Treatment of skin malignancies

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Practice recommendations

- Malignant melanomas in situ can usually be treated in consultation with a specialist (**C**). Larger lesions may require referral.

- Based on best available evidence, surgical excision is the first-line treatment for most nonmelanoma skin cancers, with cure rates as high as 98% with proper margins (**C**).

- Consider Mohs surgery for larger lesions, sclerosing lesions with morpheaform histology, or for cosmetically sensitive areas (**A**).

- With properly selected lesions, curettage/electrodesiccation and cryosurgery have cure rates comparable to that of surgical excision (**B**).

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Reliable criteria exist to guide primary care physicians in the evaluation of malignant melanoma.[1] Once a diagnosis of malignant melanoma is made, physicians should promptly consult with a skin malignancy specialist (**Figure 1**).

Several well-accepted treatment options exist for primary nonmelanoma skin cancer, but direct comparisons are lacking. The best evidence recommends surgical excision as first-line treatment for most nonmelanoma skin cancer. Cure rates up to 98% can be expected with appropriate margins.
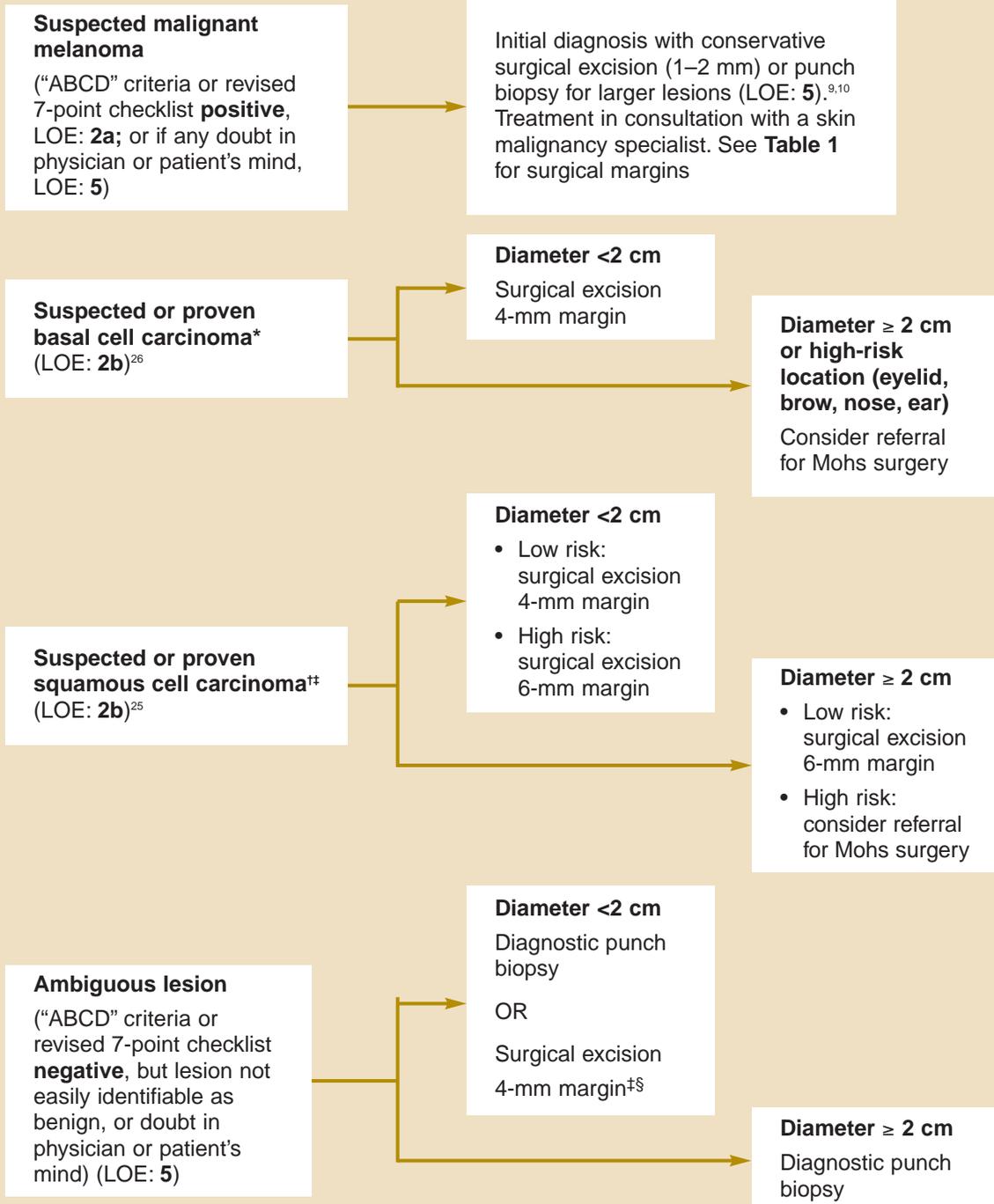
Curettage/electrodesiccation and cryosurgery are probably equally effective with properly selected lesions. Physicians should be aware of those cases when nonmelanoma skin cancers are at higher risk for recurrence or metastasis and tailor their treatment plan accordingly.

Mohs micrographic surgery is the preferred treatment for high-risk and recurrent primary nonmelanoma skin cancer.

In this Applied Evidence review, we examine the guidance that can be gleaned from currently available evidence, and review each option in detail.

FIGURE 1

Surgical excision of suspected skin malignancies

Suspected malignant melanoma

("ABCD" criteria or revised 7-point checklist **positive**, LOE: **2a;** or if any doubt in physician or patient's mind, LOE: **5**)

→ Initial diagnosis with conservative surgical excision (1–2 mm) or punch biopsy for larger lesions (LOE: **5**).[9,10] Treatment in consultation with a skin malignancy specialist. See **Table 1** for surgical margins

Suspected or proven basal cell carcinoma*
(LOE: **2b**)[26]

→ **Diameter <2 cm**
Surgical excision 4-mm margin

→ **Diameter ≥ 2 cm or high-risk location (eyelid, brow, nose, ear)**
Consider referral for Mohs surgery

Suspected or proven squamous cell carcinoma†‡
(LOE: **2b**)[25]

→ **Diameter <2 cm**
- Low risk: surgical excision 4-mm margin
- High risk: surgical excision 6-mm margin

→ **Diameter ≥ 2 cm**
- Low risk: surgical excision 6-mm margin
- High risk: consider referral for Mohs surgery

Ambiguous lesion

("ABCD" criteria or revised 7-point checklist **negative**, but lesion not easily identifiable as benign, or doubt in physician or patient's mind) (LOE: **5**)

→ **Diameter <2 cm**
Diagnostic punch biopsy

OR

Surgical excision 4-mm margin‡§

→ **Diameter ≥ 2 cm**
Diagnostic punch biopsy

For an explanation of levels of evidence, see page 484.

*Consider referral for sclerosing basal cell carcinoma with morpheaform histology by diagnostic biopsy.

†Suspected squamous cell carcinoma defined as "high risk" for metastasis if located on scalp, ears, eyelids, nose, or lips.

‡Consider inclusion of subcutaneous fat in biopsy of suspected squamous cell carcinoma.

§Consider 6-mm margin for high-risk location as defined for squamous cell carcinoma.

| FIGURE 2 **Excisional biopsy** | FIGURE 3 **Punch/Incisional biopsy** |

A fusiform, full-thickness skin incision is made with a 3-to-1 length-to-width ratio, with the long axis parallel to the lines of least skin tension (Langer's lines). The scalpel blade is held perpendicular to the surrounding skin surface while cutting, thereby creating wound margins that are perpendicular to the skin, parallel to each other, and thus reapproximate with minimal scarring.

A full-thickness, cylindrical tissue sample is obtained using a circular blade that is rotated down and through the epidermis and dermis and into the subcutaneous fat. Stretch the skin perpendicular to the lines of least skin tension (Langer's lines) before cutting in order to create an elliptical wound that is more easily closed with sutures.

■ CONFIRMING THE DIAGNOSIS

Our previous article in THE JOURNAL OF FAMILY PRACTICE, "Diagnosing skin malignancy: Assessment of predictive clinical criteria and risk factors,"[1] presented a comprehensive review for the initial evaluation of skin malignancies. (This article is available online at www.jfponline.com.)

Nonmelanoma skin cancer includes basal cell carcinomas and squamous cell carcinomas. Nonmelanoma skin cancer, which accounts for most cases of skin cancer, has a high 5-year survival rate, more than 95%.[2] Malignant melanoma represents only 1% of skin malignancies but leads to more than 75% of skin cancer deaths.[3] Up to 83% of family physicians treat skin malignancies in their offices.[4]

When the diagnosis is uncertain on clinical grounds alone, an initial diagnostic biopsy may be used. Techniques include excisional, punch, and shave biopsies.

Excisional biopsy (**Figure 2**) is the preferred method for primary care evaluation of suspected skin malignancy (level of evidence [LOE]: **5**).[5,6] Excision wounds are easily cared for by patients and provide good cosmesis. Surgical excision may also be used for definitive treatment, as discussed below.

Punch biopsy or *incisional biopsy* (**Figure 3**) provides a full-thickness tissue sample with minimal scarring. A 3-mm punch is sufficient for most lesions (LOE: **5**).[5] Punch biopsy is a reasonable alternative when excision is impractical due to the size or location of a lesion.

Punch biopsy is not recommended if malignant melanoma is suspected by history or physical exam—an excisional biopsy should be done (LOE: **5**).[6] Even when performed mistakenly on a malignant melanoma, however, punch biopsy has not been shown to alter prognosis or cause dissemination of a tumor (LOE: **1b**).[7]

Shave biopsies (**Figure 4**) are useful for benign-appearing lesions or elevated, nodular lesions suggestive of basal cell carcinoma or squamous cell carcinoma. Shave biopsy sites typically heal more slowly than excisional biopsies but do so with good cosmesis.

In general, shave biopsy of pigmented lesions is contraindicated, but may be performed by an experienced physician confident of a benign clinical diagnosis. According to a National Institutes of Health consensus panel, suspected malignant melanoma should *not* be shaved, as the maximal depth of the tumor cannot be assessed.[8]

■ MALIGNANT MELANOMA TREATMENT

Overview

If a skin lesion is suspected clinically to be malignant melanoma, use the ABCD criteria and the revised 7-point checklist to guide biopsy decisions.[1] If the physician or patient has any doubt, perform a biopsy.

If malignant melanoma is suspected, the initial biopsy should be conservative, with 1–2 mm margins (LOE: **5**),[9,10] and excisional, in order to determine the thickness of the tumor (Breslow's measurement) and the histologic level of invasion (Clark's level). Tumor depth at the time of diagnosis is the main factor guiding treatment and is the principal indicator predicting death due to malignant melanoma.[8] Long-term survival of patients (10 years) with malignant melanoma <0.76 mm in thickness is greater than 90%; mortality rises linearly with increasing tumor thickness (LOE: **2b**).[11]

Although knowledge of biopsy type is important for proper pathologic evaluation, it does not affect survival (LOE: **1b**).[7] Reviewing initial pathology results, a skin malignancy specialist (dermatologist, surgical oncologist, or plastic surgeon) can help determine the surgical margin necessary for curative excision. While most primary care physicians can treat lesions in situ, larger lesions require referral.
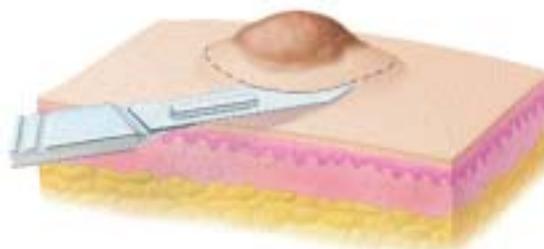
The lesion is excised by moving the cutting instrument into, but not through, the underlying dermis and then advancing parallel to the surface of the surrounding skin. The remaining dermal cells provide a strong framework over which a healthy epidermal layer may regenerate without leaving a scar. Use local anesthetic judiciously, as large amounts will distort the lesion size and result in a residual dimple when the would heals.

Current recommendations for excision margins are shown in **Table 1**.

Options for lymph node management include observation, sentinel lymph node biopsy, and elective lymph node dissection. The choice of treatment depends on clinical staging, tumor thickness, ulceration, location, and patient age, and should be managed by a melanoma specialist.

Systemic therapy

Dacarbazine is the accepted treatment of choice for metastatic malignant melanoma. A systematic review found no randomized controlled trials comparing systemic therapy with supportive care or placebo. Several trials used dacarbazine as the control agent and found response rates varying from 9.1% to 29% (no test agent was found superior). Combination chemotherapy should be reserved for clinical studies and trials (LOE: **1a**).[14]

Interferon alfa-2b is used as adjuvant therapy after surgical resection. It has an overall

> For suspected malignant melanoma, peform an excisional biopsy with conservative 1–2 mm margins

5-year survival advantage over placebo (46% vs. 37%; number needed to treat [NNT]= 11, *P*=.0237) (LOE: **1b**).[15] Additionally, an economic analysis of this treatment found it to be cost-effective for high-risk melanomas (LOE: **2b**).[16]

Vaccine therapy has shown preliminary benefit in several case-control studies but needs to be investigated further before it can be recommended (LOE: **3b**).[17]

■ NONMELANOMA SKIN CANCER TREATMENT

Overview

Treatments for nonmelanoma skin cancer include surgical excision, Mohs micrographic surgery, curettage and electrodesiccation, cryosurgery, fractionated radiotherapy, topical chemotherapy, carbon dioxide laser, photodynamic therapy, intralesional interferon, and retinoids.

Some of these therapies are untested or not widely available. Immunotherapy and photodynamic therapy remain experimental.[18] Laser treatment offers theoretical advantages for certain patients, such as those taking anticoagulants. However, safety hazards and inconvenience limit their use even by dermatologists (LOE: **5**).[19]

Two meta-analysis reviews have attempted to compare cure rates for treatment of basal cell carcinoma by conventional methods.[20,21] In these studies, standard excision was recommended for nodular-ulcerative and superficial basal cell carcinoma <2 cm in diameter and away from the face. Consideration of Mohs surgery was recommended for larger lesions, sclerosing lesions with morpheaform histology, and for cosmetically sensitive areas where large tissue loss or recurrence would be disfig-

TABLE 1		
Excision margins for malignant melanoma		
Tumor thickness	**Surgical margin**	**Level of evidence**
In situ	5 mm	5[8]
<1 mm	1 cm	1b[12]
1–4 mm	2 cm	1b[13]
>4 mm	3 cm	1b[12,13]

uring (eyelid, ear, nose, lips) (LOE: **1a**).[20] Results are summarized in **Table 2.**

It should be noted that lack of uniformity in the method of reporting prohibited direct comparison of recurrence rates for different treatments. No similar meta-analysis reviews of treatment for squamous cell carcinoma were found.

Recurrence and metastasis

The average rate of metastasis is 3.6% for squamous cell carcinoma. However, certain nonmelanoma skin cancer lesions are at higher risk for recurrence or metastasis and merit special consideration: larger lesions, those involving a mucous membrane, and lesions located on the scalp, ears, eyelids, nose, lips, or genitals. The rate of metastasis with lesions at high-risk locations may approach 30%.[5]

The majority of squamous cell carcinoma is actinically induced on sun-exposed areas. Squamous cell carcinoma occurring at a chronic scar or ulcer, such as that caused by a thermal or radiation burn, is also more likely to metastasize (LOE: **5**).[22] Metastatic spread most commonly involves regional lymph nodes, lungs, and liver. Basal cell carcinomas have an extremely low rate of metastasis (<0.1%).[23]

The overall rate of recurrence is also low— less than 1% for lesions removed from the neck, trunk, and extremities.[24] Risk factors for recurrence include size of lesion and mor-

Effectiveness of treatment modalities for basal cell carcinoma[20]

Treatment modality	Raw recurrence rate %*	Mean raw recurrence %	Cumulative 5-year recurrence rate %†
Surgical excision	1.4–2.9	N/A	5.3
Mohs micrographic surgery	0.5–1.3	0.8 (21/2660)	N/A
Curettage and electrodesiccation	3.8–18.1	N/A	13.2
Cryosurgery	0–11.4	3.0 (24/798)	N/A

N/A, not available

*Absolute number of patients with recurrence divided by number of patients with primary basal cell carcinoma at start of study (unknown number lost to follow-up).
†Life-table cumulative 5-year recurrence rate.

pheaform histology found with sclerosing basal cell carcinoma (with associated subclinical infiltration). Lesions of the face are at higher risk for recurrence with rates up to 43% on the lateral canthus, 33% on the superior orbital rim and brow, 24% on the ear, and 19% on the nose.[18] Primary care physicians should consider referral for such high-risk lesions, depending on their level of training and experience.

Surgical excision

Surgical excision is generally considered the gold standard for evaluation and treatment of suspected skin malignancy (LOE: **5**).[5,6] Advantages include rapid healing, excellent cosmesis, and an option to obtain a pathological evaluation of the excised tissue.

Conversely, excision is a more time-consuming prodedure than curettage and electrodesiccation or cryosurgery, and it may sacrifice more normal tissue than Mohs surgery. A surgical margin of normal-appearing tissue is routinely excised to eliminate microscopic tumor extension.

Two studies provide objective data regarding the margins necessary to ensure tumor clearance for basal cell carcinoma and squa-mous cell carcinoma. Both were prospective studies using Mohs surgery as the gold standard. Histological, subclinical tumor extension was then compared with ink markings placed preoperatively on the normal-appearing skin.

The first study enrolled 111 consecutive patients, aged 51 to 95 years, presenting with invasive squamous cell carcinoma. The results are summarized in **Table 3**.[25] Importantly, 30% of the tumors extended into the subcutaneous fat. The researchers recommend that excision of all squamous cell carcinomas should include subcutaneous fat (LOE: **2b**).

The second study enrolled 117 patients with previously untreated, well-demarcated basal cell carcinoma. The investigators concluded that a 4-mm lateral margin will totally eradicate 98% of tumors <2 cm in diameter (3.79 mm; 95% confidence interval [CI], 3.21–4.86) (LOE: **2b**).[26] Vertical extension of tumor was not addressed. No recommendations were made for tumors ≥2 cm in diameter.

Interestingly, no tumors in this study required a 4-mm margin in all directions. Rather, the basal cell carcinomas were found to send out extensions in an irregular pattern.

Surgical margins for treatment of squamous cell carcinomas[25]

Tumor diameter and risk level	Margin needed to completely clear 95% or more of tumors
0–19 mm	4 mm
≥20 mm	6 mm
"High-risk,"* 0–19 mm	6 mm
"High-risk,"* ≥20 mm	Indeterminate†

*High risk of metastasis if located on scalp, ears, eyelids, nose, or lips (47 of 141 tumors in study located here).
†Only 90% of tumors completely cleared even with 6 mm margin;
author recommends Mohs surgery in this case.

Mohs micrographic surgery

Mohs surgery is generally considered the preferred treatment for high-risk primary nonmelanoma skin cancer and recurrent nonmelanoma skin cancer (LOE: **5**).[18] It is clearly superior for treatment of locally recurrent squamous cell carcinoma, with a 5-year cure rate of up to 90%, compared with 76.7% obtained with standard excision (LOE: **2a**).[27]

The benefit of Mohs surgery for small (<1 cm), low-risk skin cancers is probably slight. Cure rates for primary nonmelanoma skin cancer are as high as 99.8% for basal cell carcinoma and 98.8% for squamous cell carcinoma, but standard excision also has high cure rates, up to 98% with proper surgical margins.[19]

Disadvantages include length of the procedure, need for special equipment, and dependence on highly trained personnel (a fellowship-trained dermatologist and histotechnologist). Not surprisingly, availability of this procedure is limited. The high initial cost may be balanced by the lower cost of treating recurrent tumors, but no cost-effectiveness studies are available.[28]

Curettage and electrodesiccation

Curettage and electrodesiccation is performed using a sharp curette to remove soft material from the tumor until the underlying dermis is reached. The base of the tumor is then destroyed using hyfrecation. The procedure may be repeated once or twice to achieve a base of healthy tissue (LOE: **5**).[19,29]

Curettage and electrodesiccation is the most common way dermatologists treat small (<1 cm) primary basal cell carcinoma.[18] It is safe, well tolerated, and has 5-year cure rates >90%.[5] Other advantages include speed and suitability for patients with multiple lesions.[19]

Curettage and electrodesiccation is also appropriate for small (<1 cm) primary squamous cell carcinoma below the neck (LOE: **5**).[22] This technique should not be used for malignant melanoma and is not suitable for tumors with high risk of metastasis or recurrence (LOE: **5**).[22]

Cryosurgery

Cryosurgery with liquid nitrogen or nitrous oxide is used for small (<1 cm) superficial lesions and those locations where surgery is technically difficult, such as the lips, nose, ears, eyelids, and hands. It is also ideal for patients on chronic anticoagulation or with significant comorbidities.

For properly selected lesions, 5-year cure rates are excellent at 97% (LOE: **1a**).[20] Cure

rates for larger lesions are reportedly high, but study follow-up was inconsistent (LOE: **2b**).[30] Small lesions heal completely in 4 to 6 weeks, while larger lesions may take up to 14 weeks to resolve (LOE: **5**).[31] Despite the prolonged healing time, cosmesis is often excellent.

Guidelines for the treatment of non-melanoma skin cancer with cryosurgery are presented in **Figure 5**. Importantly, published cure rates for cryosurgery are based on several case series, the largest of which employed a temperature-monitoring thermocouple needle to guarantee adequate depth of freezing. Cryosurgery without a thermocouple device may therefore result in higher recurrence rates than expected.[31]

Topical agents

Topical chemotherapeutic agents offer great promise in the treatment of properly selected tumors, but quality evidence is lacking. The most commonly used topical agent is the DNA synthesis inhibitor 5-fluorouracil (5-FU). 5-FU is a proven treatment for actinic keratoses and has been used to treat squamous cell carcinoma in situ and superficial basal cell carcinoma. However, 5-FU is contraindicated in invasive squamous cell carcinoma and basal cell carcinoma, as it may bury tumor tissue and lead to continued, subclinical spread (LOE: **5**).[19]

Imiquimod 5% cream also shows great promise for the treatment of superficial basal cell carcinoma. This cytokine and interferon inducer is primarily used for treatment of external genital and anal warts. Twice daily, once daily, or 3 times weekly application over 10 to 16 weeks produces histological clearing of low-risk, small superficial basal cell carcinoma (LOE: **2b**).[32] Adverse events are limited to local skin reactions with severity increasing with more frequent dosing. Research examining rates of recurrence is ongoing. As with 5-FU, effectiveness for large tumors and those at high-risk locations has not been established.

FIGURE 5

Guidelines for cryosurgery

1. Use cryosurgery only for selected basal cell carcinoma and squamous cell carcinoma lesions with sharply delineated borders, size <1 cm, and documented by biopsy.
2. Avoid use near the vermilion border, free margins of the ala nasi, or auditory canal.
3. Avoid use in dark-skinned patients due to risk of hypopigmentation.
4. Consider temperature monitoring: Ensure rapid cooling to –50 to –60ºC in all regions of the tumor, including deep and lateral margins, using one or more thermocouple needles.
5. Complete at least 2 freeze-thaw cycles.

Radiotherapy

Currently, radiotherapy is used in special situations, such as nonmelanoma skin cancer near the eye, nose, and ear (LOE: **5**).[22] In specialty centers, radiation is used in conjunction with other modalities for recurrent or highly aggressive lesions.

While cure rates in low-risk areas are over 90%, long-term cosmesis, particularly for young patients with basal cell carcinoma, is less favorable than with other modalities.[20] Other disadvantages include long-term radiation risks, high cost, and need for multiple visits over several weeks.[22]

Follow-up

Periodic population-based screening for nonmelanoma skin cancer has not been proven to extend life. However, in patients who have already had nonmelanoma skin cancer, periodic surveillance is probably important.

Of patients with squamous cell carcinoma, 30% will develop an additional squamous cell

> More than one third of patients
> with basal cell carcinoma
> will develop another within 5 years

carcinoma after 5 years and over 50% will develop an additional nonmelanoma skin cancer.[33] More than one third of patients with basal cell carcinoma will develop an additional basal cell carcinoma after 5 years.[33]

One accepted approach is to have patients with newly diagnosed nonmelanoma skin cancer follow-up every 3 months for the first year and then at 6-month intervals thereafter (LOE: **5**).[5] New primary lesions should be treated accordingly, while recurrent lesions may be referred to a dermatologist.

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