 25(9): p. 1043-7.

Morrison, W., P. Wong, and L. Peters, *Radiotherapy for Basal and Squamous Cell Skin Cancinomas.* Cancer Bulletin, 1993. 45: p. 256-260.

Morrison, W.H., A.S. Garden, and K.K. Ang, *Radiation therapy for nonmelanoma skin carcinomas.* Clin Plast Surg, 1997. 24(4): p. 719-29.

Morton DL, E.R., Balch CM, *Surgical excision of distant metastases*, in *Cutaneous Melanoma*, B.C.e. al., Editor 2003, Quality Medical Publishing, Inc.: St. Louis, MO. p. 547-572.

Mudigonda, T., et al., *The economic impact of non-melanoma skin cancer: a review.* J Natl Compr Canc Netw, 2010. 8(8): p. 888-96.

Nagore, E., et al., *Detection of Epstein-Barr virus and human herpesvirus 7 and 8 genomes in primary cutaneous T- and B-cell lymphomas.* Br J Dermatol, 2000. 143(2): p. 320-3.

Navi, D., et al., *The Stanford University experience with conventional-dose, total skin electron-beam therapy in the treatment of generalized patch or plaque (T2) and tumor (T3) mycosis fungoides.* Arch Dermatol, 2011. 147(5): p. 561-7.

Nestle FO, K.H.I.e.D., *Melanoma*, in *Dermatology*, J.J. Bolognia J, Rapini RP, et al, Editor 2003, Mosby: London. p. 1789-1815.

Nguyen TH, Y.J., *Squamous Cell Carcinoma*, in *Cancer of the Skin*, D.L. Rigel DS, Reitgen DS, Bystryn JC, Marks R, Editor 2005, Elsevier Saunders: Philadelphia. p. 133-150.

O'Brien, C.J., et al., *Adjuvant radiotherapy following neck dissection and parotidectomy for metastatic malignant melanoma.* Head Neck, 1997. 19(7): p. 589-94.

Olivier, K.R., et al., *A higher radiotherapy dose is associated with more durable palliation and longer survival in patients with metastatic melanoma.* Cancer, 2007. 110(8): p. 1791-5.

Olsen, E.A. and P.A. Bunn, *Interferon in the treatment of cutaneous T-cell lymphoma.* Hematol Oncol Clin North Am, 1995. 9(5): p. 1089-107.

Ott, M.J., et al., *Multimodality management of Merkel cell carcinoma.* Arch Surg, 1999. 134(4): p. 388-92; discussion 392-3.

Overgaard, J., H. von der Maase, and M. Overgaard, *A randomized study comparing two high-dose per fraction radiation schedules in recurrent or metastatic malignant melanoma.* Int J Radiat Oncol Biol Phys, 1985. 11(10): p. 1837-9.

Pentenero, M., et al., *Evidence for a possible anatomical subsite-mediated effect of tobacco in oral potentially malignant disorders and carcinoma.* J Oral Pathol Med, 2011. 40(3): p. 214-7.

Petrovich, Z., et al., *Treatment results and patterns of failure in 646 patients with carcinoma of the eyelids, pinna, and nose.* Am J Surg, 1987. 154(4): p. 447-50.

Petrovich, Z., et al., *Carcinoma of the lip and selected sites of head and neck skin. A clinical study of 896 patients.* Radiother Oncol, 1987. 8(1): p. 11-7.

Petrovich, Z., et al., *Treatment of carcinoma of the skin with bone and/or cartilage involvement.* Am J Clin Oncol, 1988. 11(2): p. 110-3.

Pollock PM, W.A., Trent JM, *Genetics and molecular staging*, in *Cutaneous Melanoma*, B.C.e. al., Editor 2003, Quality Medical Publishing, Inc.: St. Louis, MO. p. 687-712.

Ponten F, L.J., *Principles of tumor biology and pathogenesis of BCCs and SCCs*, in *Dermatology*, J.J. Bolognia JL, Rapini RP et al, Editor 2003, Mosby: London. p. 1675.

Quiros, P.A., et al., *Total skin electron beam therapy followed by adjuvant psoralen/ultraviolet-A light in the management of patients with T1 and T2 cutaneous T-cell lymphoma (mycosis fungoides).* Int J Radiat Oncol Biol Phys, 1997. 38(5): p. 1027-35.

Ratner, D., et al., *Merkel cell carcinoma.* J Am Acad Dermatol, 1993. 29(2 Pt 1): p. 143-56.

RD, H., *Skin*, in *The Radiotherapy of Malignant Disease*, P.R. Eassen EC, Editor 1985, Springer-Verlag: New York, NY. p. 135.

Roberge, D., et al., *Does adjuvant alpha-interferon improve outcome when combined with total skin irradiation for mycosis fungoides?* Br J Dermatol, 2007. 156(1): p. 57-61.

Roenigk, H.H., Jr. and W.A. Caro, *Skin cancer in the PUVA-48 cooperative study.* J Am Acad Dermatol, 1981. 4(3): p. 319-24.

Rollison, D.E., A.R. Giuliano, and J.C. Becker, *New virus associated with merkel cell carcinoma development.* J Natl Compr Canc Netw, 2010. 8(8): p. 874-80.

Rowe, D.E., R.J. Carroll, and C.L. Day, Jr., *Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up.* J Dermatol Surg Oncol, 1989. 15(3): p. 315-28.

Rowe, D.E., R.J. Carroll, and C.L. Day, Jr., *Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma.* J Dermatol Surg Oncol, 1989. 15(4): p. 424-31.

Rowe, D.E., R.J. Carroll, and C.L. Day, Jr., *Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection.* J Am Acad Dermatol, 1992. 26(6): p. 976-90

Samlowski, W.E., et al., *Multimodality treatment of melanoma brain metastases incorporating stereotactic radiosurgery (SRS).* Cancer, 2007. 109(9): p. 1855-62.

Sarasin, A. and G. Giglia-Mari, *p53 gene mutations in human skin cancers.* Exp Dermatol, 2002. 11 Suppl 1: p. 44-7.

Sarin, R., et al., *Treatment results and prognostic factors in 101 men treated for squamous carcinoma of the penis.* Int J Radiat Oncol Biol Phys, 1997. 38(4): p. 713-22.

Sarin R, T.H., *Current Concepts in the Management of Penile Cancer*, in *Treatment Options in Urological Cancer*, W. J, Editor 2002, Blackwell Science, Ltd.: Oxford, UK. p. 366-381.

Sause, W.T., et al., *Fraction size in external beam radiation therapy in the treatment of melanoma.* Int J Radiat Oncol Biol Phys, 1991. 20(3): p. 429-32.

Schmid-Wendtner, M.H., et al., *Fractionated radiotherapy of lentigo maligna and lentigo maligna melanoma in 64 patients.* J Am Acad Dermatol, 2000. 43(3): p. 477-82.

Schwartz, R.A., *Verrucous carcinoma of the skin and mucosa.* J Am Acad Dermatol, 1995. 32(1): p. 1-21; quiz 22-4.

Scott, M.P. and K.F. Helm, *Cytokeratin 20: a marker for diagnosing Merkel cell carcinoma.* Am J Dermatopathol, 1999. 21(1): p. 16-20.

Seegenschmiedt, M.H., et al., *Palliative radiotherapy for recurrent and metastatic malignant melanoma: prognostic factors for tumor response and long-term outcome: a 20-year experience.* Int J Radiat Oncol Biol Phys, 1999. 44(3): p. 607-18.

Senff, N.J., et al., *European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas.* Blood, 2008. 112(5): p. 1600-9.

Sézary A, B.Y., *Erythrodermie avec présence de cellules monstrueuses dans le derme et le sang circulant.* Bull Soc Derm Syphil, 1938. 45: p. 254-260.

Shibamoto, Y., et al., *Incidence of brain atrophy and decline in mini-mental state examination score after whole-brain radiotherapy in patients with brain metastases: a prospective study.* Int J Radiat Oncol Biol Phys, 2008. 72(4): p. 1168-73.

Shimm, D.S. and R.B. Wilder, *Radiation therapy for squamous cell carcinoma of the skin.* Am J Clin Oncol, 1991. 14(5): p. 383-6.

Silverman, M.K., et al., *Recurrence rates of treated basal cell carcinomas. Part 4: X-ray therapy.* J Dermatol Surg Oncol, 1992. 18(7): p. 549-54.

Silverman, M.K., et al., *Recurrence rates of treated basal cell carcinomas. Part 1: Overview.* J Dermatol Surg Oncol, 1991. 17(9): p. 713-8.

Sim, F.H., et al., *Lymphadenectomy in the management of stage I malignant melanoma: a prospective randomized study.* Mayo Clin Proc, 1986. 61(9): p. 697-705.

Skelton, H.G., et al., *Merkel cell carcinoma: analysis of clinical, histologic, and immunohistologic features of 132 cases with relation to survival.* J Am Acad Dermatol, 1997. 37(5 Pt 1): p. 734-9.

Skibber, J.M., et al., *Cranial irradiation after surgical excision of brain metastases in melanoma patients.* Ann Surg Oncol, 1996. 3(2): p. 118-23.

Solan MJ, B.L., Binnick SA, *Skin*, in *Principles and Practice of Radiation Oncology*, B.L. Perez CA, Editor 1997, Lippincott-Raven: Philadelphia, PA. p. 723-744.

Stern, R.S., et al., *Risk of cutaneous carcinoma in patients treated with oral methoxsalen photochemotherapy for psoriasis.* N Engl J Med, 1979. 300(15): p. 809-13.

Stevens, G., et al., *Locally advanced melanoma: results of postoperative hypofractionated radiation therapy.* Cancer, 2000. 88(1): p. 88-94.

Stock, R.G., et al., *Enhanced radiosensitization with interferon-alpha-2b and cisplatin in the treatment of locally advanced cervical carcinoma.* Gynecol Oncol, 1997. 67(3): p. 309-15.

Stoll HL Jr, M.H., Traenkle HL, *Results of Roentgen therapy of carcinoma of the nose.* Arch Dermatol, 1964. 90: p. 577-580.

Strom, E.A. and M.I. Ross, *Adjuvant radiation therapy after axillary lymphadenectomy for metastatic melanoma: toxicity and local control.* Ann Surg Oncol, 1995. 2(5): p. 445-9.

Surveillance, E., and End Result (SEER) Program, Public Use Data (1973-1999). 2002; Available from: http://www.seer.cancer.gov.

Taylor G, M.D., Heilman ER, *Merkel cell carcinoma*, in *Cancer of the Skin*, R.D.e. al., Editor 2005, Elsevier-Saunders: Philadelphia, PA. p. 323327.

Thissen, M.R., M.H. Neumann, and L.J. Schouten, *A systematic review of treatment modalities for primary basal cell carcinomas.* Arch Dermatol, 1999. 135(10): p. 1177-83.

Traenkle, H.L., H.L. Stoll, Jr., and A. Lonkar, *Results of roentgen therapy of carcinoma of the lip.* Arch Dermatol, 1962. 85: p. 488-9.

Tsang, R.W., et al., *Lentigo maligna of the head and neck. Results of treatment by radiotherapy.* Arch Dermatol, 1994. 130(8): p. 1008-12.

Tward, J.D., et al., *Survival and recurrence in nonmycosis fungoides primary cutaneous lymphoma.* Cancer J, 2009. 15(1): p. 87-92.

UKCCCR Anal Cancer Trial Working Party. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UK Co-ordinating Committee on Cancer Research. Lancet, 1996. 348(9034): p. 1049-54.

Veness, M., et al., *The role of radiotherapy alone in patients with merkel cell carcinoma: reporting the Australian experience of 43 patients.* Int J Radiat Oncol Biol Phys, 2010. 78(3): p. 703-9.

Vermeer, M.H., et al., *Primary cutaneous large B-cell lymphomas of the legs. A distinct type of cutaneous B-cell lymphoma with an intermediate prognosis. Dutch Cutaneous Lymphoma Working Group.* Arch Dermatol, 1996. 132(11): p. 1304-8.

Veronesi, U., et al., *Delayed regional lymph node dissection in stage I melanoma of the skin of the lower extremities.* Cancer, 1982. 49(11): p. 2420-30.

Vongtama, R., et al., *Efficacy of radiation therapy in the local control of desmoplastic malignant melanoma.* Head Neck, 2003. 25(6): p. 423-8.

Weinstock, M.A. and A.J. Sober, *The risk of progression of lentigo maligna to lentigo maligna melanoma.* Br J Dermatol, 1987. 116(3): p. 303-10.

Werlinger, K.D., G. Upton, and A.Y. Moore, *Recurrence rates of primary nonmelanoma skin cancers treated by surgical excision compared to electrodesiccation-curettage in a private dermatological practice.* Dermatol Surg, 2002. 28(12): p. 1138-42; discussion 1142.

Whiteman, D.C., W.J. Pavan, and B.C. Bastian, *The melanomas: a synthesis of epidemiological, clinical, histopathological, genetic, and biological aspects, supporting distinct subtypes, causal pathways, and cells of origin.* Pigment Cell Melanoma Res, 2011.

Wilder, R.B., et al., *Recurrent basal cell carcinoma treated with radiation therapy.* Arch Dermatol, 1991. 127(11): p. 1668-72.

Willemze, R., et al., *EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer.* Blood, 1997. 90(1): p. 354-71.

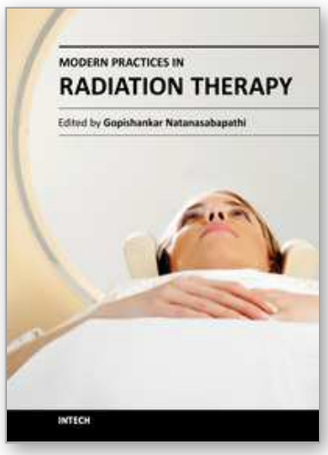
Wilkinson, E.J., *Normal histology and nomenclature of the vulva, and malignant neoplasms, including VIN.* Dermatol Clin, 1992. 10(2): p. 283-96.

Wilson, L.D., B.M. Kacinski, and G.W. Jones, *Local superficial radiotherapy in the management of minimal stage IA cutaneous T-cell lymphoma (Mycosis Fungoides).* Int J Radiat Oncol Biol Phys, 1998. 40(1): p. 109-15.

Yiengpruksawan, A., et al., *Merkel cell carcinoma. Prognosis and management.* Arch Surg, 1991. 126(12): p. 1514-9.

Zackheim, H.S., et al., *Relative frequency of various forms of primary cutaneous lymphomas.* J Am Acad Dermatol, 2000. 43(5 Pt 1): p. 793-6.

Zochling, N., et al., *Human herpesvirus 8-specific DNA sequences in primary cutaneous B-cell lymphomas.* Arch Dermatol, 1998. 134(2): p.246-7.



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Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries. It is an enormous global health encumbrance, growing at an alarming pace. Global statistics show that in 2030 alone, about 21.4 million new cancer cases and 13.2 million cancer deaths are expected to occur, simply due to the growth, aging of the population, adoption of new lifestyles and behaviors. Amongst the several modes of treatment for cancer available, Radiation treatment has a major impact due to technological advancement in recent times. This book discusses the pros and cons of this treatment modality. This book "Modern Practices in Radiation Therapy" has collaged topics contributed by top notch professionals and researchers all around the world.

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