Practical Radiation Oncology (2020) **10**, 8-20

www.practicalradonc.org

Clinical Practice Guideline

Definitive and Postoperative Radiation Therapy for Basal and Squamous Cell Cancers of the Skin: Executive Summary of an American Society for Radiation Oncology Clinical Practice Guideline

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Sources of support: This work was funded by the American Society for Radiation Oncology.

Disclosures: Before initiating work on this guideline, all task force members completed disclosure statements and disclosures are published within this report. Where potential conflicts were detected, remedial measures to address them were taken. Dr Awan reports honoraria from Elekta. Dr Barker reports past travel expenses from Alpha Tau Medical; past honoraria from Elsevier; research for Amgen, Elekta, the University of California, San Francisco, and Merck; past honoraria and travel expenses from the National Comprehensive Cancer Network; a past advisory board position with Regeneron; and past honoraria from the University of Florida and University of Rochester. Dr Bhatnagar reports a position of state chapter president for the Arizona Radiologic Society; stock with Cancer Treatment Services International; and consulting and research for Icad. Dr Devlin is the task force chair and reports membership of the Massachusetts Medical Society Finance and Audit Committee and past honoraria, travel expenses, and advisory board membership for Sirtex. Dr Geiger, an American Society of Clinical Oncology representative, reports research and advisory board membership for Regeneron and research for Genentech/Roche. Dr Likhacheva is task force vice chair and reports spouse employment with Reflexion and travel expenses from the Russian Society of Clinical Oncology. Drs Brady (Society of Surgical Oncology representative), Buzurovic, Parvathaneni, and Zaky reported no disclosures.

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https://doi.org/10.1016/j.prro.2019.10.014

Received 26 September 2019; accepted 1 October 2019

Abstract

Purpose: This guideline reviews the evidence for the use of definitive and postoperative radiation therapy (RT) in patients with basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC).

Methods: The American Society for Radiation Oncology convened a task force to address 5 key questions focused on indications for RT in the definitive and postoperative setting for BCC and cSCC, as well as dose-fractionation schemes, target volumes, basic aspects of treatment planning, choice of radiation modality, and the role of systemic therapy in combination with radiation. Recommendations were based on a systematic literature review and created using a predefined consensus-building methodology and system for grading evidence quality and recommendation strength.

Results: The guideline recommends definitive RT as primary treatment for patients with BCC and cSCC who are not surgical candidates while conditionally recommending RT with an emphasis on shared decision-making in those situations in which adequate resection can lead to a less than satisfactory cosmetic or functional outcome. In the postoperative setting, a number of indications for RT after an adequate resection are provided while distinguishing the strength of the recommendations between BCC and cSCC. One key question is dedicated to defining indications for regional nodal irradiation. The task force suggests a range of appropriate dose-fractionation schemes for treatment of primary and nodal volumes in definitive and postoperative scenarios. The guideline also recommends against the use of carboplatin concurrently with adjuvant RT and conditionally recommends the use of systemic therapies for unresectable primaries where treatment may need escalation.

Conclusions: Defining the role of RT in the management of BCC and cSCC has been hindered by a lack of high-quality evidence. This document synthesizes available evidence to define practice guidelines for the most common clinical situations. We encourage practitioners to enroll patients in prospective trials and to approach care in a multidisciplinary fashion whenever possible.

Preamble

As the leading organization in radiation oncology, the American Society for Radiation Oncology (ASTRO) is dedicated to improving quality of care and patient outcomes. A cornerstone of this goal is the development and dissemination of clinical practice guidelines based on systematic methods to evaluate and classify evidence, combined with a focus on patient-centric care and shared decision-making. ASTRO develops and publishes guidelines without commercial support, and members volunteer their time.

Disclosure Policy—ASTRO has detailed policies and procedures related to disclosure and management of industry relationships to avoid actual, potential, or perceived conflicts of interest. All task force members are required to disclose industry relationships and personal interests from 12 months before initiation of the writing effort. Disclosures go through a rigorous review process with final approval by ASTRO's Conflict of Interest Review Committee. For the purposes of full transparency, task force members' comprehensive disclosure information is included in this publication. The complete disclosure policy for Formal Papers is available online.

Selection of Task Force Members—The Guideline Subcommittee strives to avoid bias by selecting a multidisciplinary group of experts with variation in geographic region, gender, ethnicity, race, practice setting, and areas of expertise. Representatives from organizations and professional societies with related interests and expertise are also invited to serve on the task force.

Methodology—The task force uses evidence-based methodologies to develop guideline recommendations in accordance with the National Academy of Medicine (formerly Institute of Medicine) standards. The evidence identified from key questions is assessed using the **P**opulation, **I**ntervention, **C**omparator, **O**utcome, **T**iming, **S**etting (PICOTS) framework. A systematic review of the key questions is completed, which includes creation of evidence tables that summarize the evidence base task force members use to formulate recommendations. Table 1 describes ASTRO's recommendation grading system.

Consensus Development—Consensus is evaluated using a modified Delphi approach. Task force members confidentially indicate their level of agreement on each recommendation based on a 5-point Likert scale, from "strongly agree" to "strongly disagree." A prespecified threshold of ≥75% (≥90% for expert opinion

Table 1 ASTRO recommendation grading classification system

ASTRO's recommendations are based on evaluation of multiple factors including the QoE, individual study quality, and panel consensus, all of which inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments.

Strength of Recommendation	Definition	Overall QoE Grade	Recommendation Wording
Strong	• Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. • All or almost all informed people would make the recommended choice.	Any (usually high, moderate, or expert opinion)	"Recommend/ Should"
Conditional	• Benefits are finely balanced with risks and burden or appreciable uncertainty exists about the magnitude of benefits and risks. • Most informed people would choose the recommended course of action, but a substantial number would not. • A shared decision-making approach regarding patient values and preferences is particularly important.	Any (usually moderate, low, or expert opinion)	"Conditionally Recommend"

Overall QoE Grade	Type and Quality of Study	Evidence Interpretation
High	• 2 or more well-conducted and highly generalizable RCTs or meta-analyses of such trials.	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.
Moderate	• 1 well-conducted and highly generalizable RCT or a meta-analysis of such trials **OR** • 2 or more RCTs with some weaknesses of procedure or generalizability **OR** • 2 or more strong observational studies with consistent findings.	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.
Low	• 1 RCT with some weaknesses of procedure or generalizability **OR** • 1 or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes **OR** • 2 or more observational studies with inconsistent findings, small sample sizes, or other problems that potentially confound interpretation of data.	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.
Expert Opinion*	• Consensus of the panel based on clinical judgment and experience, due to absence of evidence or limitations in evidence.	Strong consensus (≥90%) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect. Further research may better inform the topic.

Abbreviations: ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCT = randomized controlled trial.

* A lower quality of evidence, including expert opinion, does not imply that the recommendation is conditional. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials, but there still may be consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden.

recommendations) of raters that select "strongly agree" or "agree" indicates consensus is achieved. Recommendation(s) that do not meet this threshold are removed or revised. Recommendations edited in response to task force or reviewer comments are resurveyed before submission of the document for approval.

Annual Evaluation and Updates—Guidelines are evaluated annually beginning 2 years after publication for new potentially practice-changing studies that could result in a guideline update. In addition, the Guideline Subcommittee will commission a replacement or reaffirmation within 5 years of publication.

Full-Text Guideline—The reader is encouraged to consult the full-text guideline supplement for the supportive text, abbreviations list, and additional information on radiation therapy for basal and squamous cell cancers of the skin because the executive summary contains limited information.

Introduction

Skin cancer is the most prevalent cancer type in the United States with an incidence rate of over 5 million cases annually.[1] Basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) account for over 95% of all skin cancer diagnoses. A variety of treatment options are available and include surgical excision, cryotherapy, radiation therapy (RT), and topical agents. Although surgical excision is considered to be the primary treatment approach for curative treatment of BCC and cSCC, RT can play an integral role in both the definitive and adjuvant settings.

The role of RT for BCC and cSCC has been poorly defined owing to lack of high-quality evidence. To the best of our knowledge, no evidence-based clinical practice guidelines endorsed by a large professional organization currently exist to provide direction on the use of RT for these malignancies. In view of the lack of consensus on this subject, ASTRO commissioned a task force to formulate evidence-based recommendations for the use of definitive and postoperative RT in patients with BCC and cSCC.

Methods

Task force composition

The task force consisted of a multidisciplinary team of radiation, medical, and surgical oncologists, dermatopathologists, a radiation oncology resident, a medical physicist, and a dermatologist. This guideline was developed in collaboration with the American Society of Clinical Oncology and the Society of Surgical Oncology, who provided representatives and peer reviewers.

Document review and approval

The guideline was reviewed by 17 official peer reviewers (see Appendix 1 of the full-text guideline for the reviewer's disclosure information, available online at https://doi.org/10.1016/j.prro.2019.10.014) and revised accordingly. The modified guideline was posted on the ASTRO website for public comment in April 2019. The final guideline was approved by the ASTRO Board of Directors and endorsed by the American Association of Physicists in Medicine, the American Brachytherapy Society, American College of Radiology, American Head and Neck Society, and the Society of Surgical Oncology.

Evidence review

A systematic literature review of human subject studies indexed in MEDLINE (through PubMed) was conducted. The inclusion criteria required research to involve adults ($\geq$18 years of age) who had received a diagnosis of non-metastatic invasive BCC or cSCC, to be published in English from May 1988 through June 2018, and for RT to be delivered with curative intent. The literature search excluded preclinical and dosimetric studies in addition to publications addressing re-irradiation or palliation. Key question (KQ)1 studies were limited to those with $\geq$100 patients, KQs 2 to 4 used $\geq$50 patients, and KQ5 reduced the patient number to $\geq$15 because minimal evidence exists on chemotherapy, biologic, and immunotherapy agents. Both Medical Subject Heading (MeSH) terms and key search terms for all KQs included: *skin neoplasms [Mesh]; basal cell*; *squamous cell*; *neoplasms, basal cell[Mesh]*; *neoplasms, squamous cell[Mesh]*; *dose fractionation[Mesh]*; *radiotherapy[Mesh]*; *radiation*; and *radiotherapy*. Additional terms specific to the KQs and hand searches supplemented the electronic search.

A general conclusion from this search is that there are limited, well-conducted modern randomized trials to underpin clinical paradigms for treatment of patients with cSCC and BCC with radiation treatment. The task force had to rely on synthesis of retrospective study results and expert opinion, which is reflected in the low-to-moderate quality of evidence designation for the majority of the recommendations. The online data supplement includes the evidence tables (available online at https://doi.org/10.1016/j.prro.2019.10.014). References selected and published in this document are representative and not all-inclusive. See Appendix 3 (available online at https://doi.org/10.1016/j.prro.2019.10.014) in the full-text guideline for the detailed search protocol and Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing the number of articles screened, excluded, and included in the evidence review.

Scope of the guideline

This guideline covers only the subjects specified in the KQs (see Table 2 in the full-text guideline for KQs and outcomes of interest). The guideline refers to the most current staging system for BCC and cSCC, which is the eighth edition of the TNM (tumor, node, metastasis) staging system published by the American Joint Committee on Cancer[2] (Table 3 in the full-text guideline). It should be noted that in contrast to the seventh edition, the eighth edition for skin carcinomas is limited to cancers located on the head and neck. The recommendations herein address management of primary sites of the head and neck, trunks,

Table 2 Recommendations for definitive RT

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. In patients with BCC and cSCC who cannot undergo or decline surgical resection, definitive RT is recommended as a curative treatment modality.	Strong	Moderate [2–7]
2. In patients with BCC and cSCC in anatomic locations where surgery can compromise function or cosmesis, definitive RT is conditionally recommended as a curative treatment modality.	Conditional	Moderate [8–10]
3. Definitive RT for BCC and cSCC is conditionally **not** recommended in patients with genetic diseases predisposing to heightened radiosensitivity.	Conditional	Expert Opinion

Abbreviations: BCC = basal cell carcinoma; cSCC = cutaneous squamous cell carcinoma; KQ = Key Question; RT = radiation therapy.

and limbs. Outside the scope of this guideline are several related topics, including RT and systemic therapy in the setting of metastatic BCC and cSCC, dermatopathologic aspects of skin cancer diagnosis, nuances of surgical management, and the technical details of radiation delivery for skin cancer. Additionally, this guideline does not pertain to the management of mucosal head and neck squamous cell carcinoma, vulvar, penile, or perianal skin carcinoma.

Key Questions and Recommendations

Key Question 1: Indications for definitive RT (Table 2)

See online data supplement (Guideline Evidence Tables, available online at https://doi.org/10.1016/j.prro.2019.10.014) for the evidence supporting the recommendations for KQ1.

What are the appropriate indications for definitive RT for BCC and cSCC?

RT is an effective therapy for durable local control of BCC and cSCC characterized by an appealing combination of therapeutic efficacy and functional and cosmetic preservation. These features make definitive RT an attractive alternative to surgery in a number of clinical scenarios, but strict recommendations regarding the comparative effectiveness of the 2 approaches is stymied by the absence of prospective randomized trials comparing different local therapies including surgery, RT, and other local ablative treatments. Ample retrospective and single-arm prospective studies consistently show that definitive RT is associated with high local control rates.[5,6,30–32]

Given the noninvasive nature of RT, physician- and patient-reported cosmetic outcome has been an important secondary endpoint in most studies.[6,33–35] Definitive radiation may be considered as a curative option when surgery can compromise function or cosmesis in an anatomically sensitive area. Good functional outcomes are especially relevant for commonly sun-exposed area of the face (eg, ears, nose, lips, eyelids).

The use of definitive RT is discouraged for the treatment of cSCC or BCC in patients with genetic conditions predisposing them to heightened radiosensitivity, such as ataxia telangiectasia, nevoid basal cell carcinoma syndrome (Gorlin syndrome), or Li-Fraumeni syndrome. Poorly controlled connective tissue disorders are a relative contraindication to treatment.

Key Question 2: Indications for postoperative radiation therapy (Table 3)

See online data supplement (Guideline Evidence Tables, available online at https://doi.org/10.1016/j.prro.2019.10.014) for the evidence supporting the recommendations for KQ2.

What are the appropriate indications for postoperative radiation therapy (PORT) for BCC and cSCC?

The use of RT in the postoperative setting is widely felt to be justified for poor prognostic features that have been established by a few prospective and multiple retrospective studies.[7,11–17,23–28,36,37] Cutaneous SCC is a much more aggressive entity than BCC with a far greater risk for regional and nodal spread. Thus, the task force recommends more wide-ranging utilization of PORT in the cSCC population.[12,26,38]

It is notable that most studies establishing risk factors for local recurrence for BCC and cSCC are limited to patients with skin carcinomas of the head and neck.[7,11–16,28,38] Treatment of the trunk and limb skin cancer thus requires further extrapolation from this literature. It should be noted that cosmetic and functional implications relevant to the head and neck anatomic location are less relevant in the treatment of tumors arising on the trunk and extremities. In patients whose tumors arise on the trunk or extremities, reresection of recurrent tumors is likely to be less challenging than in patients with tumors of the head

Table 3 Recommendations for PORT

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
Both BCC and cSCC		
1. PORT is recommended for gross perineural spread that is clinically or radiologically apparent.	Strong	Moderate [11–15]
cSCC		
2. PORT is recommended for patients with cSCC having close or positive margins that cannot be corrected with further surgery (secondary to morbidity or adverse cosmetic outcome).	Strong	Low [16]
3. PORT is recommended for patients with cSCC in the setting of recurrence after a prior margin-negative resection.	Strong	Moderate [17–22]
4. In patients with cSCC, PORT is recommended for T3 and T4 tumors.*	Strong	Moderate [23–25]
5. In patients with cSCC, PORT is recommended for desmoplastic† or infiltrative tumors in the setting of chronic immunosuppression.	Strong	Moderate [23,25]
BCC		
6. PORT is conditionally recommended in patients with BCC with close or positive margins that cannot be corrected with further surgery (secondary to morbidity or adverse cosmetic outcome).	Conditional	Low [7,26]
7. PORT is conditionally recommended in patients with BCC in the setting of recurrence after a prior margin-negative resection.	Conditional	Low [7,26–28]
8. PORT is conditionally recommended in patients with BCC with locally advanced or neglected tumors involving bone or infiltrating into muscle.	Conditional	Low [7,24,26]

Abbreviations: BCC = basal cell carcinoma; cSCC = cutaneous squamous cell carcinoma; KQ = Key Question; PORT = postoperative radiation therapy; RT = radiation therapy.

* American Joint Committee on Cancer staging table, eighth edition.[29]

† The presence of desmoplasia on light microscopy is defined as fine branches of tumor cells at the periphery and a surrounding stromal reaction. All cSCC in which at least one-third of the representative tumor specimen meet these criteria is classified as desmoplastic cSCC. One study reported findings that perineural or perivascular invasion were always associated with desmoplasia.[25]

and neck, where salvage therapy for recurrence may be more morbid and less effective.[12]

The task force believes that the dose for treating gross perineural spread that is detectable on imaging should be equivalent to definitive doses as outlined in KQ4 and preferably be delivered using conventional fractionation. Optimal dose and fractionation for elective treatment of subclinical disease along the potential nerve pathways is less clearly defined, but giving a high priority to radiation tolerance of adjacent critical structures is encouraged.[39]

Key Question 3: Indications for RT for treating regional nodes and regional disease management (Table 4)

See online data supplement (Guideline Evidence Tables, available online at https://doi.org/10.1016/j.prro.2019.10.014) for the evidence supporting the recommendations for KQ3.

What are the appropriate indications for RT for treating regional nodes? What dose and fractionation should be used for management of regional disease?

Patients with clinically or radiographically apparent lymph node metastasis should undergo therapeutic lymphadenectomy unless they are medically inoperable or the lymphadenopathy is surgically unresectable. Retrospective studies (Table E1, available online at https://doi.org/10.1016/j.prro.2019.10.014) have demonstrated an association of higher regional disease control rates with surgery and adjuvant RT. The quality of the neck dissection is an important factor in the decision-making algorithm. In patients with clinically or radiographically apparent lymph node metastasis that are ineligible for surgery (medically inoperable or technically unresectable), definitive RT for lymph node metastasis is appropriate, albeit with anticipated outcomes inferior to that of surgery and adjuvant RT. Although some practitioners consider adding systemic

Table 4 Recommendations for RT for treating regional nodes and regional disease management

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with cSCC or BCC that metastasized to clinically apparent regional lymph nodes, therapeutic lymphadenectomy followed by adjuvant RT is recommended, with the exception of patients who have a single, small (<3 cm) cervical lymph node harboring carcinoma, without extracapsular extension.	Strong	Moderate [19,38,40-55]
2. For patients with cSCC or BCC that metastasized to clinically apparent regional lymph nodes, definitive RT is only recommended for patients who are medically inoperable or surgically unresectable.	Strong	Moderate [45-47,50,52-54,56]
3. For patients with cSCC at high risk of regional nodal metastasis, imaging and sentinel lymph node biopsy are conditionally recommended to guide the need for and target of lymph node basin RT. Implementation remark: Close clinical follow-up of the lymph node basin is important for patients in whom sentinel lymph node biopsy is unlikely to be accurate due to (1) an extensive initial primary resection and/or reconstruction or (2) tumor location in the head and neck area.	Conditional	Expert Opinion [25]
4. For patients with cSCC at high risk of regional nodal metastasis (thickness >6 mm), elective lymph node basin RT is conditionally recommended only for those undergoing RT to the primary site with overlap of the adjacent nodal basin.	Conditional	Low [23,25,26,56-68]
5. For patients with BCC or cSCC undergoing *adjuvant* RT after therapeutic lymphadenectomy, a dose of 6000-6600 cGy (conventional fractionation [180-200 cGy/fx]) is recommended.	Strong	Moderate [49,56,69-71]
6. For patients with cSCC undergoing *elective* RT in the absence of a lymphadenectomy, a dose of 5000-5400 cGy (conventional fractionation [180-200 cGy/fx]) is recommended.	Strong	Moderate [49,56,69-71]

Abbreviations: BCC = basal cell carcinoma; cSCC = cutaneous squamous cell carcinoma; fx = fraction; KQ = Key Question; PORT = postoperative radiation therapy; RT = radiation therapy.

therapy to definitive RT in this situation, there is no high-quality evidence demonstrating that this improves outcomes, as discussed further in KQ5.

Limited data support the use of elective lymph node basin RT in patients at high risk for recurrence (Table E2, available online at https://doi.org/10.1016/j.prro.2019.10.014) but do suggest a lower than expected rate of regional recurrence in high-risk patients (median 5-year regional relapse-free survival of 99%), suggesting that the elective treatment is effective. To balance the benefits and risk of elective nodal radiation in the absence of quality evidence, practitioners may choose to selectively target the high-risk echelons of the draining lymphatics. Nevertheless, lymph node basin RT is associated with adverse events (eg, dermatitis, lymphedema, mucositis), so careful selection of patients for this treatment is encouraged. Patients who are having adjuvant RT to a high-risk primary tumor located at a site that overlaps a draining lymph node basin may be good candidates for elective lymph node basin RT. It may be prudent in selected patients to decrease the probability of requiring reirradiation of the same anatomic site. The task force initially discussed a recommendation against routine elective lymph node basin RT, but ultimately it was felt that insufficient data were available to make that recommendation.

Finally, the radiation doses used as part of lymph node management should be considered carefully given the potential morbidity of treatment. Current standards of care are largely derived from experience in the treatment of other cancers from the same anatomic sites in which regional lymph node metastases from these skin cancers occur. A prospective clinical trial of patients with locally advanced cSCC receiving adjuvant RT required 6000 to 6600 cGy to be given at 200 cGy/fraction.[49] This observation, in addition to a single-institution study of adjuvant RT for mucosal SCC demonstrating no benefit of adjuvant RT with doses >6000 cGy at 200 cGy/fraction, suggest that a dose of 6000 cGy at 200 cGy/fraction is sufficient after a therapeutic lymphadenectomy has been performed.[69-71] Although some practitioners favor a dose of 6600

Table 5 Recommendations for radiation techniques and dose-fractionation schedules for primary site management

KQ4 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. In patients with BCC and cSCC receiving RT in the definitive setting, the following dose-fractionation schemes* are recommended: ○ Conventional (180-200 cGy/fx): BED_{10} 70-93.5 ○ Hypofractionation (210-500 cGy/fx): BED_{10} 56-88 Implementation remark: Conventional fractionation is delivered 5 days per week; hypofractionation is delivered daily or 2-4 times per week.	Strong	Low 9,65,66,68,72-78
2. In patients with BCC and cSCC receiving RT in the postoperative setting, the following dose-fractionation schemes* are recommended: ○ Conventional (180-200 cGy/fx): BED_{10} 59.5-79.2 ○ Hypofractionation (210-500 cGy/fx): BED_{10} 56-70.2 Implementation remark: Conventional fractionation is delivered 5 days per week; hypofractionation is delivered daily or 2-4 times per week.	Strong	Low 4,28,74,77,79-84

Abbreviations: BCC = basal cell carcinoma; BED_{10} = biologically effective dose assuming an $\alpha/\beta = 10$; cSCC = cutaneous squamous cell carcinoma; fx = fraction; KQ = Key Question; RT = radiation therapy.
* See Table 6 with specific fractionation schemes.

cGy at 200 cGy/fraction in situations of microscopically positive margins or extranodal extension of carcinoma, no data support use of this higher adjuvant dose. In extrapolation from head and neck mucosal SCC, RT should begin as healing from surgery is complete, preferably within 6 weeks of surgery.[69-71] Far less data are available on the outcome of elective lymph node basin RT, but the existing series have generally used a dose of 5000 cGy at 200 cGy/fraction or an equivalent regimen (ie, 5400 cGy at 180 cGy/fraction).[23,25,26,56-68]

Key Question 4: Radiation techniques and dose-fractionation schedules for primary site management (Table 5)

See online data supplement (Guideline Evidence Tables, available online at https://doi.org/10.1016/j.prro.2019.10.014) for the evidence supporting the recommendations for KQ4.

What are the preferred dose-fractionation schedules and radiation techniques for the management of the primary site in BCC and cSCC?

Multiple RT modalities can be used to appropriately treat BCC and cSCC. Megavoltage (MV) electrons, brachytherapy (low-dose-rate and high-dose-rate [HDR]), kilovoltage, and MV photons have been successfully used to treat BCC and cSCC.[6,65,78,84,85]

A thorough literature review on this topic suggests that appropriate use of any of the 4 major radiation modalities results in similar local control and cosmetic outcome.[3,4,9,28,31,64-66,68,72-84,86-88] Thus, the decision of which modality and fractionation scheme to use should be based on both tumor characteristics (eg, shape, contour, depth, and location) and normal tissue considerations.

Electronically generated low-energy sources (ELS) are defined as equipment using x-ray sources with a peak voltage of up to 120 kVp to deliver a therapeutic radiation dose to clinical targets.[89] Although electronic brachytherapy is classified within this ELS category, the authorized user requirements for this particular modality are different than those of superficial x-ray therapy. ELS do not require special shielding or compliance with the Nuclear Regulatory Commission regulations that are imposed on authorized users of low-dose-rate or HDR brachytherapy or MV equipment. Brachytherapy uses a radioactive isotope to deliver therapeutic radiation near or inside the tumor target. Although the use of low-dose-rate brachytherapy remains historically significant, HDR has become more common after the advent of HDR afterloaders, which offer versatility in treatment volume design, minimal exposure to the staff and shorter treatment times. The physical properties of MeV electron therapy (6-20 MeV) and MV photon therapy (6-15 MV) allow for treatment of deeper structures, and these methods are commonly used for targeting more advanced disease. It should be noted that both ELS and skin surface brachytherapy lend themselves particularly well to moderate and extreme hypofractionation. Dose falloff for these modalities is rapid, resulting in relative sparing of deeper structures.

Table 6 provides further details of fractionation schemes according to each modality. It is important to remember that the dose delivered to the skin can vary based on multiple factors including modality, the energy of the beam, field size, bolus thickness, and filters. The fractionation schemes outlined in this guideline were drawn from studies that met our inclusion criteria (outlined in Evidence Review), and we recognize that these schemes

Table 6 Dose fractionation schemes (derived from studies with at least 50 patients* treated with definitive or postoperative RT)

Total dose, cGy	No. of fx	Fx size, cGy	Weekly fx	BED_{10}	Definitive†	Postop†	Modality	Refs
Conventional Fractionation								
5040	28	180	5	59.5	—	X	ELS	4
5940	33	180	5	70.1	X	—	HDR	33
6000	30	200	5	72	—	X	ELS, electrons, MV	4,83
6480	36	180	5	76.5	X	—	HDR	33
6600	33	200	5	79.2	X	X	ELS, MV	90
7000	35	200	5	84	X	—	ELS, MV	90
7400	37	200	5	88.8	X	—	ELS	4
7920‡	44	180	5	93.5	X	—	HDR	33
Hypofractionation								
4000	8	500	2	60	X	—	HDR	77
4050	9	450	bid for 9 fx/wk	58.7	X	X	HDR	74
4400	10	440	4	63.4	X	X	Electrons	81
4400	14	300 (first dose); 400 (last dose)	bid for 10 fx/wk	58.0	X	—	HDR	75
4500	9	500	bid for 9 fx/wk	67.5	X	X	HDR	74
4500	10	450	4	65.3	X	X	ELS	28,79
4500	15	300	5	58.5	X	X	ELS, electrons, MV	4,83
4800	16	300	5	62.4	X	—	HDR	77
5000	20	250	5	62.5	X	X	ELS, electrons, MV	79,80,83
5100	17	300	5	66.3	X	—	ELS	4
5400	18	300	4-5	70.2	X	X	Electrons, ELS	28,81
5500	20	275	5	70.1	X	X	ELS, MV	4,80
6120	18	340	5	82	X	X	HDR, ELS, MV	90

Abbreviations: BED_{10} = biologically effective dose assuming an $\alpha/\beta = 10$; bid = twice daily; ELS = electronically generated, low-energy radiation sources; fx = fraction; HDR = high-dose-rate; MV = megavoltage photons.

* The majority of these studies included over 100 patients.

† Some studies included both definitive and postoperative cases, and the distinction in dose for the different treatment times were not necessarily outlined in the studies.

‡ Lesions >4 cm were boosted up to 80 Gy after a 3-week break.

are not all-inclusive. These recommendations aim to summarize the wide variety of appropriate regimens that have been reported to provide excellent local control with good cosmetic outcomes. Biological effective dose (BED) ranges are used instead of specific doses and fractionation in an attempt to address the wide variation in dosing schemes within the examined literature. BED calculations involve the use of an established radiobiological equation to compare different fractionation regimens by converting them to comparable values for a given tissue of interest. BED calculations are most appropriately determined and compared within a specific modality.

The process of care in radiation oncology is an involved undertaking requiring coordination of many complex activities. Readers may refer to ASTRO's update to the *Safety Is No Accident* publication, which provides a framework for high-quality radiation treatment preparation and delivery.[91] Image-guided RT is instrumental for accurate delivery of photon-based RT when treating regional lymphatics and nerve tracks in the head and neck. For local treatment of skin targets, the task force emphasizes the importance of regular and frequent visual confirmation of surface coverage by the treating radiation oncologist (ie, biweekly "see-on-table" verification). Daily imaging is neither necessary nor useful when treating with electron beam, ELS, or skin surface brachytherapy. Anatomic location, patient preference, and cost of treatment should be part of the consideration when choosing the treatment regimen. Choice of hypofractionated regimens using superficial therapy or electron beam therapy without 3-dimensional planning are considered more cost-effective.[92] However, caution should be exercised when treating anatomically sensitive areas (ie, periorbital and perioral skin) with hypofractionated regimens. Compared with standard fractionation, hypofractionation, especially when used with more deeply

Table 7 Recommendations for use of chemotherapy, biologic, and immunotherapy agents before, during, or after RT

KQ5 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. In patients with resected locally advanced cSCC, the addition of concurrent carboplatin to adjuvant RT is **not** recommended.	Strong	Moderate [49]
2. In patients with unresected locally advanced cSCC, the addition of concurrent drug therapies to definitive RT is conditionally recommended.	Conditional	Low [93]

Abbreviations: cSCC = cutaneous squamous cell carcinoma; KQ = Key Question; RT = radiation therapy.

penetrating modalities (eg, MV electrons and photons), can lead to more skin atrophy and fibrosis, potentially jeopardizing otherwise excellent functional outcomes. Conventional regimens are typically delivered on a daily basis, whereas hypofractionated regimens can be delivered daily or 2 to 4 times per week with a goal of achieving even spacing between the fractions in any given week.

Key Question 5: Use of chemotherapy, biologic, and immunotherapy agents before, during or after RT (Table 7)

See online data supplement (Guideline Evidence Tables, available online at https://doi.org/10.1016/j.prro.2019.10.014) for the evidence supporting the recommendations for KQ5.

When is it appropriate to use chemotherapy, biologic, and immunotherapy agents before, during, or after RT in the treatment of BCC or cSCC?

Systemic therapy in BCC and cSCC is considered an adjunct to the definitive modalities of surgical excision and RT in various clinical scenarios deemed at high risk for recurrence. Although a benefit to the addition of radiosensitizing cisplatin to RT in the adjuvant setting was demonstrated for mucosal head and neck squamous cell carcinoma,[94,95] a prospective randomized trial failed to demonstrate a benefit when weekly administered radiosensitizing carboplatin was added to PORT in patients with high-risk resected cSCC.[49]

The use of concurrent platinum-based chemoradiation is well established in advanced mucosal SCC through randomized trials and meta-analyses.[96,97] In cSCC, however, the data are much less robust and consist only of small retrospective reports[98,99] and a small phase II study.[93] Single-arm prospective evidence for use of targeted therapy in the neoadjuvant setting[100] has also been described in cSCC.

Hedgehog inhibitors (vismodegib and sonidegib) and immunotherapy agents (cemiplimab) are approved palliative therapies in patients with BCC and cSCC; thus, treating physicians are strongly advised to avoid their use in settings where curative-intent surgery or RT is feasible.

Conclusions and Future Directions

The paucity of prospective and randomized data both hinders RT use for BCC and cSCC and offers a ripe opportunity for future research to characterize the role of RT in management of this disease. Whenever possible, patient outcomes should be collected as part of clinical trials and prospective registries to bolster the overall quality of data on this topic. It is our hope that this guideline will help further this goal. Specific areas of interest identified by our task force are standardization of radiation fractionation schemes, defining optimal management of microscopic perineural invasion, management of regional nodal basins, and the role of systemic therapy in neoadjuvant, adjuvant, and concurrent settings.

Acknowledgments

We are grateful to Yimin Geng, MSLIS, MS, the University of Texas MD Anderson research medical librarian, for her assistance with creating the search strategy for this guideline. The task force also thanks Musaddiq Awan, MD, Nicholas DeNunzio, MD, PhD, Elisha Fredman, MD, William Grubb, MD, Blair Murphy, MD, Steven Seyedin, MD, Fauzia Shaikhfor, MD, and Michael Stolten, MD, for literature review assistance and Dean Shumway, MD, who contributed to the guideline during the early phase of development.

The task force thanks the peer reviewers for their comments and time reviewing the guideline (see Appendix 1 for their names and disclosures, available online at https://doi.org/10.1016/j.prro.2019.10.014), and Michael Diehl, who served as the patient representative of the task force.

We also thank task force participants Murad Alam, MD, for providing a dermatologic perspective and Valencia Thomas, MD, and Michael Tetzlaff, MD,

for providing a dermatopathologic perspective, who withdrew from authorship.

Supplementary Data

Supplementary material for this article can be found at https://doi.org/10.1016/j.prro.2019.10.014.

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