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REVIEW

The Value of Adjuvant Radiotherapy in Cutaneous Squamous Cell Carcinoma: A Review☆

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Abstract Cutaneous squamous cell carcinoma (cSCC) is the second most common cancer in humans and its incidence is rising. Although surgery is the treatment of choice for cSCC, postoperative adjuvant radiotherapy has an important role in local and locorregional disease control. In this review, we analyze the value of postoperative radiotherapy in the management of high-risk cSCC (in particular, cases with perineural invasion), cSCC with positive surgical margins, and locally advanced cSCC (with parotid gland and/or lymph node metastasis).

PALABRAS CLAVE
Carcinoma escamoso cutáneo;
Radioterapia;
Adyuvancia;
Postoperatorio;
Alto riesgo

Utilidad de la radioterapia en adyuvancia en el carcinoma epidermoide cutáneo

Resumen El carcinoma epidermoide cutáneo (CEC) es el segundo tumor más frecuente en humanos y tiene una incidencia creciente. Aunque la cirugía representa el tratamiento de elección del CEC, la radioterapia adyuvante postoperatoria tiene un papel relevante en el control local y locorregional de la enfermedad. En esta revisión analizamos la utilidad de la radioterapia postoperatoria en el manejo del CEC de alto riesgo (especialmente con infiltración perineural), en el control del CEC con márgenes positivos tras la cirugía y en el CEC localmente avanzado (con metástasis parotídeas o ganglionares).

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Introduccion

Cutaneous squamous cell carcinoma (cSCC) is the second most common cancer in human. Its incidence has risen in epidemic proportions in recent decades[1] and is probably underestimated.[2] In the United States, approximately 700 000 new cases of cSCC are diagnosed every year,[2] and the lifetime risk of developing this cancer is between 7% and 11%,[3] with slightly higher rates in men.[4] In Spain, the estimated incidence is 38.16 cases per 100 000 person-years.[5] The overall risk of metastasis in cSCC ranges between between 2% and 6%.[6] The overall mortality attributable to cSCC is 2%,[2] but when the disease spreads, 5-year mortality rates vary between 20% and 50%.[6] cSCC accounts for most deaths attributable to skin cancer in individuals older than 85 years,[2] and in some areas of the United States, death from cSCC is comparable to that from renal or oropharyngeal carcinoma or melanoma.[2]

Although surgery is the treatment of choice in cSCC, radiotherapy can be useful in selected cases,[7] particularly when a patient cannot or chooses not to undergo surgery or has an unresectable tumor.[8] Radiotherapy has proven to be useful as a first-line treatment with curative intent (radical radiotherapy), as an adjuvant to surgery, and as palliative treatment.[9–14] Although it provides an alternative to surgery, it has lower cure rates and an appreciable proportion of tumors exhibiting aggressive behavior recur after treatment.[7,15,16] In this review, we focus on the adjuvant role of radiotherapy in cSCC. There is some controversy on its usefulness in patients with positive margins after excision or with high-risk criteria, such as perineural invasion (PNI). We will also discuss the evidence for the use of adjuvant radiotherapy in locally advanced cSCC (i.e., cSCC with parotid gland or cervical lymph node involvement).

Introduction to Radiotherapy

Ionizing radiation damages DNA and primarily leads to the death of cells with the lowest degree of differentiation and the highest level of mitotic activity. To prevent damage to healthy tissue, it is essential that the therapeutic dose is deposited in the tumor. Tumor heterogeneity, histologic features (including degree of differentiation), and total cell volume are all key factors in radiocurability.[17–19]

The dose absorbed from ionizing radiation is measured in Grays (Gy). One Gy is equivalent to 100 cGy or 100 rads and the corresponding radiation is 1 Joule of energy absorbed per 1 kg of mass of irradiated material. Radition does not cause the immediate death of cells, but rather affects their mitotic capacity and this may not occur for 2 or 3 cell cycles. It is therefore important not to prematurely assess treatment response. An assessment made after approximately 3 months can be considered to be reliable. Inactive tumor remnants can take months or even years to be totally reabsorbed, and it is therefore advisable to adopt a prudent, vigilant attitude.[17,19]

Numerous techniques, together with diverse regimens and total doses, exist for administering radiotherapy (Table 1). The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for cSCC accept the use of different radiotherapy modalities (in particular external modalities) depending on the experience and availability at each center,[20] as it has been demonstrated that they perform similarly in terms of effectiveness, safety, and cosmetic outcomes.[21–27] Choice of technique is also influenced by tumor type, treatment intention (radical, adjuvant, or palliative), tumor depth, and anatomic location. Megavoltage radiotherapy, which is delivered by a linear accelerator, has a greater penetration capacity and is therefore useful for treating internal malignancies while largely sparing the skin. Low-energy radiation (kilovoltage and orthovoltage), is preferred when treating cutaneous lesions where deep penetration and skin preservation are not desirable. The dose of radiotherapy administered is known as a *fraction*. The standard fraction used in oncological dermatology is 2.5 Gy administered 5 days a week, generally from Monday to Friday. Shorter regimens spanning just 2 to 3 days have been attempted, but they do not seem to offer significant advantages, as they lengthen the overall treatment time and may reduce local disease control. Hypofractionation refers to the use of higher doses (4-7 Gy) per fraction, which results in a lower total dose. Hypofractionation (higher doses and fewer fractions) is useful for small lesions or for frail or elderly patients.[28,29] Fractionated schedules tend to minimize long-term adverse effects, improving thus treatment effectiveness and tolerability.

The limitations of radiotherapy include adverse effects and complications on the one hand and contraindications on the other. Skin reactions triggered by radiotherapy are referred to as *radition-induced dermatitis* or *radiodermatitis*. They can be acute or delayed. Acute reactions last for several weeks and initially consist of erythema and slight dry scaling followed by a somewhat moister scaling and mild bleeding. Delayed reactions usually appear months or years after treatment and are more common with higher treatment doses. The most common late reactions are hypopigmentation and hyperpigmentation, telangiectasisas, epidermal atrophy, skin fragility, sebaceous gland atrophy, alopecia, fibrosis, necrosis, and an increased risk of certain tumors, such as angiosarcoma.[30] Of note among the contradidications for radiotherapy are *1*) young age, *2*) verrucous squamous cell carcinoma, *3*) genodermatoses with a predisposition for cancer, and *4*) immunodepression.[7]

Another potential limitation is the cost of treatment and the need for infrastructure. The cost of treating a single cSSC ranges from $512.38 in the case of certain superficial therapies to almost $8000 for outpatient brachytherapy modalities,[31] making it more expensive than conventional surgery and even Mohs micrographic surgery.[32]

Radiotherapy in cSCC With PNI

PNI is observed in between 2.5% and 14% of cSCCs and is normally detected as an incidental histologic finding.[33] It has been linked to poor prognosis and a higher rate of metastasis and disease-specific death.[33–38] The risk factors in cSCC are male sex, recurrent disease, a centro-facial location, poor histologic differentiation, and deep subclinical extension.[34] Although there is some evidence supporting better disease control following postoperative radiotherapy in patients with clinical PNI or cranial nerve involvement,[39]