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Braquiterapia electrónica en el carcinoma basocelular superficial y nodular

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Departament de Medicina

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Los directores de la tesis *"Braquiterapia electrónica en el carcinoma basocelular superficial y nodular"* certifican que Rosa Ballester Sánchez es la autora de la misma.

Y para que conste a los efectos, firman la siguiente certificación:

Valencia, 11 de septiembre de 2017

Dr. Rafael Botella Estrada Dr. José Pérez Calatayud

Als meus Peps

"Y fue tanta la inmensidad del mar… que el niño quedó mudo de hermosura. Y pidió a su padre: ¡ayúdame a mirar!"

Eduardo Galeano

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ÍNDICE

Resumen

El carcinoma basocelular es el cáncer cutáneo más frecuente. Presenta un crecimiento local con poca capacidad de diseminación a distancia, lo que supone una importante morbilidad. Su elevada incidencia conlleva una importante demanda asistencial que genera elevados costes sanitarios. El manejo terapéutico de este tipo de tumor varía en función de las características del paciente (edad, comorbilidades, tratamientos y preferencias) y de la lesión (subtipo, tamaño y localización). Su manejo terapéutico en los casos localizados se basa en la aplicación de terapias invasivas (cirugía convencional o cirugía micrográfica) y no invasivas (radioterapia, terapia fotodinámica, crioterapia o imiquimod). Actualmente la cirugía es considerada la primera opción de tratamiento seguida de la radioterapia.

La radioterapia se ha usado con fines radicales, adyuvantes o paliativos, y se han utilizado distintas técnicas en función de las características tumorales y de la disponibilidad de cada centro. A pesar del gran volumen asistencial que supone su manejo y tratamiento, existen muy pocos estudios prospectivos de calidad que evalúen los distintos tipo de radioterapia en el carcinoma basocelular.

Recientemente han aparecido en el mercado novedosos equipos de braquiterapia electrónica. Se trata de un tipo de radioterapia de contacto que utiliza fuentes de rayos X. Debido a su reciente incorporación existe muy poca información clínica

sobre su implementación, eficacia y seguridad en el tratamiento del carcinoma basocelular. Sobre esta base diseñamos un estudio piloto prospectivo unicéntrico para tratar con braquiterapia electrónica un número limitado de pacientes con carcinoma basocelular con subtipos no invasivos (superficial y nodular). En total incluimos 40 pacientes con 60 lesiones en dos grupos consecutivos de 20 pacientes con dos dosis distintas de tratamiento: 36,6 y 42 Gy. Evaluamos la eficacia, la toxicidad y los resultados cosméticos con un seguimiento a 6 meses, 1 año y 2 años tras el tratamiento. Realizamos además dos subestudios para determinar el papel de la ecografía cutánea de alta frecuencia en la determinación de la profundidad tumoral y el uso de la dermatoscopia en la delimitación del margen lateral. Obtuvimos buenos resultados de eficacia, con respuestas completas superiores al 95% con un seguimiento a dos años. La toxicidad fue leve y pasajera y los resultados cosméticos buenos o excelentes en todos los casos. Aunque no encontramos diferencias estadísticamente significativas en la determinación de la profundidad con ecografía comparado con la biopsia, pensamos que es una técnica útil para delimitar los márgenes. Por último, la dermatoscopia resultó de utilidad para la delimitación del margen lateral previamente al tratamiento con radioterapia.

Abstract

Basal cell carcinoma is the most common skin cancer. It presents a local growth with little capacity of dissemination, which implies an important morbidity. Its high incidence cause an important demand for health care, which generates high health costs. The therapeutic management of this type of tumour varies according to the characteristics of the patient (age, comorbidities, treatments and preferences) and of the lesion (subtype, size and location). Its therapeutic management in the localized cases is based on the application of invasive therapies (conventional or micrographic surgery) and non-invasive (radiotherapy, photodynamic therapy, cryotherapy or imiquimod). Currently surgery is considered the first treatment option followed by radiation therapy.

Radiotherapy has been used for radical purposes, adjuvants or palliatives, and different techniques may be used depending on the tumour characteristics and the availability of each centre. Despite the great burden of care derived from its management and treatment, there are very few prospective studies of quality that evaluate the different types of radiotherapy in basal cell carcinoma.

New electronic brachytherapy equipment has recently appeared on the market. It is a type of contact radiotherapy that uses X-ray sources. Because of its recent incorporation there is very little clinical information on its implementation, efficacy and

safety in the treatment of basal cell carcinoma. On this basis we designed a prospective unicentric pilot study to treat with electronic brachytherapy a limited number of patients with basal cell carcinoma with non-invasive subtypes (superficial and nodular). In total we included 40 patients with 60 lesions in two consecutive groups of 20 patients with two different treatment doses: 36.6 and 42 Gy. We evaluated the efficacy, toxicity and cosmetic results with a follow-ups at 6 months, 1 year and 2 years after treatment. We also performed two sub-studies to determine the role of high frequency cutaneous ultrasound in the determination of tumour depth and the use of dermoscopy in lateral margin delimitation. We obtained good efficacy results, with complete responses above 95% with a two-year follow-up. The toxicity was mild and transient and the cosmetic results were good or excellent in all cases. Although we did not find statistically significant differences in depth determination with ultrasound compared to biopsy, we thought it was a useful technique to define margins. Finally, dermoscopy was useful for delimiting the lateral margin prior to treatment with radiotherapy.

INTRODUCCIÓN

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I. El carcinoma basocelular y su tratamiento

El carcinoma basocelular (CBC) es un tumor maligno de origen epidérmico. Se trata del cáncer cutáneo más frecuente, representando aproximadamente el 75% de todos los cánceres de piel. Asimismo, es el subtipo más frecuente de cáncer cutáneo no melanoma (CCNM), representando el 80-90% del total[1], aunque su incidencia es imprecisa ya que no contamos con registros protocolizados. El CBC es más frecuente en la raza caucásica, en países más próximos al ecuador y en sujetos de edad avanzada. Para su desarrollo participan factores genéticos y ambientales, principalmente la exposición a la radiación ultravioleta (RUV). Otros factores de riesgo establecidos incluyen la inmunosupresión, la exposición a radiaciones ionizantes, la fototerapia, el uso de fármacos fotosensiblizantes, la exposición crónica a arsénico o la presencia de enfermedades genéticas como el síndrome de Gorlin. Su incidencia está en aumento debido a un envejecimiento de la población general así como al incremento en la exposición a la radiación ultravioleta, lo que origina una gran demanda asistencial y por tanto un elevado gasto sanitario[2]. Los pacientes con antecedentes de CBC tienen mayor riesgo de desarrollar nuevos CBC (el 40% desarrollarán otro tumor en los siguientes 5 años)[3], de lo que deriva la importancia del seguimiento de estos pacientes. Algunos síndromes genéticos

(como el síndrome de Gorlin, síndrome de Bazex, síndrome de Rombo o xeroderma pigmentoso) también promueven el desarrollo de múltiples CBCs.

El diagnóstico del CBC es principalmente clínico, aunque se suele confirmar histológicamente mediante biopsia cutánea previa al tratamiento si éste no va a ser la escisión quirúrgica, en cuyo caso el mismo acto es a menudo diagnóstico y curativo. Debe realizarse el diagnóstico diferencial fundamentalmente con otras dermatosis (molluscum, queratosis liquenoide benigna, micosis, hiperplasias sebáceas, morfea…) tumores benignos (nevus, tumores anexiales,...) y con otros tumores malignos o lesiones premalignas (carcinoma epidermoide, queratosis actínicas, melanoma, metástasis,…).

Aproximadamente el 70% de los casos aparecen en la cara (debido a una fotoexposición continua), seguido del tronco. Existen varios subtipos que se diferencian por la clínica y por la histología. Los más frecuentes son el CBC nodular y superficial, que se consideran variantes no invasivas[4]. Otros subtipos considerados como variantes invasivas son el CBC micronodular, multicéntrico, morfeiforme y basoescamoso. Un porcentaje no desdeñable de lesiones presenta un patrón mixto[5]. Las lesiones pueden estar o no ulceradas y/o pigmentadas. Histológicamente se observa una proliferación tumoral de nidos y cordones de células basaloides que mantienen contacto con la epidermis e invaden la dermis, con una frecuente separación artefacta entre los nidos y el estroma. Es también característica la observación en

los nidos tumorales de células en empalizada de disposición periférica.

Se trata de un tumor de lento crecimiento con invasión local y bajo poder metastásico (menor del 0,5%)[6]. En casos evolucionados puede invadir estructuras profundas (músculo, periostio, hueso, nervios u órganos de los sentidos). Tienen mayor riesgo de recidiva local aquellos tumores de mayor tamaño, los localizados en áreas de riesgo (área central de la cara, nariz, labios, región periocular y región auricular), los subtipos morfeiforme y basoescamoso y los tumores recidivados. Aunque el índice de mortalidad es bajo, este tumor puede suponer una importante morbilidad. Debido a la invasión local puede llegar a destruir órganos como el globo ocular, cartílago, músculo o hueso, causando desfiguración. En lesiones localmente avanzadas la ulceración, el sangrado, el dolor y la infección local son fenómenos frecuentes.

El manejo terapéutico en estadios localizados (que suponen la gran mayoría de los casos) se basa en la aplicación de terapias invasivas (cirugía convencional o cirugía de Mohs), o no invasivas (crioterapia, curetaje y coagulación, imiquimod tópico, terapia fotodinámica y radioterapia). Estas modalidades terapéuticas presentan diferentes tasas de respuestas, complicaciones y resultados cosméticos. La elección de una u otra modalidad dependerá fundamentalmente del subtipo histológico, la localización, las comorbilidades del paciente, la experiencia del médico y las técnicas disponibles en el centro en que se encuentre. Se deben tener en cuenta las limitaciones físicas y funcionales que

pueden afectar a la capacidad del paciente para tolerar la cirugía, realizar curas, aplicar terapias tópicas o volver a la consulta. Asimismo, debe considerarse el resultado cosmético y la preferencia por parte del paciente. Las técnicas invasivas se consideran de primera elección en la mayoría de los pacientes al haber demostrado menores tasas de recurrencias[7]. La cirugía convencional es un método sencillo y rápido, mientras que la cirugía controlada de Mohs es una técnica más compleja y especializada que se reserva para aquellos casos con elevado riesgo de recurrencia o en situaciones en las que el ahorro de tejido sano es de vital importancia por razones funcionales o cosméticas. Las terapias no invasivas y locales presentan generalmente menores tasas de respuesta y se reservan para aquellos casos de bajo riesgo.

En general, las recurrencias locales aparecen en el 50% durante el primer año, el 66% durante los dos primeros años y el 80% antes de los 5 años[8].

A pesar de la elevada incidencia del CBC, apenas se han realizado estudios randomizados para definir las pautas de tratamiento. En un meta-análisis de la Biblioteca Cochrane publicado en el año 2007 se recogen un total de 27 estudios y los autores concluyen que la cirugía y la radioterapia (RT) son los tratamientos con menores tasas de recurrencias[9].

II. Radioterapia en el carcinoma basocelular

La RT es una alternativa terapéutica en el manejo de pacientes seleccionados con CCNM[4]. Los principales tumores con indicación terapéutica con RT son el CBC, el carcinoma espinocelular, el carcinoma de células de Merkel, el dermatofibrosarcoma protuberans, el angiosarcoma, algunos carcinomas anexiales y el melanoma. El tratamiento puede tener intención curativa (radical), adyuvante o complementaria a la cirugía (en caso de márgenes de resección positivos o invasión perineural), para mejorar el control local y prevenir la aparición de recidivas, y paliativa en casos inoperables o metástasis sintomáticas, para tratar los síntomas producidos por el tumor (dolor, hemorragia, compresión nerviosa)[10].

Uno de los mecanismos más importantes por el cual se produce la muerte celular es el daño directo del ADN, afectando a células tumorales por su mayor indiferenciación y actividad mitótica (las células son más sensibles a la radiación en G2 o síntesis proteica y en M o mitosis). Por ello el empleo de radiaciones ionizantes en la práctica médica se basa en la mayor destrucción de tejido neoplásico que sano y en la optimización de los planes de tratamiento para que la dosis al tejido tumoral sea superior a la impartida al tejido sano. La administración de RT en dosis fraccionadas permite aumentar el efecto mediante fenómenos de reoxigenación, redistribución, reparación intracelular y repoblación[11].

La respuesta tumoral a la RT se prolonga en el tiempo más allá de los tres meses ya que la neoplasia no desaparece de forma rápida tras finalizar el tratamiento. Esto se debe a una discordancia clínico-patológica temporal debido a que se pueden seguir observando restos tumorales que sean biológicamente inviables y que pueden requerir meses o incluso años en reabsorberse. Por ello es aconsejable adoptar actitudes prudentes y no abusar de biopsias o cirugías prematuras[12,13,11]. Según las guías RECIST[14] sobre evaluación de la respuesta a la RT en tumores sólidos se considera respuesta completa cuando desaparece la lesión, respuesta parcial si la disminución del diámetro es ≥30%, progresión cuando existe un aumento del diámetro ≥20% y enfermedad estable cuando no llega a los parámetros anteriores.

La radioterapia aplicada a la piel está parcialmente contraindicada en pacientes jóvenes (de menos de 50 años) debido al riesgo de malignización a largo plazo[15]. Está también contraindicada en pacientes con genodermatosis (xeroderma pigmentoso, síndrome de Gorlin o epidermólisis ampollosa) por su predisposición al cáncer de piel radioinducido debido a alteraciones en la reparación del ADN. Otras contraindicaciones son las conectivopatías, carcinomas verrucosos, zonas previamente radiadas o localizaciones acrales y genital[10].

Durante y después del tratamiento con RT se observan efectos adversos que se clasifican en agudos (hasta los 6 meses tras la irradiación) y crónicos (a partir de los 6 meses tras finalizar el tratamiento). Los agudos tienen un periodo de latencia de 1-2 días y suele aparecer eritema, descamación o dermatitis húmeda en

función de la dosis administrada. Los efectos tardíos o crónicos son debidos a la reparación del tejido irradiado por proliferación de tejido conjuntivo, lo que da lugar a cambios morfológicos y funcionales. Los más frecuente son atrofia, cambios en la pigmentación, alopecia, telangiectasias, ulceración y necrosis. Para cuantificar la morbilidad del tratamiento se utilizan escalas establecidas por la *European Organization for Research and Treatment of Cancer* (EORTC) y el *Radiation Therapy Oncology Group* (RTOG)[16,17].

Son escasos los estudios que evalúan la utilidad de la RT en el tratamiento del CBC, siendo en su mayoría estudios retrospectivos y con gran variabilidad tanto de técnicas como de dosis de radiación utilizadas. Cho et al[18] revisan todos los estudios publicados sobre el uso de RT en CBC e identifican 11 estudios con tasas de respuesta del 79,2% al 100%, y con tasas de curación a los 5 años entre 79,2-95,8% (evaluado en 4 estudios). A día de hoy únicamente existen dos estudios randomizados que hayan evaluado la eficacia de la RT en el CBC. Hall et al[19] compararon la eficacia de la RT y la crioterapia en una serie de 93 pacientes e identificaron una mayor tasa de recurrencia en el grupo tratado con crioterapia (39%) comparado con el grupo de radioterapia (4%), sin identificar diferencias significativas en los resultados cosméticos. Avril et al[20] trataron 347 CBC localizados en región facial con radioterapia y cirugía, y realizaron un seguimiento de los pacientes durante 4 años. Sólo un paciente del grupo de cirugía presentó una recurrencia tumoral comparado con 11 pacientes en el grupo de radioterapia, por lo que concluyeron que la cirugía debería ser un tratamiento de primera línea. El resultado

cosmético también fue significativamente superior para el grupo de cirugía comparado con RT. Hay que recalcar que el grupo de RT era muy heterogéneo ya que se incluyeron pacientes tratados con braquiterapia intersticial, con contacterapia y con RT convencional. Existe otro estudio randomizado donde se compara la cirugía con la RT en el tratamiento del CBC facial pero donde sólo evalúan el resultado cosmético y no la eficacia, siendo superior para el grupo de cirugía con un seguimiento de 4 años[21].

Cabe destacar que en la actualidad la mayoría de los pacientes remitidos a RT suelen ser pacientes con lesiones irresecables o pacientes inoperables por su avanzada edad o sus comorbilidades. Este hecho puede inducir un sesgo a la hora de interpretar los resultados y compararlos con los obtenidos por otros procedimientos terapéuticos. Algunos autores han señalado que la RT podría ser una alternativa terapéutica eficaz en pacientes con expectativa de vida limitada, donde se pueden obtener buenas tasas de control tumoral y buen resultado cosmético. Nguyen et al[22] realizaron un estudio retrospectivo en el que incluyeron 15 pacientes con edad media de 81 años, a los que se les realizó tratamiento con RT con dosis entre 45Gy y 72,5Gy. Tras una media de seguimiento de 34 meses, no se objetivaron recurrencias loco-regionales, alcanzando en todos los pacientes respuestas completas con muy buen resultado cosmético.

II.A. Breve historia

Las radiaciones ionizantes se utilizan en oncología desde hace más de 100 años. Este tipo de terapia se aplicó por primera vez en

el cáncer de piel[23]. Desde entonces, las técnicas y usos han ido variando a lo largo del tiempo de la mano de la tecnología y la legislación en el empleo de radiaciones ionizantes y de las competencias de cada especialista. A pesar de las diferencias legislativas de cada país, podemos decir que en general durante la primera mitad del siglo XX los dermatólogos eran los responsables del tratamiento radioterápico del cáncer cutáneo mientras que los oncólogos radioterapeutas lo fueron a partir de la segunda mitad del siglo, debido a las regulaciones en la legislación.

Tras el descubrimiento de los rayos X a finales del siglo XIX se fueron desarrollando en las siguientes décadas aparatos de rayos X para el tratamiento del cáncer cutáneo, inicialmente aparatos de rayos Grenz de baja energía (10-30 kV) y posteriormente aparatos de terapia superficial (30-125 kV) y ortovoltaje (125-500 kV). También las fuentes radiactivas de Ra-226 fueron muy utilizadas en las primeras décadas del siglo XX y llegaron a utilizarse hasta los años 60[24,25].

Posteriormente, en la década de 1950 se introdujo el acelerador lineal de electrones, que permite el tratamiento con haces de electrones o fotones de energías del orden del MeV. La fuente es externa y distante al paciente. Consecuentemente constituye una técnica de teleterapia (radioterapia a distancia). Actualmente, para el tratamiento del CCNM, se siguen utilizando electrones y/o fotones no muy energéticos, de modo que la dosis absorbida sea máxima en la superficie del paciente.

A partir de 1960 se introdujeron nuevas tecnología que permitieron el desarrollo de la braquiterapia de alta tasa de dosis (BT-HDR) y que fueron ganando popularidad. En la BT-HDR se usan isótopos radioactivos de alta actividad en contacto o a poca distancia (menos de 10 cm) del tumor, lo que permite una mayor precisión en el tratamiento, un mayor ahorro de tejido sano y menores tiempos de tratamiento. El isótopo radioactivo más usado en la actualidad es el Iridio-192, que se ubica temporalmente en el tejido a través de moldes, aplicadores superficiales o catéteres intersticiales. Su uso sigue ampliamente aceptado y existen trabajos que avalan su eficacia en el CCNM[26,27,28,29,30].

A partir de 1980, gracias a una mejor tecnología que permitía mayor precisión con dosis más altas, se introdujo el concepto de hipofraccionamiento. Consiste en administrar dosis mayores por sesión y un menor número de sesiones, lo que garantiza un tratamiento más corto[31]. Se ha demostrado que los efectos tardíos de la RT en piel se minimizan con esquemas de tratamiento más fraccionados[32].

En los últimos años se han desarrollado fuentes pequeñas de rayos X que han dado lugar a la denominada braquiterapia electrónica (BTE). Como su nombre indica es una terapia que usa rayos X y por tanto evita el uso de isótopos radioactivos. Hoy en día es una técnica emergente y prometedora pero que cuenta con un número limitado de estudios clínicos debido a su reciente aparición.

El objetivo del desarrollo y la introducción de nuevas técnicas y equipos siempre es el de mejorar las tasas de control tumoral y el buen resultado cosmético preservando la funcionalidad y una baja tasa de complicaciones.

El porcentaje de pacientes con CCNM tratados con RT también ha ido variando con el tiempo. Durante la primera mitad del siglo XX más de la mitad de las clínicas dermatológicas contaban con equipos de radioterapia. Con la llegada de la cirugía de Mohs (y sus altas tasas de curación) y el paso de las competencias del uso de radiaciones ionizantes a los oncólogos radioterápicos, la RT en el CCNM fue declinando en favor de la cirugía. En las últimas dos décadas, debido a la estandarización de las técnicas de HDR-BT y a la incorporación de técnicas novedosas como la BTE, el uso de la RT en el CCNM ha vuelto a ganar interés.

II.B. Tipos de radioterapia

Existen diversas técnicas especializadas para tratar el cáncer de piel: RT superficial-Dermopan, electrones del acelerador lineal, fotones de megavoltaje del acelerador lineal, braquiterapia de alta tasa de dosis (BT-HDR), braquiterapia de baja tasa de dosis (BT-LDR), y la braquiterapia electrónica (BTE). La elección de la técnica depende del tipo de tumor, tamaño, espesor y localización anatómica. Las distintas técnicas implican diferencias en las características y profundidad donde actúa la radiación, que dependerán del tipo de tumor a tratar. La elección cualitativa de la radiación se selecciona a partir de la relación entre las dosis administradas en superficie y en profundidad idóneas para el

tratamiento específico. El esquema de tratamiento, la dosis total y el fraccionamiento (dosis/sesión y sesiones/semana) se indica en base a tolerabilidad, efectos secundarios y resultados cosméticos. Una menor dosis/sesión y un mayor número de sesiones (mayor fraccionamiento) implican la minimización de estos efectos no deseables.

La RT superficial-Dermopan (fotones de ortovoltaje) utiliza rayos X y se emplea en tumores superficiales[23]. Los equipos pueden contar con una o varias energías (50-300 kV). Las radiaciones de más baja energía son las que se utilizan para lesiones más superficiales.

Los electrones del acelerador lineal se depositan en el tejido a muy poca profundidad, por lo que se usan para tratar lesiones superficiales. La profundidad del tejido tratado por el haz de electrones está en función de su energía. Los electrones no depositan su máxima energía en superficie sino por debajo, por lo que resulta necesario utilizar un material similar al tejido humano denominado "bolus" que se coloca sobre la piel con el fin de depositar la máxima energía en el tejido tumoral y cubrir así la profundidad requerida. Usa energías que oscilan entre los 6 y 20 MeV. Debido a que el haz de radiación debe incidir perpendicularmente a la zona a tratar para evitar la infradosificación su uso se limita a tratar áreas planas, lo que limita el uso de la técnica[11].

Los fotones de megavoltaje del acelerador lineal se usan para tumores localmente avanzados que invaden tejidos profundos

(hueso o cartílago)[11]. Se irradia con haz de fotones generalmente de 6 MeV. Precisa también del uso de bolus para optimizar la dosis en superficie.

La braquiterapia de alta tasa de dosis (BT-HDR) es una técnica de contacto en la que se utilizan aplicadores estándar (Freiburg, Leipzig o Valencia) o personalizados, que permiten el tratamiento de áreas irregulares o curvas. Se usa como fuente radiactiva el Iridio-192 de alta tasa de dosis, por lo que es necesario tratar en una sala blindada. En el CCNM se usan dosis entre 66-70 Gy, habitualmente 5 sesiones semanales durante 7 semanas[10]. La proximidad de la fuente al tumor permite una mayor precisión en el volumen a tratar y por tanto mayor preservación de tejido sano, lo cual posiciona a esta técnica como idónea para el tratamiento del CBC en estadios precoces (T1 y T2)[33]. La dosis es máxima (100%) en superficie (a 0 mm), alcanza los 3-5 mm de profundidad y sufre una caída exponencial[34], resultando así en una dosis mínima a mayor profundidad. Esta técnica es la que suele emplearse en la actualidad para el tratamiento del CCNM primario en estadios precoces[35].

La braquiterapia de baja tasa de dosis (BT-LDR) se administra durante horas o días de forma continua por lo que requiere ingreso hospitalario, y es útil para el tratamiento de tumores cutáneos periorificiales en regiones de fusión embrionaria de la cara[11]. Se usan fuentes radiactivas, por lo que se deben de disponer habitaciones de ingreso hospitalario blindadas y medidas de control y seguridad para el personal sanitario. Se utilizan dosis de 55-65 Gy con tasa de dosis ≤2 Gy/h.

La braquiterapia electrónica (BTE) es un tipo de radioterapia de contacto desarrollada en las últimas décadas que utiliza fuentes de rayos X con el objetivo de dirigir la dosis de radiación al tamaño y forma del tumor, preservando los tejidos sanos adyacentes. Las fuentes generadoras de rayos X presentan algunas ventajas reconocidas frente a las fuentes radiactivas, principalmente relacionadas con la protección radiológica. Al emitir fotones generalmente de menor energía, los blindajes estructurales son menores, y junto con el hecho que no emiten radiación cuando están apagadas, la dosis al personal sanitario es también menor.

La braquiterapia (BT) es una modalidad de tratamiento de radioterapia en la que se coloca una fuente de radiación ionizante cerca, en contacto o en el interior del volumen a tratar. La energía emitida por dicha fuente hace que el tejido que se desea tratar absorba una determinada cantidad de dosis. La dosis absorbida se define como la energía absorbida por unidad de masa y se mide en unidades de Gy (1 Gy equivale a 1 J/kg). La fuente de radiación utilizada puede ser o una fuente radiactiva como el Ir-192 o bien un generador de rayos X[43]. En el segundo caso la modalidad de tratamiento recibe el nombre de braquiterapia electrónica (BTE).

La BTE en el tratamiento del carcinoma basocelular constituye una novedad dentro del campo de la RT del CCNM. Diversos equipos, tanto americanos como europeos, se han incorporado recientemente al mercado. Sus bases de desarrollo se asientan sobre los estudios previos realizados con HDR-BT sobre eficacia y

seguridad. Hasta 2013 no existían estudios clínicos publicados sobre eficacia y seguridad de estos nuevos dispositivos.

Esteya® (Elekta Brachytherapy, Veenendaal, The Netherlands) es un equipo de braquiterapia electrónica diseñado específicamente para el tratamiento de lesiones superficiales que se introdujo en el mercado en 2013. Consiste en un tubo de rayos X con una tensión pico de 69.5 kVp y un conjunto de colimadores circulares[44]. Con ello se consigue colimar la radiación al tamaño del campo de tratamiento, mientras que se blinda el resto de radiación que sólo contribuiría a irradiar el tejido sano. El colimador se puede cambiar, pudiendo escoger entre el de 10, 15, 20, 25 y 30 mm de diámetro. Existe también un colimador específico para medidas de control de calidad. El diámetro de la apertura del colimador delimita el tamaño del campo de radiación. Por ejemplo, el colimador de 3 cm de diámetro da lugar a un haz de rayos X también de 3 cm de diámetro (sin contar la penumbra, aunque ésta es pequeña, en torno a 1 mm)[44]. La penumbra es una longitud que da una idea de cómo de rápido cae la dosis lateralmente por efecto de dispersión de la radiación. La penumbra mide la distancia lateral desde que la dosis pasa de ser del 80 al 20% del máximo. Cuanto menor sea el valor de la penumbra más abrupta es la caída de la dosis lateral. Esto supone una ventaja porque se irradia menos tejido sano.

Adicionalmente, cada colimador tiene una caperuza de plástico, que es la que queda en contacto con la superficie del paciente durante el tratamiento. Esta caperuza permite mantener plana la superficie de tratamiento, mantiene constante la distancia entre el

foco y la superficie (que es crítico desde el punto de vista dosimétrico) y absorbe la contaminación electrónica. Con el aplicador en su lugar, la distancia entre el foco del tubo y la superficie de tratamiento es de 6 cm[45].

Entre el foco del haz de radiación y el colimador existe un filtro aplanador de aluminio. Su función es proporcionar una distribución de dosis homogénea a unos 3 mm de profundidad, aunque justo en la superficie (profundidad 0) también se consigue muy buena homogeneidad del campo. Se consigue una simetría en el perfil de radiación de entre un 95% y un 105% dentro de los primeros 5 mm de profundidad. El filtro da lugar a un espectro de fotones con una energía media de unos 36,1 keV, y una tasa de dosis máxima en superficie de 3,3 Gy/min. El gradiente de dosis en profundidad es de en torno al 7%/mm[46], es decir, que cada mm que penetra la radiación en el tejido la energía que se absorbe localmente disminuye en un 7% en relación con la energía absorbida en el mm anterior. Este gradiente tan elevado hace que la irradiación de tejidos más profundos sea pequeña.

Esteya® tiene además un panel de control desde donde se controla el haz de radiación. Por motivos de protección radiológica, el panel de control se coloca fuera de la sala de tratamiento. Está conectado a un ordenador y en él se puede planificar el tratamiento. Para ello, se deben introducir los datos del paciente (con foto opcional), la dosis prescrita, la profundidad de prescripción (es decir, profundidad a la cual se desea que se absorba la dosis prescrita) y el tamaño del colimador a utilizar. El tubo de rayos X puede generar una corriente de electrones

variable en función de la dosis prescrita. Típicamente dicha corriente es de 1,6 mA, aunque se ajusta automáticamente a 1,0 mA para dosis prescritas de entre 2 y 4 Gy, y a 0,5 mA para dosis inferiores. Los tiempos de tratamiento suelen ser de entre 2 y 3 minutos por fracción. El equipo requiere un mantenimiento cada 4000 fracciones aproximadamente[44].

En el tratamiento, es muy crítico el centrado del haz de radiación. Para ayudar en esta tarea, el cabezal de Esteya® tiene un generador de luz que se ajusta al campo a tratar. Sin embargo, nuestro grupo de investigación ha diseñado una plantilla para cada uno de los colimadores que facilita notablemente el centrado y mejora la precisión.

Figura: Esteya® Electronic Brachytherapy System. Imagen reproducida de http://www.esteya.com.

III. Uso de técnicas para determinación de márgenes

En las etapas del proceso radioterápico tras una evaluación clínica inicial, decisión terapéutica y localización tumoral, es necesario la delimitación del volumen tumoral previa a la dosimetría clínica y puesta en marcha del tratamiento.

En el tratamiento del CCNM el tamaño del campo a tratar depende fundamentalmente del tamaño del tumor, su localización y el tipo de radiación empleada. El error de los márgenes estimados es la causa más frecuente de fallo en el tratamiento[11]. Es importante tener en cuenta que márgenes muy estrechos pueden determinar una cobertura inadecuada del tumor a tratar, mientras que márgenes demasiado amplios pueden incrementar la cantidad de tejido sano que será irradiado. Antes de iniciar el tratamiento es fundamental precisar la extensión tumoral subclínica tanto en superficie como en profundidad para poder realizar un correcto tratamiento de todo el volumen tumoral con el fin de evitar recidivas. Para ello pueden emplearse técnicas no invasivas e invasivas, ya sean de imagen o histopatológicas.

III.A. Margen lateral

Para una correcta delimitación de los márgenes es necesario definir el GTV (Gross tumour volume), el CTV (Clinical target volume), así como el PTV (Planning target volume). La mayoría de los estudios determinan el GTV mediante una delimitación de la

lesión clínicamente visible y posteriormente añaden 5-10 mm para delimitar el CTV, que representaría la extensión microscópica del tumor[36]. Hasta la fecha esta delimitación del margen lateral se ha realizado clínicamente con el ojo desnudo, sin usar ninguna técnica de imagen o de amplificación.

La dermatoscopia es una técnica sencilla, rápida y no invasiva que ha demostrado aumentar la precisión diagnóstica en los tumores cutáneos[37]. Los criterios dermatoscópicos del CBC clásicamente descritos incluyen los vasos arboriformes, las hojas de arce, los grandes nidos ovoides azul-gris y las estructuras en rueda de carro. Varios estudios han demostrado la utilidad de la dermatoscopia en la delimitación pre-quirúrgica del CBC, consiguiendo una mayor tasa de extirpaciones tumorales completas, con mayor ahorro de tejido sano peritumoral[38,39]. Sin embargo, el uso de la dermatoscopia para la delimitación de los márgenes previos al tratamiento radioterápico no ha sido objeto de estudio por el momento.

III.B. Margen profundo

Otro aspecto a tener en cuenta antes de iniciar el tratamiento radioterápico es la determinación de la profundidad de la lesión, ya que determinará un cambio en la dosis a utilizar. El *gold estándar* para la determinación de la profundidad es la biopsia incisional, sin embargo, tiene la desventaja de que únicamente permite el análisis de una mínima porción del tejido tumoral. Este hecho ha sido corroborado en diversos estudios, en los que se han

descrito tasas de concordancia diagnóstica entre los resultados de la biopsia incisional y escisional del 50-89% según las series[5].

El reciente desarrollo de la ecografía cutánea de alta frecuencia (ECAF) permite la visualización de las diferentes capas de la piel. Es un procedimiento en tiempo real, seguro y no invasivo, que utiliza frecuencias entre 10 y 50 Mhz y que puede ser utilizado en una gran variedad de procesos dermatológicos, siendo de gran utilidad en el campo de la dermatología oncológica para el diagnóstico, clasificación y caracterización del tamaño y morfología tumoral[40]. La imagen ecográfica del CBC superficial se ha definido como un patrón ecográfico hipoecoico, aplanado y heterogéneo de bordes irregulares mientras que el CBC nodular suele representarse como una imagen hipoecoica ovalada y bien delimitada con puntos hiperecoicos en su interior[41]. Diversos estudios publicados comparan los hallazgos obtenidos por ecografía e histología e identifican altas tasas de concordancia entre ambas técnicas. Bobadilla et al[1] llevaron a cabo un estudio prospectivo con 25 pacientes con CBC e identificaron una correlación del 90% en el establecimiento del tamaño tumoral. Por el contrario, otros estudios han identificado menores tasas de concordancia, como es el caso de Nassiri-Khasani et al[42] que compararon la capacidad de la ecografía y la histología para la determinación del diámetro y la profundidad e identificaron una correlación del 27% en el diámetro y del 45% en la profundidad. Por tanto, a pesar de que la ecografía no sustituye a la histología, podría representar una herramienta útil para la estimación del tamaño tumoral, delimitación de los márgenes pre-tratamiento,

establecimiento del plan terapéutico e identificación de lesiones de alto riesgo[5].

IV. Hipótesis y objetivos

Con la oportunidad de ser pioneros en el uso de Esteya® para el tratamiento del carcinoma basocelular y nodular, nuestro grupo ha llevado a cabo un estudio piloto prospectivo no randommizado tratando a 40 pacientes con 60 lesiones.

La **hipótesis principal** de nuestra investigación es la siguiente: la braquiterapia electrónica puede constituir una técnica útil en el tratamiento del carcinoma basocelular superficial y nodular.

Los **objetivos específicos,** que se tratarán en cada uno de los artículos, son los siguientes:

i) *Correlacionar los resultados obtenidos mediante ecografía cutánea e histología en la determinación del tamaño y extensión tumoral previa al tratamiento.*

ii) *Evaluar la eficacia de la dermatoscopia en la delimitación del margen lateral previa al tratamiento.*

iii) *Determinar la eficacia clínica de la braquiterapia electrónica en el tratamiento del carcinoma basocelular superficial y nodular.*

iv) *Evaluar la toxicidad de la braquiterapia electrónica en el tratamiento del carcinoma basocelular superficial y nodular.*

v) *Evaluar los resultados cosméticos obtenidos con braquiterapia electrónica en el tratamiento del carcinoma basocelular superficial y nodular.*

CAPÍTULO 1

Depth determination of skin cancers treated with superficial brachytherapy: ultrasound vs. histopathology

Depth determination of skin cancers treated with superficial brachytherapy: ultrasound vs. histopathology

Ballester-Sánchez R, Pons-Llanas O, Llavador-Ros M, Botella-Estrada R, Ballesta-Cuñat A, Tormo-Micó A, Celada-Álvarez FJ, Rodríguez-Villalba S, Santos-Ortega M, Ballester-Pallarés F, Pérez-Calatayud J (2014) Depth determination of skin cancers treated with superficial brachytherapy: ultrasound vs. histopathology. *Journal of Contemporary Brachytherapy*, **6 (4)**: 356–361.

Doctoral thesis adapted version. Original paper. IF 1. 413.

Abstract

Purpose: the purpose of this study is to compare high frequency ultrasonography (HFUS) and histpathologic assessment done by punch biopsy to determine depth of basal cell carcinoma (BCC), in both superficial and nodular BCCs prior to brachytherapy treatment.

Material and Methods: this study includes 20 patients with 10 superficial and 10 nodular BCCs. First, punch biopsy was done to confirm the diagnosis and to measure tumour depth (Breslow rate). Subsequently, HFUS was done to measure tumour depth to search for correlation of these two techniques.

Results: neither clear tendency nor significance of the punch biopsy *vs*. HFUS depth determination is observed. Depth value differences with both modalities resulted patient dependent and then consequence of its uncertainty. Conceptually, HFUS should determine the macroscopic lesion (gross tumour volume or GTV) while punch biopsy is able to detect the microscopic extension (clinical target volume or CTV). Uncertainties of HFUS are difficult to address while punch biopsy is done just on a small lesion section, not necessarily the deepest one.

Conclusions: according to the results, HFUS is less accurate at very shallow depths. Nodular cases present higher depth determination differences than superficial ones. In our clinical practice, we decided to prescribe at 3 mm depth when HFUS measurements give depth lesion values smaller than this value.

1. Purpose

Basal cell carcinoma (BCC) is a common skin cancer arising from the basal layer of the epidermis and its appendages. It is particularly common in Caucasian people, increases with age and is basically related to exposure to ultraviolet radiation[47]. The incidence is increasing worldwide[47]. It is a malignant locally invasive epidermal tumour with a good prognosis due to a slow growth-rate and low metastatic potential. Local invasion and tissue destruction, however, cause patient morbidity.

There are several clinical and histopathologic types of BCC. The most common types are nodular and superficial BCC, which occur for the most part on the face[47]. Less frequent types include micronodular, morpheaform and basoesquamous cell carcinomas. The diagnosis of BCC is made clinically, aided by dermoscopy. A skin biopsy is usually performed to provide histological confirmation. Once diagnosis is established, appropriate treatment offers a high probability of cure. The patient does, however, have an increased risk of additional skin malignancies. The choice of appropriate is dependent upon the characteristics of the lesion and patient-specific factors. Treatment modalities include electrodesiccation and curettage, cryotherapy, surgical excision including Mohs surgery, topical 5-fluouracil or imiquimod, photodynamic therapy and radiotherapy[48,49,7,50].

Determining tumour extension and defining accurate lateral and deep safety margins are very important aspects in the

treatment approach for BCC. It is not possible to determine lesion depth based on clinical observations alone, because there might be an overestimation of the extension which may lead to unnecessary tissue excision or radiation. This in turn could then result in aesthetic problems for the patient[1]. In addition, the rate of incomplete excision of BCCs has been reported to be 5%–25%[51,52,53,54,55,56,57,58].

Although surgery is the first-line treatment for non-melanoma skin cancers, radiotherapy can be indicated in selected cases. When radiotherapy is the treatment of choice, brachytherapy (BT) may be a good option for shallow, widespread lesions, or lesions on anatomic sites (e.g., hand, full scalp) that lie immediately above structures which are vulnerable to irradiation[59]. High-Dose-Rate (HDR) BT approaches offer significant advantages in this setting due to adaptability, patient protection and variable dose fractionation schedules and achieve excellent cure rates and cosmetic results[60]. Several innovative applicators have been introduced to the BT community and the use of skin BT has significantly increased over the years. The Valencia applicator[61,62,63,30] (Elekta Brachytherapy, Veenendaal, the Netherlands) is a new superficial device that improves the dose distribution compared with that of the Leipzig applicator[64,65,66,67] (Elekta, Stockholm, Sweden and Varian Medical Systems, Palo Alto, CA, USA). Recently, electronic brachytherapy using specific applicators has also become available, as Xoft[68,59] (Xoft Inc., San Jose, CA, USA) and Esteya[44] (Elekta, Stockholm, Sweden).

Brachytherapy provides minimal dose delivery to surrounding healthy tissue, thus enabling good functional and cosmetic results. Brachytherapy appears to be most effective for small, primary, and/or superficial squamous cell carcinomas and basal cell carcinomas, where it is associated with excellent cosmetic results. The primary benefit of BT compared to external beam radiation therapy is the ability of BT to deliver radiation to the target tissue, with less injury to surrounding normal-appearing skin.

Lateral and deep tumour delimitations are the main challenges when treating basal cell carcinomas with BT. Lateral delimitation may be aided by dermoscopy[69] and deep demarcation can be estimated by biopsy and/or imaging techniques. In superficial BT the dose is prescribed to the deepest point of the target which results in a higher dose between the source and this prescription point[70,30].

A punch biopsy provides confirmation of the tumour's histopathology as well as determining its depth. However it is an invasive technique which only measures the depth in a portion of the tumour which cannot be representative. Ultrasonography on the other hand is a non-invasive, painless, non-ionizing, low risk and non-expensive method which is of academic interest in diagnosing BCC[71]. In normal skin, the dermis is markedly echogenic and sharply demarcated from hypo-echogenic subcutaneous fat[72]. BCCs will appear more hypo-echogenic than adjacent, normal dermis due to a medium change. The use of high frequency ultrasonography (HFUS) between 10MHz and 50 MHz has made it possible to visualize deep layers of skin and to define

very small hypo-echoic masses. Using the refraction of ultrasonography waves at the interface between the perilesional hyper-echoic area and the hypo-echoic area of the tumour itself, it is possible to precisely define the lesion[73].

HFUS has been shown to be potentially quite useful in BCC for both tumour measurement (for planning surgical resection)[74] and as a diagnostic technique[75,5]. Most of the published research in this field deals with the study of tumour size, delineation of surgical margins, and comparison of ultrasound findings with histologic results obtained following subsequent excisional biopsy of the lesion[76,77,78,79,42]. Concordance rates between HFUS findings and histology results for tumour size are between 73-98%[5]. Published rates of tumour-free margins assessed by HFUS are as high as 95%[80], but this has never been studied prior to radiotherapy treatment.

The purpose of this study is to compare both HFUS and punch biopsy methods in determining the depth of basal cell carcinomas prior to brachytherapy. We also present the strategy adopted at our department as a result of this present study.

2. Materials and Methods

2.A. Patients

This study included 10 men and 10 women, all of them Caucasian, with 10 superficial and 10 nodular BCCs.

All tumours were primary, maximum 20 mm in diameter and were located in a regular or flat area that was not adjacent to or over a burn, scar or inflammatory process. Only clinically apparent nodular and superficial BCCs were included in this study. Exclusion criteria included other BCC varieties, recurrent BCCs, and BCCs that were in locations difficult to image or treat with isotope or electronic brachytherapy applicators.

All lesions were studied by histopathology and HFUS to determine tumour depth (Breslow thickness) prior to BT treatment. The mean time between the two techniques was 53 days (range 30-92 days). In the first instance, a punch biopsy was taken. This technique allowed us to confirm the diagnosis of BCC and to measure the microscopic depth of the tumour that represents the clinical target volume (CTV) depth. Subsequently HFUS imaging was done to measure the macroscopic depth of the tumour which represents the gross tumour volume (GTV) depth. In every case, HFUS was done at least one month after the biopsy in order to avoid peritumoral inflammation due to the biopsy scar.

To investigate whether HFUS is sufficient to determine a correct prescription depth dose, the correlation between both techniques was studied.

This study was conducted under Helsinki II ethical principles after approval by the Medical Ethics Committee at our hospital.

2.B. Punch biopsy technique. Histopathology

A 3 mm diameter punch biopsy, including the whole dermis, was performed in all lesions. The deepest site estimated clinically was the site chosen for the biopsy; this is the usual method practised by dermatologists. The more nodular part usually corresponds to the deepest part of the tumour.

An intralesional injection of mepivacaine was administered prior to the biopsy and a silk suture was used to close the wound.

Histopathologic assessment of depth was done with the Leica DMD108 digital microimaging network (Leica Microsystems SLU, Barcelona, Spain). Tumour thickness was measured from the granular layer to the deepest portion of the tumour, as shown in Figure 1.

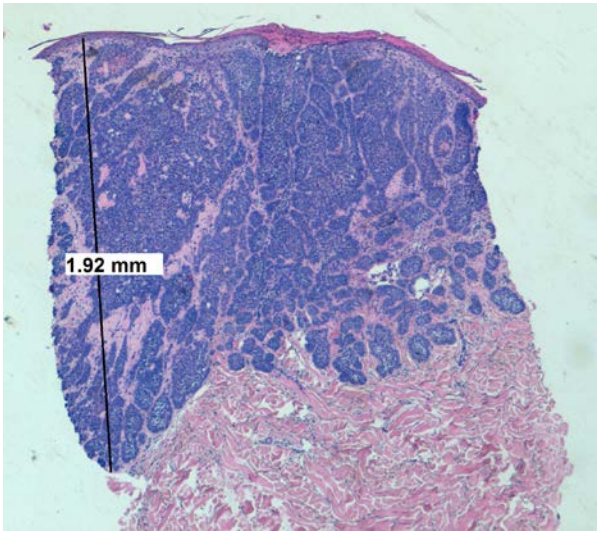


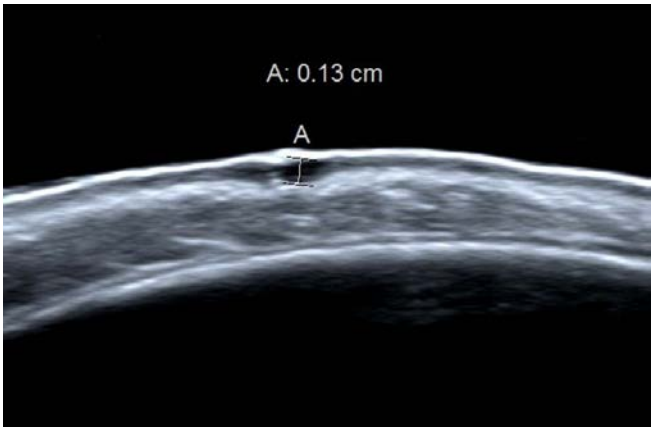
Fig. 1. Example of depth histopathologic assessment (Breslow rate) using a Leica DMD108 digital microimaging network.

2.C. High-frequency ultrasound imaging

After the biopsy, a radiologist who was an expert in skin lesions estimated the depth of the lesions. All BCCs were scanned in vivo using a high resolution B-scan with an 18 MHz hand-held transducer (Siemens Acuson S2000, Munich, Germany). A 2 cm × 9 cm gel pad (Aquaflex, Pallejà, Barcelona, Spain) was applied over the skin to enhance the air-skin interface (Figure 2). High frequencies have better resolution, but lower frequencies are often used in hospital and it has been reported in the literature that there is a good correlation between ultrasonic and histologic measurements (with complete lesion excision), even with probes emitting frequencies of 15 MHz or lower[5].

Fig. 2. Illustration of the probe plus gel pad use during the acquisition.

In each lesion, the depth (from the epidermal surface to the deepest hypo-echoic point of the tumour) was measured. Because the epidermis thickness is approximately 0.1 mm, when HFUS did not show any value, 0.1 mm was assigned. Examples are given in Figure 3 for both superficial and nodular lesions.



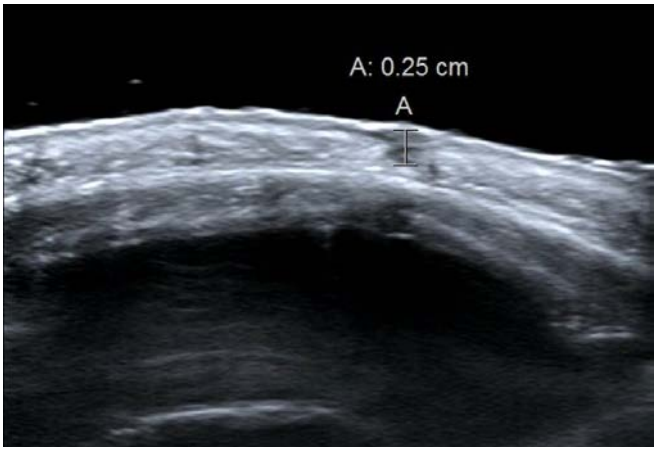


Fig. 3. HFUS examples of depth measurement. Up: superficial basal cell carcinoma. Down: nodular basal cell carcinoma.

3. Results

The clinical and histological characteristics of the lesions of the 20 patients studied are presented in Table 1. There were 10 men and 10 women, with 10 superficial and 10 nodular BCCs. The mean age of the patients was 67 years (range 51-89 years). Fifteen lesions were located on the face and 5 on the trunk.

Table 1. Clinical and histological characteristics.

Tumour	Sexe	Age (years)	Histological subtype	Location	HFUS (mm)	Breslow (mm)
1	Male	65	Superficial	Preauricular	0.1	1.0
2	Female	75	Nodular	Retroauricular	1.5	1.1
3	Male	89	Nodular	Forehead	1.3	1.4
4	Male	88	Nodular	Preauricular	0.1	2.8
5	Male	63	Superficial	Trunk	0.1	0.5
6	Female	51	Nodular	Glabellar	2.7	2.3
7	Male	70	Nodular	Cheek	3.7	2.6
8	Female	80	Nodular	Nose	1.3	1.8
9	Male	70	Superficial	Trunk	0.1	0.3
10	Female	59	Superficial	Trunk	0.1	0.3
11	Male	56	Superficial	Trunk	0.1	0.3
12	Male	67	Superficial	Cheek	0.1	0.8
13	Female	57	Nodular	Forehead	2.0	3.1
14	Male	67	Nodular	Forehead	1.6	1.4
15	Female	56	Nodular	Forehead	1.6	3.2
16	Female	66	Superficial	Trunk	0.1	1.9
17	Female	57	Superficial	Cheek	0.1	0.5
18	Male	84	Nodular	Forehead	1.3	1.2
19	Female	73	Superficial	Forehead	1.1	1.3
20	Female	81	Superficial	Forehead	1.3	0.8

HFUS: high frequency ultrasonography

Resulting lesion depths with HFUS and Breslow are presented in Figure 4 for both superficial and nodular lesions, respectively. In the superficial lesions, the Breslow rate was similar or higher than HFUS in most cases (8/10). In the nodular lesions however there was no clear trend. The largest difference between the two techniques was 2.7 mm.

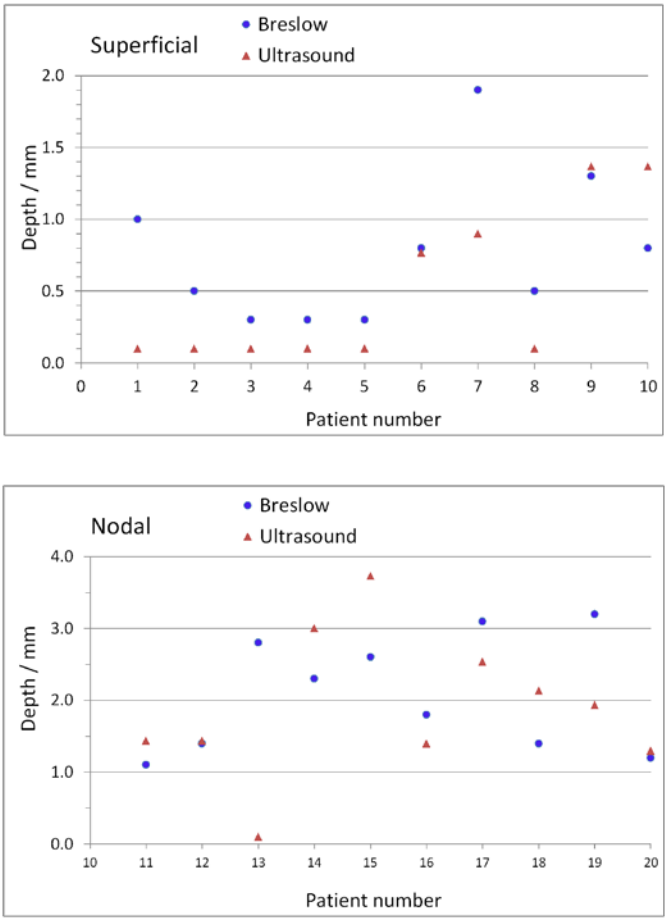


Fig. 4. Up: histopathology (Breslow rate) vs. HFUS depth determination for the 10 patients evaluated with superficial BCC. Down: the same but with nodular BCC.

Statistical analyses were performed calculating covariance and correlation matrices for the HFUS and Breslow depths. A value of $p = 0.05007 > 0.05$ was found. So, although it could be considered that some correlation exists for the scatter plot in Figure 4, it does not show any clear dependence between both variables. We also found no correlation when the different types of BCC were analysed separately.

4. Discussion

Conceptually, HFUS should determine the GTV while histopathology is able to detect the CTV. Uncertainty of HFUS depth measurements are difficult to address. Histopathologic measurements are done just on a small lesion section, which is not necessarily the deepest one.

There are some limitations in the use of HFUS in BCC. The large ultrasound probe makes access difficult in certain tumour locations, although brachytherapy is also not typically used in these locations anyway. Assessment with HFUS can also be difficult in the vicinity of scars. Small tumour aggregates are not detected by HFUS and it is also not possible to differentiate between the tumour and adjacent inflammation. Furthermore, HFUS is an operator dependent technique.

On the other hand, HFUS has an important advantage over punch-biopsy as it allows a three-dimensional analysis of the

tumour, whereas clinical measurements only permit a two dimensional view[80].

In this study, all US acquisitions were done by the same radiologist. In order to explore the intraobserver variability the images were reviewed by the radiologist 3 times with a sufficient time interval inbetween. The resulting differences were negligible.

According to the results, HFUS was less accurate at very shallow depths. The nodular cases presented with larger depth differences than the superficial ones. In most cases of superficial BCCs, the HFUS depth measurement was lower than the histopathologic one, which was in contrast to the nodular cases. Neither clear tendency nor significance was observed from this depth comparison after applying standard statistical tests to search for depth measurement correlations between the two techniques.

There are some limitations in our study:

We used an 18 MHz ultrasound probe. High frequencies have better resolution but lower frequencies are usually used in hospital. It has been reported in the literature that there is a good correlations between ultrasonic and histologic measurements, even with probes emitting frequencies of 15 MHz or lower[5].

In our study, punch biopsy was done prior to HFUS to confirm the diagnosis before measuring the tumour depth. This can lead to two problems: the biopsy could potentially remove the deepest part of the tumour, and both the scar and the inflammation after

biopsy could distort/change the echographic image. To try to avoid the latter problem, ultrasound was performed at least one month after the biopsy.

There were a limited number of patients (20) included in this study. However, the number is sufficient to demonstrate that there is no clear correlation between these two methods.

5. Conclusions

HFUS vs. histopathologic depth determination have been compared for 10 superficial and 10 nodular basal cell carcinomas. Neither a clear trend nor a significant difference in histopathology compared to HFUS depth determination was observed.

As a result of: a) the comparison results of the present study, b) the depth dose gradient, c) the maximum skin dose using radionuclide applicators or electronic BT, and d) the cosmesis experienced in clinical practice, we have decided in our protocol to prescribe to 3 mm depth when HFUS measurements give lesion depths smaller than this threshold depth.

6. Acknowledgements

This study was supported within a collaborative project with Elekta Brachytherapy (Elekta Company, Veenendaal, The Netherlands). This study was also partially supported by Generalitat Valenciana (Project PROMETEOII/2013/010) and by Spanish Government under Project No. FIS2013-42156.

CAPÍTULO 2

Dermoscopy margin delineation in radiotherapy planning for superficial or nodular basal cell carcinoma

Dermoscopy margin delineation in radiotherapy planning for superficial or nodular basal cell carcinoma

Ballester-Sánchez R, Pons-Llanas O, Pérez-Calatayud J, Botella-Estrada R (2015) Dermoscopy margin delineation in radiotherapy planning for superficial or nodular basal cell carcinoma. *British Journal of Dermatology*, **172**: 1162–1163.

Doctoral thesis adapted version. Correspondence. IF 4. 317.

Surgical excision is often the primary treatment for basal cell carcinoma (BCC), but may be accompanied with cosmetic or functional deficits due to tumour size or location. In such cases, radiotherapy constitutes an effective alternative[81]. In planning radiotherapy treatment, there are two fundamental concepts: firstly, gross tumour volume (GTV), i.e. the delineation of a clinically apparent tumour margin which is done with the naked eye, and secondly, clinical target volume (CTV), i.e. the microscopic tumour extension (subclinical), which cannot be determined clinically but rather by extension of the GTV. Radiotherapy outcome is dependent on whether the microscopic tumour extension (CTV) is adequately covered in the treatment volume. Too stringent a margin can lead to inadequate tumour coverage and local failure, whereas too generous a margin will

increase the amount of normal tissue treated and can increase morbidity unnecessarily, depending on location. Though delineating the CTV can be challenging, due to the lack of data, some studies have shown good outcomes using CTV determined from GTV expansions of 5 mm to 1 cm in relatively large patient cohorts[82,36].

Dermoscopy is a noninvasive method for skin examination that allows the examiner to see the lesion at a magnification 10 times greater than with the naked eye, allowing far better evaluation of detail. There is worldwide agreement that dermoscopy is able to improve the clinical diagnosis of basal cell carcinoma[83]. Classic dermoscopic characteristics of BCC have been defined as arborizing telangiectasia, maple leaf-like areas, large blue-grey ovoid nests, ulceration, multiple blue-grey globules and spoke-wheel areas[84].

Dermoscopy could also be used in the definition of BCC peripheral borders, which are characterized by the delimitation of two different textures: normal skin texture and tumour texture. Caressana et al[74] defined the interruption of these two textures as a negative dermoscopic pattern and referred to it as an *apophatic* pattern. Within this concept, one may include all dermoscopic pathognomonic patterns of BCC[85] if they are located at the external margins of the tumour[86] and other non-pathognomonic structures. Tumour proliferation can be seen as greyish, glassy or semitranslucent areas. Other structures, such as a whitish veil or chrysalis structures, may appear, depending on the histological BCC subtype[74]. When all these structures are found at the tumour

margins and are in direct contact to normal skin, they are useful to delineate the peripheral tumour border more accurately than the naked eye.

Determining accurate margins of BCCs is crucial not only in the presurgical evaluation of the patient, but also prior to radiotherapy. There are several studies that support the use of dermoscopy prior to BCC surgery, in order to remove the entire tumour while preserving healthy tissue[74,39,38]. However, no study published to date supports the use of dermoscopy in the delineation of lateral margins (GTV and CTV) prior to radiotherapy in BCC. This could be because dermatologists and radiation oncologists work separately resulting in little or no collaboration in treatment planning. Based on our experience, we believe that dermoscopy is of great value in delineating the GTV prior radiotherapy, in order to treat all microscopic tumour extent respecting as much healthy tissue as possible, consequently, we are certain that cooperation between dermatologists and radiation oncologists is essential when treatment is planned.

We have treated 10 patients with nodular BCC and 10 patients with superficial BCC with radioteraphy using dermoscopy (Fig. 1). The size of the lesions ranged between 5 and 20 mm; nine lesions were pigmented and five were ulcerated. To determine the peripheral extent of the skin lesion (GTV or microscopic tumour extension), we used a dermoscope (non-contact polarized dermoscopy at 10-fold magnification). The border was delineated with a red marker on the basis of dermoscopic imaging margins. Additional black marks were made at 5-mm increments in all

directions from the delineated tumour borders (CTV). In a follow-up period ranging between 8 and 10 months, none of the 20 treated cases showed evidence of tumour persistence or recurrence at the margins of the treated area.

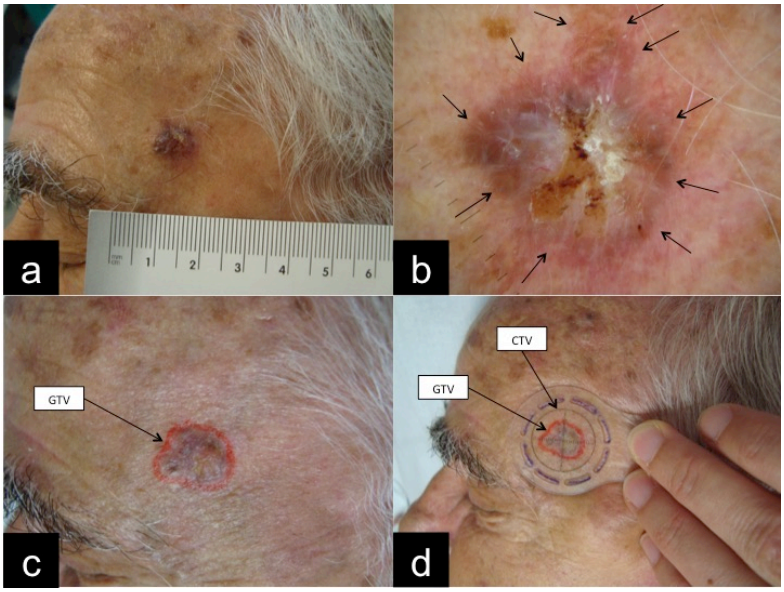


Fig. 1. a: clinical picture. b: dermoscopic picture. c: gross tumour volume (GTV) delineation. d: clinical target volume (CTV) delineation.

To conclude, when planning radiotherapy, volume delineation is critical as imprecise volume delineation can result in tumour recurrence from too tight margins or increased morbidity from too generous margins. Dermoscopic detection of BCC peripheral borders is a useful, quick and simple tool for planning radiotherapy. In our opinion, this technique is an effective, simple,

safe, noninvasive and inexpensive method to improve radiotherapy results. Thus, it is clear that greater collaboration between dermatologists and radiation oncologists is needed in order to achieve higher cure rates without sacrificing healthy tissue.

CAPÍTULO 3

Efficacy and safety of electronic brachytherapy for superficial and nodular basal cell carcinoma

Efficacy and safety of electronic brachytherapy for superficial and nodular basal cell carcinoma

Ballester-Sánchez R, Pons-Llanas O, Candela-Juan C, Celada-Álvarez FJ, de Unamuno-Bustos B, Llavador-Ros M, Ballesta-Cuñat A, Barker CA, Tormo-Micó A, Botella-Estrada R, Pérez-Calatayud J (2015) Efficacy and safety of electronic brachytherapy for supercicial and nodular basal cell carcinoma. *Journal of Contemporary Brachytherapy*, **7 (3)**: 231–238.

Doctoral thesis adapted version. Original paper. IF 1. 413.

Abstract

Purpose: surface electronic brachytherapy (EBT) is an alternative radiotherapy solution to external beam electron radiotherapy (RT) and high dose rate (HDR) radionuclide-based BT. In fact it is also an alternative solution to surgery for a subgroup of patients. The objective of this work is to confirm the clinical efficacy, toxicity and cosmesis of a new EBT system, namely Esteya in the treatment of nodular and superficial basal cell carcinoma (BCC).

Material and Methods: this is a prospective single-center, non-randomized pilot study, to assess the efficacy and safety of electronic brachytherapy in nodular and superficial basal cell

carcinoma using the Esteya system. The study was conducted from June 2014 to February 2015. The follow up time was 6 months for all cases.

Results: twenty patients with 23 lesions were included. A complete response was documented in all lesions (100%). A low level of toxicity was observed after the 4th fraction in all cases. Erythema was the most frequent adverse event. Cosmesis was excellent, with more than sixty percent of cases without skin alteration and with subtle changes in the rest.

Conclusions: EBT with Esteya appears to be an effective, simple, safe, comfortable treatment for nodular and superficial BCC associated with excellent cosmesis. It could be a good choice for elderly patients, patients with contraindications for surgery (due to comorbidities or anticoagulant drugs) or patients where surgery would result in a more disfiguring outcome. A longer follow-up and more studies are needed to confirm these preliminary results.

1. Introduction

Basal cell carcinoma (BCC) is the most common skin cancer, accounting for approximately 75% of all skin cancers. It is also the most common subtype of non-melanoma skin cancer (NMSC), representing 80-90% of the total[1]. Its incidence is increasing due to an aging general population as well as increased exposure to ultraviolet radiation, resulting in a great care burden and therefore a high healthcare spend[2].

The therapeutic management is based on the application of invasive therapies (conventional surgery or Mohs surgery) or noninvasive therapies (cryotherapy, curettage and electrodessication, topical imiquimod, photodynamic therapy and radiation). These modalities are associated with different response rates, complications and cosmetic results. The choice of treatment mainly depends on the histologic subtype, location and patient comorbidities. Surgery is the first choice because of the often simple procedure and high efficacy[9]. However, despite the high incidence of BCC, very few randomized studies have been undertaken to compare treatment modalities. In a meta-analysis of the Cochrane Library, published in 2007, a total of 27 studies were collected and the authors concluded that surgery and radiation therapy (RT) are the treatments with the lowest rates of recurrence[9].

There are several RT techniques for treating BCC. In external beam electron RT an electron beam produced with a linear

accelerator is emitted towards the patient surface. This usually requires a specific dosimetry and bolus, i.e., a water equivalent material placed at the patient surface with two purposes: a) to reduce the therapeutic depth and also the total electron range and b) to raise the full dose on the skin because the small skin underdose in electron low energies. This makes the use of electrons more difficult in clinical practice than other RT options. An alternative option is radionuclide based high dose rate (HDR) brachytherapy (BT). It uses an ^{192}Ir HDR radioactive source placed near the lesion, which emits radiation. It can be performed with moulds and flaps or with dedicated skin applicators. BT with skin applicators is an efficient solution for superficial RT of small lesions, providing a higher shielding to the surrounding healthy tissues when compared to moulds and flaps[11].

HDR surface electronic brachytherapy (EBT) is an alternative solution to external beam electron RT and HDR radionuclide-based BT. This EBT solution uses x-ray generators with specific applicators that collimate the beam and that are placed in contact with the patient surface. Currently there are three EBT systems for treatment of surface lesions: the 50 kVp Xoft Axxent® (iCad, San Jose, CA) with 1, 2, 3.5 and 5 cm diameter applicators[87,88], the 50 kVp Zeiss INTRABEAM® (Carl Zeiss Surgical Gmbh, Oberkochen, Germany), with 1 cm to 6 cm diameter applicators[89,90], and the most recent 69.5 kVp Esteya® (Elekta Brachytherapy, Veenendaal, The Netherlands), provided with 1 cm to 3 cm diameter applicators[91].

The main objective of this work is to confirm the clinical efficacy of EBT with the Esteya system in the treatment of nodular and superficial BCC. The specific objectives are: i) to determine the toxicity by CTCAE scale and ii) to evaluate the cosmetic results by RTOG-EORTC scale.

This is the first phase of a study that will be completed after two years follow-up.

2. Materials and Methods

2.A. Description of the x-ray source and surface applicators

The EBT system used in this study was Esteya®, with a 69.5 kV x-ray source and an aluminum flattening filter that produces a homogenous beam at the patient's skin surface[44,45]. Esteya® comes with a set of applicators that are able to generate circular radiation fields of different diameters: 10 mm, 15 mm, 20 mm, 25 mm and 30 mm. Each surface applicator has a plastic cap designed to maintain constant source to surface distance (SSD). With the applicator in place, the nominal SSD is 6 cm. The source is connected, controlled, and powered by a controller, which supplies a high voltage and filament current. The default current is 1.6 mA, which is automatically set to 1.0 mA for treatment fractions smaller than 4 Gy, and to 0.5 mA for prescription doses

below 2 Gy. The fraction duration is therefore kept relatively constant, between 2 and 3 minutes for commonly used fraction sizes, and is independent of the prescribed dose. The patient's treatment plan is controlled through a specific software that only requires information about prescription dose, number of fractions, prescription depth and applicator size. With these data the system automatically computes the treatment time.

2.B. Study design

This is a prospective, single-center, non-randomized, pilot study to assess the efficacy and safety of electronic brachytherapy in superficial and nodular basal cell carcinoma treatment using Esteya® surface applicators.
due to its high frequency and its biological behavior with local invasion and low metastatic capacity.

The study was conducted from June 2014 to February 2015. It was approved by the ethics committee of clinical research of La Fe Hospital. All patients or legal guardians signed a written informed consent.

2.C. Methodology

Stage T1 or T2 (according to AJCC 2010)[92] superficial or nodular BCCs, confirmed by punch biopsy, were included. Due to the applicator design the maximum diameter of the lesion should be 20 mm. The maximum depth of lesion included in this study was 4 mm, measured by biopsy and ultrasonography. Lesions can

be treated at any skin surface, except irregular or not flat surfaces. The step by step procedure is described in a previous work[91].

Patient demographics and lesion characteristics were recorded. Fitzpatrick scale was used to classify patients by phototype: I) always burns, never tans, II) usually burns, tans minimally, III) sometimes mild burn, tans uniformly, IV) rarely burns, always tans well, V) very rarely burns, tans very easily, VI) never burns, tans very easily.

2.D. Treatment

The gross tumor volume (GTV) was assessed clinically with the aid of a dermoscope[69]. A radial margin of 5 mm was added to establish the clinical target volume (CTV) and the minimum applicator that covered the whole CTV was selected (10, 15, 20, 25 or 30 mm). A specific applicator template named Templates La Fe[91] was used in order to delineate a mark on the skin to fit the external diameter of the selected applicator (Fig. 1). Tumor depth was assessed by high frequency ultrasonography (HFUS) and histopathology. A minimum depth of 3 mm by convention was used for lesions having a depth of 3 mm or less, and for deeper lesions the specific lesion depth was used for prescription, with a maximum of 5 mm[93]. After attaching the selected applicator to the machine, it was centered on the lesion using the mark made, and positioned in full contact with the lesion. The Esteya® arm has several degrees of freedom in order to place the applicator (Fig. 2).

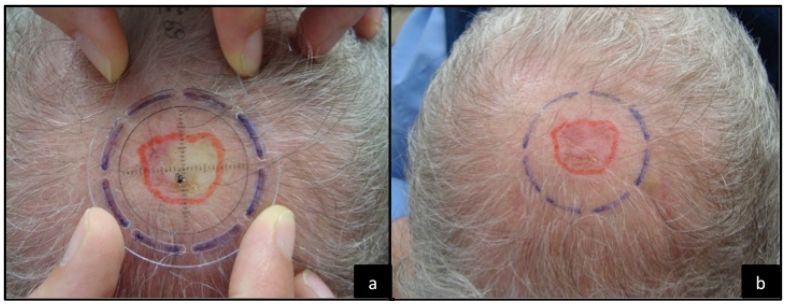


Fig. 1. a: tumor marking with template La Fe.
tumor margin (in red) and the external mark (in blue) to fit the applicator in the center.

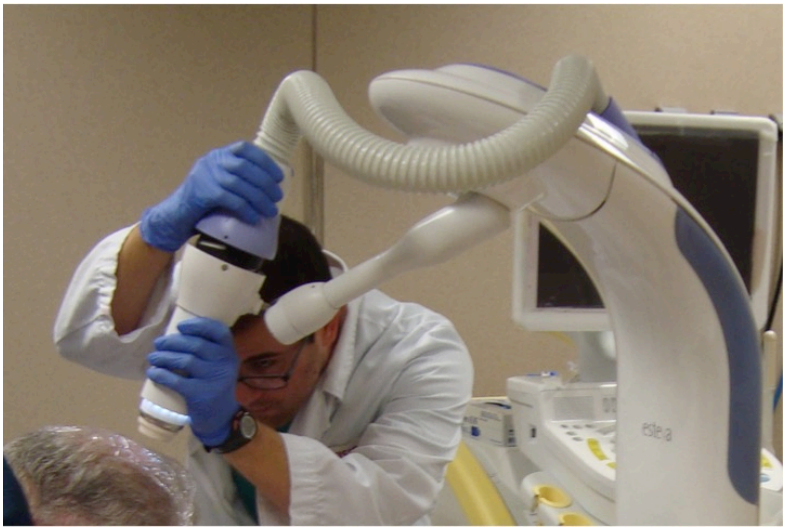


Fig. 2. The Esteya arm has several degrees of freedom in order to place the applicator.

The prescription dose was 42 Gy, divided in 6 fractions of 7 Gy, delivered twice weekly with at least 48 hours between each

fraction, according to the experience of Tormo et al with the Valencia applicator[30]. Treatment times were calculated automatically by the application console, once the applicator size, dose and depth were introduced and verified by the operator[45]. Treatment duration was less than 3 minutes in all cases.

2.E. Follow up and evaluation

After treatment, patients were instructed to avoid sun exposure and to apply a sunscreen if sun exposure was unavoidable. If lesions became ulcerated during treatment a petrolatum ointment was applied as needed.
for follow up at 2 and 6 weeks after treatment in order to assess cutaneous toxicity, and at 3 and 6 months to evaluate efficacy and cosmesis. Clinical and dermoscopic photographs were taken at each visit. Additional follow up visits are planned at one and two years after treatment.

CTCAE v4.0 (Common Terminology Criteria for Adverse Events) toxicity scales were used to assess acute toxicity and RTOG-EORTC scales related to brachytherapy were used to assess late toxicity related to cosmesis (Tables 1 and 2).

Table 1. CTCAE (Common Terminology Criteria for Adverse Events) related to skin.

Toxicity	G1	G2	G3	G4	G5
Atrophy	Mild	Marked			
Alopecia	<50%	≥50%			
Pigmentation change	Mild or localized	Marked or generalized			
Skin ulceration	<1cm	1-2 cm	>2 cm	Deep structures involvement	Death
Erythema	Mild	Moderate	Severe	Necrosis	Death

Original source: adapted from NCI CTCAE v4.0.

Table 2. Cutaneous brachytherapy related RTOG-EORTC (Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer).

G1	G2	G3	G4
Slight atrophy Pigmentation change Some hair loss	Patchy atrophy Moderate telangiectasias Total hair loss	Marked atrophy Gross telangiectasias	Ulceration

Original source: adapted from RTOG/EORTC late radiation morbidity.

2.F. Statistics

Data are reported as mean ± standard deviation. Categorical variables are presented as proportions. Differences between groups were determined using the Fisher exact test (due to the presence of a percent<5% in one group). Finally, Stepwise multivariate logistic regression model was used to identify all independent predictors of toxicity.

Statistical analysis was performed with SPSS Statistics 18® (SPSS Inc, Chicago, USA) program. We considered P values < 0.05 significant.

3. Results

3.A. Patient demographics

Twenty patients with 23 lesions were included in this study. Baseline characteristics of patients and lesions are summarized in Table 3. The mean age was 79 years (range 64- 91), with a male predominance. All patients had one or more comorbidities. More than a quarter of patients had heart disease and/or were undergoing treatment with antiplatelets or anticoagulants. All patient were hispanic and most of them were phototype III.

3.B. Lesion characteristics

The most common location was head and neck (70%). The maximum diameter of lesions ranged from 8 to 20 mm (average 11.9 mm). Most of the lesions had a diameter between 8 and 15 mm. The size of applicators most frequently used were 20 mm (48%) and 25 mm (44%). Nodular type BCC was predominant (61%), 30% of cases were pigmented and only 4% were ulcerated. All tumors were stage T1 according to AJCC 2010. Mean tumor thickness was 1.57 mm measured by histopathology (range 0.25-2.9) and 1.90 mm measured by ultrasonography (range 0.5-3.7). The depth prescription was 3 mm in 87% of lesions and 4 mm in the other cases, as justified in Ballester et al[69]. The treatment time per fraction ranged from 2.56 min (2'33") to 2.83 min (2'50"), with a mean value of 2.62 min (2'37").

Table 3. Baseline patients and lesion characteristics.

Women n (%)	8 (40)
Age (years)	79 ± 1.86
Phototype n (%)	
II	9 (45)
III	11 (55)
Comorbidities n (%)	
Peacemaker	2 (10)
Cardiopathy	5 (25)

Dementia	3 (15)
Antiplatelet/anticoagulant n (%)	6 (30)
Number of BCC n (%)	
1	17 (85)
2	3 (15)
Lesion locations n (%)	
Head and neck	16 (70)
Extremities	4 (17)
Trunk	3 (13)
Lesion diameter (mm): applicator size (mm) n (%)	
≤10: 20	11 (48)
11-15: 25	10 (44)
16-20: 30	2 (8)
Dose depth (mm) n (%)	
3	20 (87)
4	3 (13)
Treatment time (minutes)	2.62 (2.56-2.83)

3.C. Efficacy

A complete response was documented for all lesions (100%). We took clinical and dermoscopic photographs at 2 weeks, 6 weeks, 3 months, and 6 months after treatment (see Figs. 3 and 4). A punch biopsy was planned at six months if there was suspicion of residual disease, but this has not occurred. Minimum follow up was 6 months.

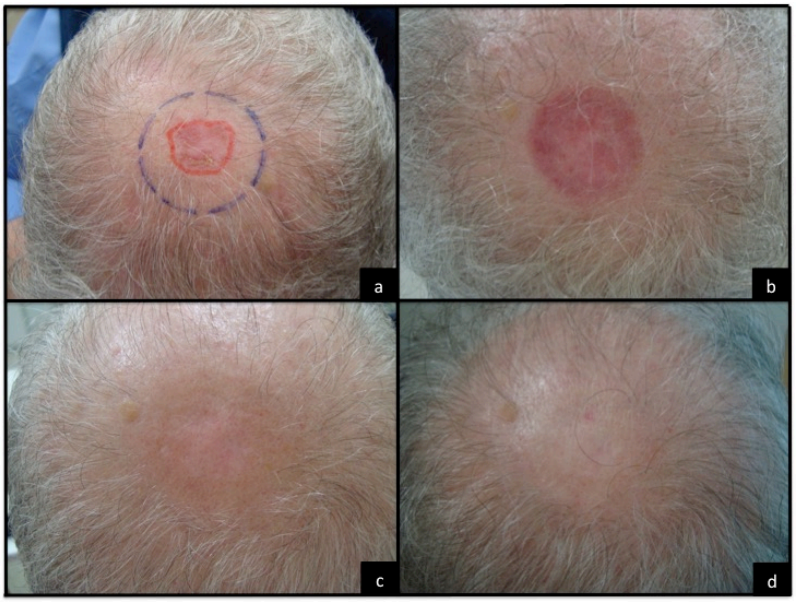


Fig. 3. a: superficial basal cell carcinoma located on the scalp prior to treatment. b: 2 weeks after last EBT fraction. c: 3 months after last EBT fraction. d: 6 months after last EBT fraction.

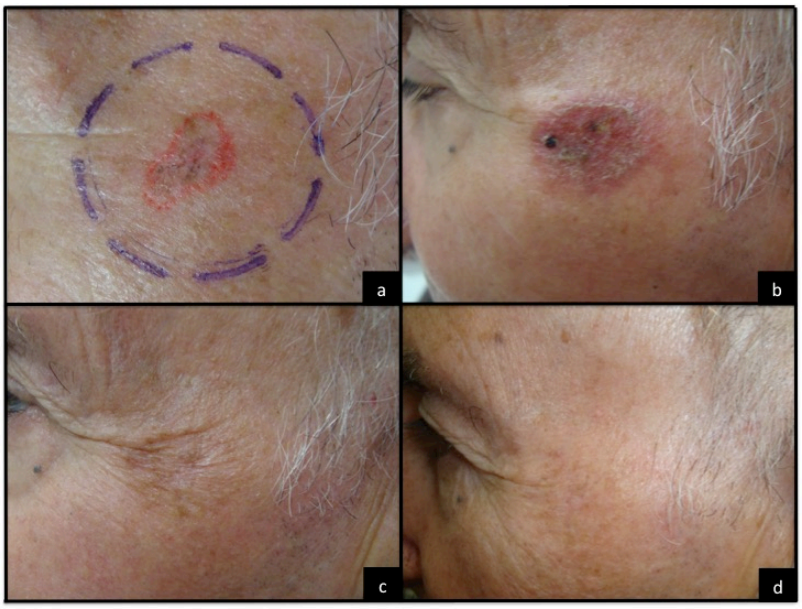


Fig. 4. a: superficial basal cell carcinoma located on the cheek prior to treatment. b: 2 weeks after last EBT fraction. c: 3 months after last EBT fraction. d: 6 months after last EBT fraction.

3.D. Toxicity

Toxicity observed during treatment started after the 4th fraction and was most severe between 2 and 6 weeks after treatment. Toxicity was assessed using the CTCAE (Common Terminology Criteria for Adverse Events) scale (Table 1). G1 or G2 toxicity was observed in all cases. Erythema was the most frequent adverse event (100%). Ulceration and crusting appeared most frequently in nodular cases and in trunk and extremities. A significantly higher incidence of ulceration in trunk and extremities cases compared with head and neck cases was found

(100% Vs 44.4±0.2%, p=0.003). In the regression model we introduced the following variables: age, antithrombotic treatment, Breslow (mm), depth prescription, tumor diameter and tumor location. The only independent predictor of toxicity was a trunk and extremities tumor location (OR=9.77, CI95% 5.02-15.21, p=0.003). We did not find a statistically significant relationship between toxicity and other parameters.

No other adverse events were reported.

3.E. Cosmetic results

Cosmesis is related to long-term toxicity. It was measured with the brachytherapy related RTOG-EORTC scale (Radiation Therapy Oncology Group and the European Organisation for Research and Treatment of Cancer) (Table 2). The potential adverse events with RT are: radiodermitis, itching, pain, ulceration, alopecia, hyperpigmentation, hypopigmentation, telangiectasia, skin atrophy and induration. We observed only pigmentation changes (central hypopigmentation with peripheral hyperpigmentation) and alopecia. Sixty-one percent of the lesions showed no skin alteration (G0). The remainder showed subtle changes (G1). When comparing the cosmetic events in head and neck cases with trunk and extremities cases we found a significantly lower percentage of cosmetic events in the head and neck cases (37.5±0.12% Vs 100%, p=0.007). Finally incidence of pigmentation changes in each phototype group was studied. A higher incidence of pigmentation change was found in the phototype III group (42.9±0.13% Vs 11.1±0.1% in the phototype II group, p=0.062).

4. Discussion

This is the first study performed with the new electronic brachytherapy system Esteya®, applying the fractionation protocol successfully used with the radionuclide based Valencia applicator[30]. The potential radiobiological correction due to the lower energy has not been taken into account and the same physical dose has been applied.

Several studies have evaluated the effectiveness of RT in the treatment of BCC. Most are retrospective and use highly variable radiation doses. Cho et al[18] recently reviewed all published studies on the use of RT in BCC and identified 11 studies with response rates of 79.2% to 100%, and cure rates at 5 years of 79.2 to 95.8 % (evaluated in 4 studies). Currently there are only two randomized studies evaluating the efficacy of RT in BCC. Hall et al[19] compared the efficacy of RT and cryotherapy in a series of 93 patients and identified a higher recurrence rate in the group treated with cryotherapy (39%) compared to the radiotherapy group (4%), without identifying significant differences in cosmetic results. Avril et al[20] treated 347 BCCs located on the face with either radiotherapy or surgery, and followed patients for 41 months. Only one patient in the surgery group presented with a tumor recurrence compared with 11 patients in the radiotherapy group. Based on these results, they concluded that surgery should be a first line treatment.

It is important to note that patients referred to RT often have unresectable tumours or contraindications for surgery due to advanced age or comorbidities. This may induce a bias in interpreting the results and comparing them with other therapeutic procedures. Some authors have suggested that RT could be an effective therapeutic alternative for patients with limited life expectancy, where you can get good rates of tumor control and a good cosmetic result. Nguyen et al[22] conducted a retrospective study that included 15 patients with a mean age of 81 years, who underwent treatment with RT at doses between 45 Gy and 72.5 Gy. After a mean follow up of 34 months, no loco-regional recurrences were observed, with a complete response being reached in all patients and a very good cosmetic result.

EBT is a type of contact radiotherapy, developed in recent years, that uses low energy x-ray sources in order to direct the radiation dose to the size and shape of the tumor while preserving the surrounding healthy tissues. Only one study has been reported to date[94], describing the results obtained by applying a total dose of 40 Gy (8 fractions of 5Gy) in 171 NMSCs, delivered with the EBT source of 50 kV. In this series complete responses were obtained in 100% of the treated lesions, with no recurrences after a year of monitoring and good cosmetic results. It should be noted that one year follow up data was only available for a subset (42) of the patients treated.

Our study shows that electronic brachytherapy for superficial and nodular BCCs is effective, safe, and comfortable for the patients and is associated with very good cosmesis. We found a

significative higher incidence of ulceration in trunk and extremities cases compared with head and neck cases. When comparing the cosmetic events in head and neck cases with trunk and extremities cases we found a significantly lower percentage of cosmetic events in the head and neck cases. We also found a relation between pigmentation changes and phototype, with a higher incidende of pigmentation changes in higher skin phototypes.

Tumor local control with radiotherapy depends heavily on a correct definition of margins and tumour volume in the treatment planning process. It is important to note that very narrow margins can result in inadequate coverage of the tumor to be treated, whilst margins which are too large may increase the amount of irradiated healthy tissue. For a correct definition of margins it is necessary to define the GTV (Gross Tumour Volume), CTV (Clinical Target Volume) and PTV (Planning Target Volume). Most studies determine the GTV by a delimitation of the clinically visible tumor and then adding a 5-10 mm margin to delimit the CTV, which represents microscopic tumor extension[36]. Dermoscopy is a simple, quick and non-invasive technique that has been shown to increase the diagnostic accuracy in skin tumors. Several studies have demonstrated the usefulness of dermoscopy in the pre-surgical division of BCC, achieving a higher rate of complete tumor resections, and better sparing of peritumoral healthy tissue[38,39]. In this way and in our opinion, the use of dermoscopy is of great value for the delimitation or BCC prior to radiotherapy[69].

Another aspect to consider before starting RT is tumor depth determination since this determines the prescription dose. The gold standard for determining the depth is the incisional biopsy, however, it has the disadvantage that it only allows analysis of a small portion of tumor tissue. The recent development of high frequency ultrasound for skin (HFUS) allows visualization of the different skin layers. Several published studies compare the findings obtained by ultrasonography and histology and identify high rates of concordance between both techniques[1]. By contrast, other studies have found lower rates of concordance[93,42]. Therefore, even though the ultrasound does not replace histology, it could represent a useful tool for estimating tumor size, margin delineation before treatment, establishment of a therapeutic plan, identification of high-risk lesions and follow up[5].

We do realize that our study has limitations: first, only a limited number of patients have been included. Second, as it was a phase II study to assess safety and efficacy, we did not compare the technique with other treatments. Finally, at present the short follow up is insufficient to assess efficacy. However our results are in line with previous publications on efficacy and safety of radiation therapy in the treatment of non-melanoma skin cancer patients. We will continue to follow the patients for at least 2 years and monitor for long term cosmesis and recurrences. Although this is the first part of a 2-year follow up study, we believe that these early results could be of interest to the new users in the implementation of this EBT system.

EBT has several advantages compared with surgery and with other RT modalities. EBT is comfortable for the patients because it is quick (less than 3 minutes) and painless. Fractionation twice weekly during three weeks allows the patient to be treated in a short time, in a comfortable schedule for elderly patients. The use of an electronic source avoids the storage requirements associated with radioisotopes and makes the treatment safer for patients and practitioners. Compared to the Valencia applicator, Esteya® provides better penumbra, very small leakage, less shielding requirements and significantly shorter treatment time[44].

Esteya® is a good choice for elderly patients, patients with contraindications for surgery due to comorbidities or anticoagulant drugs or patients where surgery would result in a more disfiguring outcome.

5. Conclusions

For nodular and superficial BCC, EBT with Esteya® is an effective, simple, safe and comfortable treatment associated with excellent cosmesis. It is a good treatment alternative for elderly patients, patients who do not want surgery, patients with multiple cancerous lesions, patients with contraindications for surgery (due to comorbidities or anticoagulant drugs) or patients where surgery would result in a more disfiguring outcome. A longer follow-up and more studies are needed to confirm these

preliminary results. In this initial phase, it has been shown that a well proven hypofractionation regimen with the Valencia applicators can be applied successfully with the Esteya® EBT.

6. Acknowledgements

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CAPÍTULO 4

Electronic brachytherapy for superficial and nodular basal cell carcinoma: a report of two prospective pilot trials using different doses

Electronic brachytherapy for superficial and nodular basal cell carcinoma: a report of two prospective pilot trials using different doses

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Abstract

Introduction: basal cell carcinoma (BCC) is a very common cancer in the Caucasian population. Treatment aims to eradicate the tumor with the lowest possible functional and aesthetic impact. Electronic brachytherapy (EBT) is a treatment technique currently emerging. This study aims to show the outcomes of two consecutive prospective pilot clinical trials using different radiation doses of EBT with Esteya® EB system for the treatment of superficial and nodular basal cell carcinoma.

Material and Methods: two prospective, single-center, non-randomized, pilot studies were conducted. Twenty patients were treated in each study with different doses. The first group (1) was treated with 36.6 Gy in 6 fractions of 6.1 Gy and the second group (2) with 42 Gy in 6 fractions of 7 Gy. Cure rate, acute toxicicty and late toxicity related to cosmesis were analyzed in the two treatment groups.

Results: in group 1, a complete response in 90% of cases was observed at the 1 year follow-up, whereas in group 2 the complete response was 95%. The differences with reference to acute toxicity and the cosmetic results between the two treatment groups were not statistically significant.

Conclusions: our initial experience with Esteya® EB system to treat superficial and nodular BCC shows that a dose of 36.6 Gy and 42 Gy delivered in 6 fraction of 7 Gy achieves a 90% and 95% clinical cure rate at 1 year respectively. Both groups had a tolerable toxicity and a very good cosmesis. The role of EBT in the treatment of BCC is still to be defined. It will probably become an established option for selected patients in the near future.

1. Introduction

Basal cell carcinoma (BCC) is the most common cancer in the Caucasian population with an increasing incidence in recent years[47]. It is a malignant epidermal tumour with a slow growth rate, limited local invasion and a very low metastatic potential. BCC is related to chronic exposure to ultraviolet radiation and therefore occurs most commonly on the face. This can have a psychological impact on the patient in terms of both the disease and the possible sequelae of treatment. Left untreated local invasion results, in very advanced cases, in destruction of soft tissues involving muscle, bone, nerves or sensory organs, such as the eyes. Further complications that may occur include ulceration, bleeding, infection and pain. All these aspects contribute to the morbidity of the disease and the consequent impact on the healthcare system. The treatment goal for BCC is eradicate the tumour with the lowest possible functional and aesthetic impact and avoid relapses.

Treatment options include surgery, radiation therapy (RT), photodynamic therapy, topical medications and systemic medical therapy. Although surgery is the first choice, RT is indicated in selected cases when surgery is not an option due either to the patient (when surgery presents a high risk) or for procedural (cosmetic or functional) reasons[7]. The radiotherapeutic options which have been used include superficial X-rays, electron beam and low or high-dose-rate brachytherapy. Electronic

brachytherapy (EBT) is a new technique which is currently emerging. It delivers low-energy radiation at a high dose rate through an applicator placed on the skin. As EBT uses an x-ray source, rather than radioactive isotopes, it requires less room-shielding. The ability to switch the radiation source on and off reduces exposure of healthy tissues to unnecessary radiation. In this study, the Esteya® (Elekta, The Netherlands) electronic brachytherapy system was used. It has an articulated arm specifically designed for surface procedures that adapts to flat lesion locations. The skin applicator is constructed with Tungsten shielding in such a way that radiation output is limited to the lesion of interest, radiation leakage to healthy tissues is virtually zero[45]. When compared to established HDR brachytherapy solutions with isotope based sources of radiation, a shorter treatment time is required so it improves both the user and the patient experience[45]. Only a handful of studies have been reported to date[95,96,97,98] suggesting EBT is an effective treatment with few recurrences or side effects and excellent cosmetic results. However, aforementioned studies are often retrospective and not peer reviewed before publishing. Higher level prospective research is needed on EBT for positioning this new technique[99] and confirming improved clinical outcome when compared to existing technologies. No studies to date have reported on optimizing fractionation schedules[43].

This study aims to investigate the outcomes of EBT using the Esteya® EBT system (Elekta, The Netherlands) for the treatment

of superficial and nodular basal cell carcinoma using two different radiation dose regimens in two groups of patients.

2. Materials and Methods

2.A. Rationale for the study fractionation schedules

The fractionation schedules used in this study aimed to deliver the same biological effective dose (BED) as in the treatment with the Valencia applicators (Elekta, The Netherlands). As opposed to an EBT system, the latter are based on a ^{192}Ir radioactive source and a surface-specific applicator, which have been shown to provide excellent results in terms of control rate and cosmesis[30].

The BED estimates the true biological dose delivered by a combination of dose per fraction and total dose to a given tissue characterized by a specific α/β ratio. It is calculated by the equation $BED=nd\ [1+d(\alpha/\beta)]$ where n is the number of fractions, d is the dose/fraction, and α/β is a radiosensitivity coefficient[100]. Different histological classes of cancers have different α/β ratios and this can result in a different clinical response despite the fact that the total dose has not changed. If the total dose is kept constant the BED will increase if the dose per fraction is increased. In general a value of $\alpha/\beta = 10$ for the tumour is accepted[101,102] although $\alpha/\beta = 8.5$ has been suggested for skin cancers[103]. In a previous study with the Valencia applicators, the BED was 71.4 Gy when considering $\alpha/\beta = 10$ and 78.8 Gy for $\alpha/\beta = 8$[91]. To achieve

this 6 fractions of 7 Gy each, prescribed at a given depth (usually 3 or 4 mm), with 2 fractions per week with at least 48h between consecutive fractions was used. In addition, the maximum skin dose (at 0 mm depth) per fraction was set to be lower than 10 Gy in order to avoid skin injuries[104].

In contrast to the Valencia applicators, Esteya® is an EBT system based on a 69.5 kVp X-ray tube and a set of circular collimators that produce photon beams of 1 cm to 3 cm in diameter at a depth of 0 mm. Thus, photons emitted in a treatment with Esteya® have considerably lower energy than photons emitted by a ^{192}Ir source. It has been reported that lower energy photons have a higher radiobiological effectiveness (RBE)[105]. This implies that a lower physical dose should be prescribed with EBT sources in order to achieve the same clinical results (i.e. the same BED) as with the higher energy brachytherapy sources (e.g. ^{192}Ir Valencia applicators). The RBE depends on the photon spectrum and the dose per fraction applied. After a review of the literature[106,107,108,109,110,111,112], it was estimated that the RBE for a 69.5 kVp x-ray source such as the one used by Esteya® is around 1.15. Based on this analysis, the same clinical results achieved with the Valencia applicators could be expected by prescribing 7 Gy / 1.15 = 6.1 Gy per fraction, during 6 fractions, with 2 fractions per week. This was the fractionation schedule used with group 1. Because the recurrence rates obtained in early results for this group were not as low as with the Valencia applicators, it was decided that the second group should be treated with the same

fractionation as with the Valencia applicators (7 Gy per fraction), i.e., no RBE correction was applied in comparison to group 1.

In both groups, because the tolerance in dose homogeneity for the Esteya® beam is within 5%, a 9.5 Gy threshold dose was established in order to be sure that the maximum skin dose per fraction was lower than 10 Gy. The dose gradient for the Esteya® source is lower than that for the Valencia applicators[44] which results in an even lower dose at the surface, and so this maximum skin dose per fraction was never reached either using 7 Gy or 6.1 Gy per fraction.

2.B. Study design

Two prospective, single-center, non-randomized, pilot studies to assess the outcome of electronic brachytherapy in superficial and nodular basal cell carcinoma treatment using Esteya® surface applicators were conducted sequentially.

Two groups of twenty patients were treated sequentially with different doses. The second group studied received a differently calculated dose because similar results to the Valencia applicator studies were not achieved with the dose used in the first group.

The first group (1) included 20 patients with 20 lesions treated with 36.6 Gy in 6 fractions of 6.1 Gy, two times a week during three weeks, with at least 2 days between each consecutive fraction. The second group (2) included 20 patients with 20 lesions treated with 42 Gy in 6 fractions of 7 Gy, two times a week during three weeks, with at least 2 days between each consecutive

fraction. Thus, all fractionation and overall times were kept the same with the exception of the dose per fraction. In one arm the 6.1 Gy/fraction resulting from the theoretical RBE calculation was used, and in the second arm (7 Gy/fraction) the same dose as in the Valencia applicator study was used.

The study was conducted from May 2014 to July 2015. It was approved by the Ethics Committee of Clinical Research of the La Fe Hospital.

2.C. Elegibility

Only adults with a primary superficial or nodular BCC with T1 and T2 clinical stage according to AJCC 2010 criteria[113] were included. T1 includes tumours ≤2 cm with less than 2 high risk features and T2 includes tumours >2 cm or any tumour with 2 or more high risk features. These high risk features are: >2 mm thickness, Clark level≥4, perineural invasion, tumour located on the ear or hair-bearing lip and undifferentiated or poorly differentiated tumours. Other forms of BCC or clinical stage more than T2 were excluded. Due to applicator design, lesions bigger than 20 mm, deeper than 4 mm or located on irregular surfaces were also excluded[91].

All patients or legal guardians signed a written informed consent.

2.D. Procedure, monitoring and follow up

All BCC's were confirmed by histopathologic examination. Tumour depth was assessed by high frequency ultrasonography (HFUS) and a 3 mm punch-biopsy taken from the clinically most representative area in terms of depth[93]. Lateral margin delimitation was assessed clinically and aided by a dermoscope[69]. A lateral margin of 5 mm was added to establish the treatment area[91].

All patients were followed for at least 1 year. Patients were seen after treatment at 2 weeks, 6 weeks, 3 months, 6 months and 1 year. Complete and partial response were defined by the absence or the presence of residual tumour clinically and aided by dermoscopy at each follow-up visit. When there was any doubt about tumour persistence or recurrence a biopsy was performed for confirmation by histopathology. Biopsies were always taken at or after the 3 months check-up. CTCAE v4.0 (Common Terminology Criteria for Adverse Events) toxicity scales[17] were used to assess acute toxicity and RTOG-EORTC scales[16] related to brachytherapy were used to assess cosmesis.

2.E. Statistics

Mean ± standard deviation was reported for continuous data, and percentage ± standard deviation for categorical data. To compare categorical data we utilized a nonparametric test (Kendall Tau B) due to the presence of a percentage of < 0.05 to be significant.

3. Results

The baseline characteristics of the two populations are shown in Table 1. Patients treated with 36.6 Gy are shown in the left column (Group 1) and patients treated with 42 Gy are shown in the right column (Group 2). Both groups were comparable in all collected baseline characteristics except age (p=0.006).

Table 1. Baseline patients characteristics.

	GROUP 1	**GROUP 2**	**P**
Women n (%)	10 (50)	8 (40)	ns
Age years	70 ± 3	79 ± 2	0.006
Skin phototype n (%)			
2	9 (45)	10 (50)	ns
3	11 (55)	10 (50)	
Antithrombotic therapy n (%)	30	30	ns
Tumour location n (%)			
Head and neck	75	75	ns
Trunk and extremities	25	25	
BCC type n (%)			
Superficial	10 (50)	8 (40)	ns
Nodular	10 (50)	12 (60)	

Pigmented BCC n (%)	9 (45)	7 (35)	ns
Ulcerated BCC n (%)	5 (25)	1 (5)	ns
Breslow (mm)	1.43 ± 0.21	1.58 ± 0.18	ns
Tumour diameter mm	11.54 ± 0.96	12.2 ± 0.68	ns
Dose depth n (%) 3 mm 4 mm	 18 (90) 2 (10)	 17 (85) 3 (15)	ns

Group 1: 20 patients treated at 36.6 Gy delivered in 6 fractions.

Group 2: 20 patients treated at 42 Gy delivered in 6 fractions.

Ns: non-significant (>0.05).

In group 1, a complete response in 90% of cases was observed, whereas in group 2 the complete response was 95% (Fig. 1). This difference was not statistically significant probably due to the small sample size.

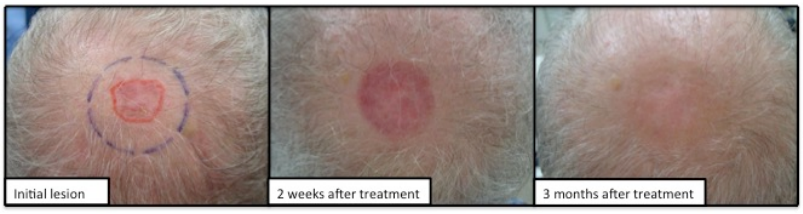

Fig. 1. Example of complete response.

Tumour persistence or recurrence was suspected clinically and dermoscopically in two patients in the first group at 3 and 6 months respectively and in one patient in the second group at 1 year follow-up. This was confirmed by histopathology after resection of the remaining tumour, which was a diagnostic as well as a curative procedure (Fig. 2).

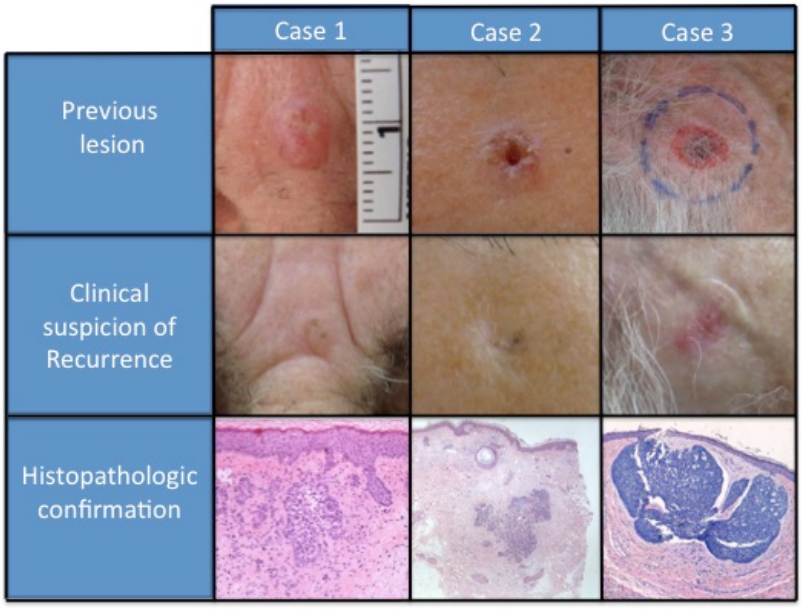

Fig. 2. Clinical and histopathological pictures of recurrent cases.

Acute toxicity in the first group was G1 in 65% of cases due to erythema and G2 in 35% due to ulceration (Fig. 3). In the second group 60% of patients presented with G1 toxicity and 40% with G2. The cosmetic result was G0 (no cutaneous alterations) in 61%

of patients in the first group and 55% in the second group. The rest of the patients only showed pigmentation alterations or alopecia, corresponding to a G1 cosmetic result (Fig. 3). These differences in acute toxicity and cosmetic results between the two treatment groups were not statistically significant ($p>0.05$). Results are shown in Table 2.

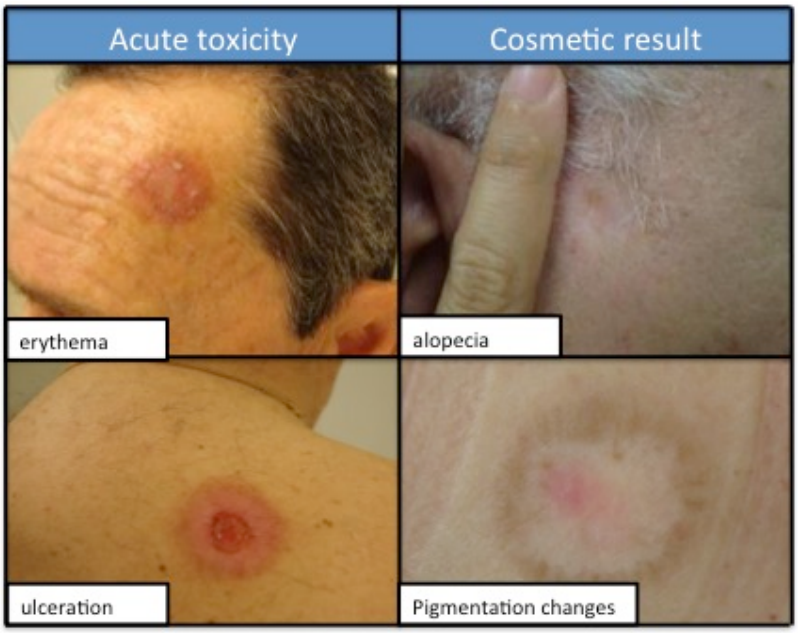

Fig. 3. Examples of acute toxicity and cosmetic result.

Table 2. Results.

	GROUP 1	GROUP 2	P
Acute toxicity (%)			
G1 (erythema)	65	60	ns
G2 (ulceration)	35	40	
Cosmetic result (%)			
G0 (no skin alteration)	61	95	ns
G1 (pigmentation changes or alopecia)	39	5	
Response			
Complete	90	95	ns
Partial	10	5	
Recurrences			
Number (%)	2 (10)	1 (5)	
Location	forehead (both)	right temple	
Tumour diameter (mm)	8 and 5	12	
Depth (mm)	2.7 and 3.1	2.2	
Applicator used (mm)	20 and 15	25	
Dose depth (mm)	3 and 4	3	
Time to recurrence (months)	3 and 6	12	
Second-line treatment	resection	resection	

Group 1: 20 patients treated at 36.6 Gy delivered in 6 fractions.

Group 2: 20 patients treated at 42 Gy delivered in 6 fractions.

Ns: non-significant (>0.05).

4. Discussion

When treating BCC dermatologists have a wide range of possibilities but surgery and RT are the treatments with the lowest recurrence rates[9]. Surgery is often the first choice due to its high efficacy and because it is a straightforward procedure. Despite the high incidence of BCC however there is only one randomized study comparing surgery to RT which was published in the late nineties[20]. In this study only primary facial BCC less than 4 cm were included. Three hundred and forty-seven patients were treated, 174 with surgery and 173 with RT followed up over 4 years. It was concluded that surgery has a lower failure rate and better cosmesis than RT. Although this was a randomized study it has several weaknesses. Firstly, the radiotherapy group was not homogeneous since patients were treated with interstitial brachytherapy, contact therapy or conventional radiotherapy. Further, doses and fractionation in each RT type were not the same. Secondly, the use of flaps and grafts to close the wounds in the surgery group may have made the detection of persistence or recurrence more difficult. Thirdly additional resection was performed in 39% of patients from the surgery group. Finally, only facial tumours were included so we have no data about other locations.

Radiotherapy has been a part of the dermatologist's treatment armamentarium for several decades but, since the eighties, this has been changing in favor of dermatologic surgery. This is

basically due to the incorporation of surgery in dermatology and the difficulties of administering radiation in unshielded offices. In addition, in many countries dermatologists are not allowed anymore to administer RT themselves, thus they have to send patients to another department or clinic if they opt for RT. Consequently, surgery has experienced a great surge in development in recent years in dermatology departments and offices, whereas RT has reduced noticeably in significance, being used only in cases when surgery is contraindicated.

EBT has appeared as an alternative to more conventional RT techniques such as electron beam or high-dose-rate radionuclide-based brachytherapy. Electron beams require a bolus and a more specific dosimetry, which makes it more complex in clinical practice. On the other hand, radionuclide-based brachytherapy uses a radioactive source, generally ^{192}Ir, which emits photons of higher energy than EBT sources. This results in EBT requiring less room shielding, and being safer, simpler and easier to apply. In radionuclide-based brachytherapy, some applicators exist which shield the radiation emitted by the ^{192}Ir source except for the region that needs to be irradiated. Among them, the Valencia applicators[30] were designed specifically to produce a collimated and homogeneous dose distribution within the patient's skin[114]. Compared to these applicators, EBT has the advantage of a shorter treatment time (2.5 minutes compared to 5 to 10 minutes), lower penumbra (i.e. sharper lateral dose fall-off)[111], less radiation leakage that implies lower peripheral dose, and a broader range of applicator sizes, resulting in a more conformal treatment. For

these reasons, EBT is a promising technique for the treatment of skin lesions.

So far, to the best of our knowledge, only four studies have been performed using EBT for BCC (despite the fact that these authors treat other NMSC too). These four groups used the Xoft Axxent® Electronic (eBx®) Brachytherapy System®. Bhatnagar et al reported 147 cases of BCC[95], Dogget et al 238 cases[96], Strimling et al 275[97] and Paravati et al 149[98]. These studies showed clinical cure rates higher than 98 % with acceptable acute toxicities and very good cosmesis. All of them used a dose of 40 Gy in 8 equal fractions, 5 Gy per fraction, delivered twice weekly with at least 48 hours between each fraction. Long-term follow-up has not yet been achieved because most patients have not reached their second year of follow-up.

In our experience with the Esteya® system, the better dose to achieve the highest clinical cure rate is 42 Gy in 6 equal fractions, i.e. 7 Gy per fraction given at the prescription depth (typically 3 mm)[115]. This is delivered twice weekly with a minimum interval of 48 hours. Tormo et al[30] also showed good toxicity results in patients treated in 6 or 7 fractions. Although most brachytherapy treatment schemas in the literature use 8 to 12 fractions[94,116,29,117,118,28], the fractionation used in this study does not result in a higher toxicity or a poorer cosmesis in comparison with a more fractionated treatment. Thus, in an elderly population, a comfortable schema that facilitates compliance is preferred. For these reasons a 6 fractions schema was chosen. In order to reduce the number of fractions to 5, while at the same

time keeping the same biological effective dose (BED), 8 Gy per fraction at the prescription depth (typically 3 mm) would be required. However, the latter would result in a skin dose (i.e. at 0 mm depth) of 9.9 Gy per fraction, which, taking into account a 5% tolerance in dose homogeneity, would fail to guarantee compliance with the FDA recommendations[104] regarding the maximum skin dose to avoid toxicity.

Table 3. Comparison between different protocols of HDR-BT and EBT for BCC.

Author, year	Num. of NMSC/BCC	Applicator	No. of fractions	Total dose (Gy)	Dose/ fraction (Gy)	Frequency	Prescription	BED keV	Median follow up (months)	Local control (%)
Köhler-Brock *et al.* 1999[28]	520/282	Leipzig	-	30-40	5-10	1-2 times a week	6-8 mm	-	6-125	91
Gauden *et al.* 2008[29]	92/	Leipzig	12	36	3	Daily	Leipzig appropiate depth	46.8	37	97
Ghaly *et al.* 2008[116]	67/	Leipzig	8	40	5	Twice a week	Leipzig appropiate depth	60.0	18	95.5
Tormo *et al.* 2014[30]	48/45	Valencia	6	42	7	Twice a week	4 mm	70.0	-	98
Delishaj *et al.* 2015[114]	53/42	Valencia	8-10	40-50	5	2-3 times a week	-	60-75	12	96.2
Bhatnagar 2013 and 2015[94,95]	297/167	EBT (Xoft)	8	40	5	Twice a week	Depth based on CT or 3 mm	50	16.5	99
Dogget *et al.* 2015[96]	565/238	EBT (Xoft)	8	40	5	Twice a week	-	50.0	12.5	99.8
Strimling *et al.* 2015[97]	508/275	EBT (Xoft)	8	40	5	Twice a week	0-5 mm	-	3.4	99.4
Paravati *et al.* 2015[98]	154/149	EBT (Xoft)	8	40	5	Twice a week	2-3 mm	-	16	98.7
Ballester *et al.* 2015	40/40	EBT (Esteya)	6	36.6-42	6.1-7	Twice a week	Esteya applicators	69.5	12	90-95

BCC: basal cell carcinoma.

BED: biological effective dose.

NMSC: non melanoma skin cancer.

Despite the solid radiobiological basis three cases showed tumour persistence or recurrence. In group 1, treated at 36.6 Gy, this occurred early, one case at 3 and one at 6 months. Both were persistent cases because the lesion was decreasing in size but never disappeared. The only failed case in group 2, treated at 42 Gy, occurred late, at 1 year follow-up. In this case the lesion initially disappeared clinically but later reappeared. These cases were analyzed separately with regard to high frequency ultrasonography, previous biopsy and histopathology from the persistent or recurrent tumour. Medical records, clinical and dermoscopic features of all visits were reviewed. Despite this, we did not find any reason that could justify the failure of the treatment.

We do realize that this study has several limitations. The small sample size and the short-term follow-up being the main ones. We included a limited number of patients because this was a pilot study. The follow-up performed is probably insufficient to assess efficacy but these early results could be a trend in terms of clinical results. All patients will have further follow-up in order to assess long-term response and to rule out recurrences.

As more studies are performed we learn more about the biology and behaviour of different cutaneous tumours. There are many patients with BCC and at the same time there are new treatments becoming available. All of this allows us to individualize treatment depending on patient and tumour characteristics. In the near future EBT will probably be one more

treatment option available for patients with BCC. Dermatologists should know about this new technique in order to add it to their current treatment strategies.

5. Conclusions

Our initial experience with the Esteya® EB system to treat superficial and nodular BCC shows that a dose of 36.6 Gy and 42 Gy delivered in 6 fractions of 7 Gy achieves a 90% and 95% clinical cure rate at 1 year respectively. Both groups had a tolerable toxicity and a very good cosmesis.

Further investigation with respect to EBT for treating skin tumours is needed, ideally high-level evidence in the form of randomized clinical trials, to compare results with modern treatment protocols with those obtained with surgery. Surgery remains the treatment of choice today and EBT's role and position is yet to be defined. It will probably become an established option for selected patients in the near future.

CAPÍTULO 5

2 year results of electronic brachytherapy for basal cell carcinoma

Two year results of electronic brachytherapy for basal cell carcinoma

Ballester-Sánchez R, Pons-Llanas O, Candela-Juan C, de Unamuno-Bustos B, Celada-Álvarez FJ, Tormo-Micó A, Pérez-Calatayud J, Botella-Estrada R (2017) Two year results of electronic brachytherapy for basal cell carcinoma. *Journal of Contemporary Brachytherapy*. In press.
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Abstract

Introduction: The use of radiation therapy (RT) for non-melanoma skin cancer (NMSC) has been changing during the last century. Over the last decades the use of radiotherapy has surged with the development of new techniques, applicators and devices. In recent years electronic brachytherapy (eBT) devices that use small x-ray sources have been introduced as alternative to radionuclide dependence. Nowadays, several devices have been incorporated, with a few series reported, and with a short follow up, due to the recent introduction of these systems. The purpose of this work is to describe the clinical results of our series after two years follow-up with a specific eBT system.

Material and Methods: This is a prospective single-center, non-randomized pilot study, to assess clinical results of electronic brachytherapy in basal cell carcinoma using the Esteya® system. The study was conducted from June 2014 to September 2016. The follow up time was 2 years for all cases.

Results: Twenty-six patients with 44 lesions achieved two year follow up. A complete response was documented in 95.5% of cases. Toxicity was mild (G1 or G2) in all cases, and due to erythema, ulceration or alopecia. Cosmesis was excellent in 88.6% of cases and good in the rest. Pigmentation change was the most frequent cosmetic alteration.

Conclusions: This work is unique in that the equipement's treatment voltage is 69.5 kV and the first prospective study with long term follow-up with Esteya®. These preliminary reports show excellent results with less toxicity and excellent cosmesis. Although surgery is nowadays the first option, some patients could benefit from eBT, especially elderly patients, those with comorbidities or undergoing anticoagulant treatment as well as those who refuse surgery or in whom it is contraindicated.

1. Introduction

The use of radiation therapy (RT) for non-melanoma skin cancer (NMSC) has been changing during the last century. The incorporation of new technologies over the time has increased the set of radiotherapeutic treatment options. The change in regulations and restrictions for the use of ionizing radiation also has adapted its procedure. At the same time, the development of Mohs surgery, its inclusion in dermatologic practice and its high cure rates led to an increase in its use for treating NMSC. Nevertheless, over the last decades the use of radiotherapy has increased with the development of new techniques, applicators and devices.

Since the early days of RT, ionizing radiation has been used for NMSC. Its first use dates back to 1903 when radium plaques were successfully applied to a facial basal cell carcinoma[119]. With the discovery of x-rays in the late 19th century, x-ray devices were increasingly being used for treatment of skin cancer over the next decades. Initially using low-energy radiation appliances like Grenz ray devices for premalignant lesions, later replaced by superficial therapy and orthovoltage devices for skin cancers when technology developed. With the development of linear accelerators in the late 1950s, electron beam therapy was introduced. Treatment with electron beams is also being referred to as teletherapy because the source of the radiation and the target tissue are distant. With this linear accelerator, daily

treatments over 5-7 weeks are needed. Brachytherapy (BT) is a targeted type of RT delivered within the tumour (interstitial), whithin a cavity (intracavitary), or adjacent to the tumour as in skin surface BT. Most of the early BT was delivered with low-dose-rate (LDR) or medium-dose-rate sources (MDR). By 1970 the concept of high dose rate (HDR) was introduced; radiation was delivered at a rate of 12 Gy per hour or higher. This allowed shorter treatments favoring especially elderly patients[120]. Moreover, a robotic controller improved radiation protection and simplified the delivery of the source. Radiobiological studies concluded that effectiveness of these treatment protocols was the same without increasing toxicity[121]. During the 1980s the concept of hypofractionation was introduced; more precise radiation technologies made it possible to give higher dose to the lesions in each fraction while surrounding healthy tissue was spared, resulting in less number of sessions and shorter total time of treatment[31]. In the last decades of the 20th century additional research and clinical experience led to the incorporation of hypofractionated regimens using brachytherapy with Ir^{192} sources with high cure rates[28,27,29,122,34,59,123]. Brachytherapy positions a radiation source, often Ir^{192}, very close to a lesion. To individualize tumour characteristics, radiation surface molds and interstitial catheters are used to position the isotope and deliver ionizing radiation to the lesion. After the 1960s several studies were published describing clinical outcome using HDR brachytherapy in combination with standardized surface molds, flaps or applicators[28,27,29,30], that are still being employed. The recent introduction of electronic brachytherapy (eBT) devices that use

small x-ray sources[43] has provided an alternative to the use of isotopes. As of today, several devices have been incorporated, such as Xoft® Axxent®, Zeiss® INTRABEAM®, and Elekta® Esteya®, with a few series reported, and with a short follow up, due to the recent introduction of these systems[26].

The Hospital Universitario y Politécnico La Fe has treated 40 patients with Esteya® eBT since 2014 and has published some articles on the different aspects of this treatment such as commissioning and periodic tests[45], dosimetric characteristics[44,46,124], clinical implementation[91], depth determination[93], use of dermoscopy for lateral margins[69], and efficacy and safety[115]. The purpose of this work is to describe the clinical results of our series after two years of maximum follow-up.

2. Material and Methods

2.A. Description of Esteya® Electronic Brachytherapy System

Esteya® Electronic Brachytherapy System (Elekta Brachytherapy, Veenendaal, The Netherlands) was specifically developed for skin surface lesions and has been commercially available since 2013. The system consists of a control panel with planning software, a treatment unit and a set of circular surface applicators of different diameters: 10 mm, 15 mm, 20 mm, 25 mm

and 30 mm. The treatment unit contains a collimated miniature x-ray source with a voltage of 69.5 kV. The beam current has a default setting of 1.6 mA, which is automatically changed to 1.0 mA for treatment fractions smaller than 4 Gy, and to 0.5 mA for prescription doses below 2 Gy. The treatment time for each field, which varies between 2 and 3 minutes, is automatically calculated by the system once the prescription dose has been entered by the user.

2.B. Study design

In 2014, 40 patients with 60 lesions were treated with Esteya® eBT. All patients had a diagnosis of basal cell carcinoma, superficial or nodular type, confirmed by biopsy. Two cm maximum diameter and 4 mm maximum depth were established based on technical requirements. Tumour depth was determined by high frequency ultrasonography (HFUS) and histopathology[93]. Only T1 and T2 stages (according to AJCC 2010)[92] were included. The methodology of this study has been detailed in previous articles[91,115]. The protocol was approved by the Ethics Committee of Clinical Research of the Hospital Universitario y Politécnico La Fe. All patients or legal guardians signed a written informed consent.

2.C. Treatment

The clinical target volume (CTV) was established by adding a 5 mm lateral margin to the gross tumor volume (GTV) which was clinically determined and confirmed with the use of a dermoscope[69]. The smallest diameter applicator that covered the

entire CTV was selected. To delineate the external mark to fit into the selected applicator, a specific applicator template was used[125]. The Esteya® surface applicator was placed in full contact with the tumour without air gaps. The treatment dose was prescribed at 3 mm for lesions with depth of 3 mm or less[93], and the specific lesion depth was employed for prescription in the remaining lesions with a maximum of 5 mm. All patients were treated over three weeks with two sessions per week separated by at least 48 hours, according to the protocol used with the Valencia applicator[30]. Two different prescription doses were used: 36.6 Gy (6 fractions of 6.1 Gy) and 42 Gy (6 fractions of 7 Gy). The rationale of these two fractionations was previously discussed[115,126]. Treatment time was automatically calculated by the console, once dose, applicator size and depth were introduced by the operator.

2.D. Follow up and end points

Patient follow up on a regular basis was performed for a period of two years. Patients were seen for follow-up at 2 and 6 weeks after treatment and at 3, 6, 12 and 24 months. Clinical and dermoscopic photographs were taken at each visit. A punch biopsy was planned at 6 months after treatment if there was any clinical suspicion of persistence or at any moment after 6 months if there was any suspicion of recurrence. Any BCC that did not completely disappear, based on clinical or dermoscopic examination, in the period of 6 months after radiation, was considered as a persistence. On the other hand, any reappearance

of a sign of BCC after a complete response was considered as a relapse.

Patient demographics and lesion characteristics were recorded. End points included efficacy, toxicity and cosmetic results. CTCAE v4.0 (Common Terminology Criteria for Adverse Events) toxicity scale[17] was used to assess toxicity and a standardized cosmetic rating scale[16] was used to assess cosmesis (Table 1).

Table 1. Cosmetic rating scale.

Excellent	No changes to slight atrophy or pigment change or slight hair loss, or no changes to slight induration or loss of subcutaneous fat
Good	Patch atrophy, moderate telangiectasia, and total hair loss; moderate fibrosis but asymptomatic; slight field contracture with less than 10% linear reduction
Fair	Marked atrophy and gross telangiectasia; severe induration or loss of subcutaneous tissue; field contracture greater than 10% linear measurement
Poor	Ulceration or necrosis

3. Results

3.A. Patient demographics and lesion characteristics

Fourty patients with 60 lesions were included into the study. Eleven patients died (from other unrelated causes) and 3 were lost to follow-up, so we have analyzed the results of 26 patients with 44 lesions with a follow-up of 2 years.

Fourteen women with 25 lesions (56.8%) and 12 men with 19 lesions (43.2%) achieved two year follow-up after electronic brachytherapy treatment for basal cell carcinoma. The mean age was 69.2 years and it ranged from 57 to 86. There were fourteen lesions (46.7%) with a phototype 2 and 30 lesions (53.3%) with a phototype 3. Seven patients (18.9%) were undergoing antiplatelet or anticoagulant treatment, that could be a contraindication for choosing surgery. The mean diameter of lesions was 13.25 mm (range 5-18). Twenty-four lesions (54.6%) were pigmented and none ulcerated. Twenty-nine basal cell carcinomas (65.9%) corresponded to a superficial type and 15 (34.1%) to a nodular type. The majority of patients (97.7%) had a T1 stage (AJCC 2010) tumour[92]. The mean maximum depth was 1.44 mm measured by histopathology (range 0.26-3.2) and 1.23 mm measured by HFUS (range 0.1-3.7). Four sizes of skin applicator were used: 15 mm in 2 lesions (4.6%), 20 mm in 11 lesions (25%), 25 mm in 17 lesions (38.6%) and 30 mm in 14 lesions (31.8%). Dose prescription depth was 3 mm in 42 cases (95.4%) and 4 mm in 2 (4.6%).

3.B. Efficacy, safety and cosmetic results

Results by lesions are shown in Table 2. Forty-two lesions (95.5%) achieved a complete response and 2 a partial response (4.5%). One patient treated with 36.6 Gy persisted at 6 months and the other patient was treated with 42 Gy and recurred at 12 months after treatment. Both patients were rescued with surgery, being histologically confirmed the recurrence.

All treated areas showed some degree of acute toxicity: 14 G1 (31.8%) and 30 G2 (68.2%). Acute toxicity was erythema (31.8%), ulceration (53.3%) or alopecia (4.6%). No cases of G3 or G4 toxicity were observed.

Cosmetic results were evaluated as excellent in 39 cases (88.6%) and good in 5 (11.4%). No fair or poor cases were observed. Cosmetic alterations were due to alopecia in 3 cases (18.75%), pigmentation changes in 30 cases (66.7%) or telangiectasia in 4 cases (9.1%). No cases of ulceration, necrosis, contracture or induration were observed.

There were no differences between the different schedules employed in terms of toxicity or cosmesis.

Table 2. Efficacy, toxicity and cosmetic results.

	36.6 Gy (n=26)	**42 Gy (n=18)**	**Total n (%)**
Efficacy			
Partial response	1	1	2 (4.5)
Complete response	25	17	42 (95.5)
Acute toxicity			
G1			14 (31.8)
G2			30 (68.2)
Erythema	6	8	14 (31.8)
Ulceration	20	10	30 (68.2)
Alopecia	0	2	2 (4.6)
Cosmesis			
Good			5 (11.4)
Excellent			39 (88.6)
Alopecia	2	1	3 (18.75)
Pigmentation changes	19	11	30 (66.7)
Telangiectasias	2	2	4 (9.1)

4. Discussion

RT for NMSC has seen significant changes during the last century. Different radiation therapy techniques have been used to treat NMSC. It includes superficial x-rays, orthovoltage x-rays, megavoltage x-rays, electron beam irradiation, and radionuclide-based BT[43]. Electronic brachytherapy have become increasingly popular in the last 5 years.

eBT is currently a topic of discussion amongst dermatologists. The most common criticisms are the little data on long-term outcomes and the lack of randomized trials comparing with surgery. Therefore, long-term studies and appropriate use criteria for eBT will be necessary to position this new technology.

eBT has some advantages over external RT. Firstly, less normal tissue is irradiated compared to teletherapy treatments due to close contact with the tumour and minimal radiation leakage as a result of the improved shielding. Furthermore, smaller margins can be used due to more precise treatment. Unlike other devices, molds are not necessary for this small lesions with eBT, and the use of standardized applicators simplifies the procedure. A bolus is not necessary either as with electrons, which facilitates the treatment. Moreover, shorter treatment time is needed per session and for global treatment. Finally, the devices are small and mobile and minimal shielding is required because of the low energy and no radioactive isotope is used[43,26]. Comparison between Esteya® device with other series with radioactive

sources have been already revised in a previous work[126]. Several devices are currently available, such as Xoft Axxent® (USA), Zeiss INTRABEAM® (Germany) and Elekta Esteya® (Netherlands). All three incorporate an x-ray source. Esteya® is specifically designed for cutaneous tumours; the other systems may also be used for other tumour types when used in combination with different applicators (intracranial, breast or gynecological). Aspects of dosimetry and clinical practice of skin brachytherapy with these devices has been reported by The American Brachytherapy Society in the working group report[43,26]. Each device has different sizes of surface applicators. Axxent® uses 10, 20, 35 and 50 mm diameter field size and the dose can be prescribed between 2-5 mm depth. INTRABEAM® uses 10, 20, 30 and 40 mm diameter field size. Esteya® can be prescribed between 3-5 mm depth and has 5 applicators with of a field size of 10, 15, 20, 25 and 30 mm of diameter. Esteya® has several design characteristics that make it an excellent tool for treating skin cancer: the Tungsten shielding reduces radiation to healthy tissue to a minimum[127], overdose at the skin surface is kept to a minimum, workflow is extremely simple and the source has a guaranteed life time of at least 4000 fractions.

Zeiss INTRABEAM® has been commercially available before 2013, but no clinical outcomes about cutaneous treatments have been published. Xoft Axxent® is the longest in the market, since 2009, so it has the largest and longest series published until now. Different groups in the USA have been using it for treating NMSC and several clinical series have been reported, all of them using

the same protocol: 40 Gy in 8 fractions, delivered twice weekly, with a standard depth prescription of 3 mm. Bhatnagar[128] has treated 282 lesions in 187 patients with NMSC (53% basal cell carcinoma). He reported a 98.7% local control rate in 238 lesions with a median follow up of 12.5 months. Most patients were satisfied with the treatment. Dogget et al[119] have treated 524 NMSC (BCC, SCC or SCC *in situ*) with more than 99% local control rate. Paravati et al[98] reported 127 patients with 154 NMSC (149 BCC) with a 98.7% control rate with a median of 16 months follow-up. In all cases the authors referred to local control rate as the absence of signs of tumour at the last examination, without histopathological confirmation. Cosmesis was good to excellent in most cases in all series. Hypopigmentation was the most common late toxicity, appearing in 7.9% of cases[128]. Elekta Esteya® has been available since 2013. Having treated the very first patients with this device, we believe to have the longest follow-up. Efficacy at 6 months has already been reported[115] but now we report patients with long-term follow-up (over 2 years posttreatment). We have used two different prescription doses, 36.6 and 42 Gy, in 6 fractions, twice weekly during three weeks. A 95.5% local control rate was achieved with good to excellent cosmesis in all cases. Pigmentation changes constituted the most common cosmetic alteration.

5. Conclusions

Electronic brachytherapy for NMSC is nowadays being employed in clinical practice, and it results begins to be published. This work is unique in that the treatment voltage is 69.5 kV rather than 50 kV seen in Xoft Axxent® and Zeiss INTRABEAM®. This is also the first prospective study with long term follow-up with Esteya®.

There are clear advantages of eBT over traditional RT with radioisotopes. The treatment devices are mobile, do not require shielding or storing of radioisotopes. There is less total body dose and lower peripheral dose.

While surgery remains the first choice as a treatment, some patients could benefit from eBT, especially elderly patients, those with comorbidities or undergoing anticoagulant treatment as well as those who refuse surgery or in whom it is contraindicated.

Large series with long term follow-up and high quality clinical trials comparing eBT with surgery are essential in order to ascertain the adequate position of eBT within the armamentarium of NMSC.

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DISCUSIÓN GENERAL

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El uso de técnicas de imagen no invasivas (ecografía cutánea y dermatoscopia) en la práctica diaria en dermatología ha ido ganando peso durante el tiempo de trabajo de esta tesis. La dermatoscopia ya era una técnica bien establecida e incorporada a la práctica clínica habitual de la mayoría de dermatólogos (sobre todo con la incorporación de las nuevas generaciones, las cuales se han formado con un dermatoscopio en la mano). La ecografía cutánea en cambio, inicialmente era muy poco usada en la práctica clínica habitual debido a la barrera que supone remitir a un paciente a otro servicio distinto. Además, las sondas utilizadas de rutina en radiología no permitían en muchos casos ver con detalle lesiones pequeñas y superficiales. En los últimos años se han ido incorporando progresivamente a los servicios de dermatología ecógrafos con sondas de alta frecuencia para explorar lesiones cutáneas. Esto ha ido acompañado de una adecuada formación dirigida a dermatólogos sobre ecografía en patología cutánea. En poco tiempo ha ido creciendo la literatura médica en este campo, que hasta la fecha era escasa o nula. Pero la ecografía cutánea todavía tiene un largo camino que recorrer ya que es una técnica operador-dependiente que requiere de un entrenamiento y una destreza que se adquiere con el tiempo. La ventaja de poder disponer de estas técnicas en la consulta es que en tiempo real y de manera sencilla y rápida el mismo médico puede disponer de una gran cantidad de información que puede integrar para

hacerse una mejor idea de la lesión y poder planificar el tratamiento.

La ecografía cutánea es una técnica económica, sencilla, no dolorosa, rápida e inocua. En una misma exploración se puede observar la lesión en tres dimensiones (en lugar de dos dimensiones que nos ofrece la histopatología), por lo que podemos determinar en el caso del CBC longitud, amplitud y profundidad. En general, la ecografía tiende a sobreestimar la extensión tumoral respecto a la histopatología debido a que la pieza no se encoge[5]. Antes de realizar nuestra investigación ya había trabajos publicados comparando la ecografía con la biopsia escisional previa a la cirugía del CBC, con altas tasas de concordancia que oscilan entre el 73-98%[5]. Hay trabajos publicados posteriormente al nuestro que posicionan la ecografía cutánea como una herramienta diagnóstica de primera línea en el diagnóstico, clasificación y manejo del CBC[5,41,129]. Nuestro trabajo ha sido pionero en la comparación de ECAF y biopsia previa al tratamiento con radioterapia. Posteriormente, ha aparecido otro estudio similar publicado por Goyal et al en 2015[130] donde incluyen 20 casos de CBC. Estos autores realizan primero una biopsia por rebanado para confirmación patológica de la lesión y en un segundo tiempo realizan una ECAF de 14-18 MHz para determinar el margen lateral y profundo. A la medida lateral le añaden un margen de 7 mm y tratan a los pacientes con BTE con una dosis media de 40 Gy. Los autores no encuentran recidivas con una media de seguimiento de 12 meses.

En nuestro trabajo no hemos encontrado una correlación estadísticamente significativa entre estas dos técnicas (ECAF y biopsia) en la determinación del margen profundo previo a la BTE. Esto podría ser debido a las siguientes causas: la inclusión de un bajo número de pacientes, el uso de una sonda de 18 MHz y no superior, la realización de la biopsia previa a la ECAF, el hecho que la biopsia toma sólo una parte del tumor que puede no ser la de mayor profundidad, la falta de discriminación de la ECAF para diferenciar componente tumoral e inflamatorio y/o el hecho que la ecografía sea una técnica dependiente del operador. Si distinguimos por tipo de CBC podemos observar que en el caso de los CBCs superficiales la biopsia sobreestima respecto de la ECAF porque la mayoría de casos son indetectables mediante ecografía. En cambio, en los CBC nodulares la ecografía sí que es capaz de detectarlos y existe una mejor correlación entre las dos técnicas aunque ésta no sea estadísticamente significativa (probablemente debido a un número bajo de lesiones). De todas maneras, nosotros seguimos pensando que la ECAF es una técnica muy útil que con el tiempo irá ganando papel en el manejo y la planificación de los tumores cutáneos, aunque todavía se necesitan más estudios al respecto. A pesar de esto, la ecografía no sustituye hoy en día a la histopatología en la confirmación diagnóstica del carcinoma basocelular[71]. Según las guías internacionales[4] siempre se debe de realizar la confirmación histológica mediante biopsia, por lo que la ECAF no sustituiría en ningún caso a la biopsia sino que sería una herramienta útil en la determinación del subtipo histológico y en la delimitación de márgenes laterales y profundos, no en el diagnóstico.

La dermatoscopia es una técnica económica, sencilla y no invasiva que magnifica las lesiones cutáneas. Actualmente está al alcance de cualquier centro, y la mayoría de dermatólogos la utilizan durante su práctica clínica habitual. Hasta la fecha se ha empleado para el diagnóstico de lesiones cutáneas tumorales y no tumorales pero también para la delimitación de márgenes laterales previa a cirugía de manera más exacta que el ojo desnudo. Existen estudios publicados que resaltan la importancia de la técnica para poder tratar todo el volumen tumoral intentando respetar al máximo el tejido sano, pudiendo así estrechar los márgenes de exéresis con un menor número de recidivas tumorales[74,39,38]. Nuestro grupo ha sido pionero en utilizar esta técnica para la delimitación del margen lateral previa a la BTE del CBC. Probablemente no se haya realizado previamente porque en general los dermatólogos, que son los que están familiarizados con la técnica, no participan de manera activa en el proceso de tratamiento radioterápico. Hasta la fecha han sido los oncólogos radioterapeutas, que tienen menos experiencia clínica con el CBC, los que han delimitado clínicamente la lesión previa al tratamiento. Según nuestra experiencia, el trabajo conjunto de ambas especialidades puede mejorar los resultados clínicos en el tratamiento del CBC. De las 60 lesiones que hemos tratado hemos observado recidiva en tres de ellas, todas centrales y ninguna localizada en el margen lateral, por lo que podemos afirmar que la dermatoscopia ha resultado de utilidad en la determinación del margen lateral previa a la BTE.

El objetivo principal de este trabajo era la determinación de la eficacia y seguridad de la BTE en el tratamiento del CBC superficial y nodular. Para ello se diseñó un estudio piloto prospectivo no randomizado realizado en un único centro (Hospital Universitario y Politécnico la Fe de Valencia).

De los criterios de inclusión hay algunos generales para cualquier paciente que va a ser sometido a un tratamiento de RT (edad, patologías de base, fármacos radiosensibles, alteración cutánea, linfática o vascular en el territorio a tratar,...) y algunos específicos de la técnica utilizada. De estos últimos, destacar que debido al diseño actual de los aplicadores por su superficie rígida y plana no se pueden tratar lesiones de más de 2 cm en caso de dejar un margen de 5 mm (el aplicador más grande mide 3 cm) y tampoco se pueden tratar lesiones de más de 4 mm de Breslow ya que la dosis en profundidad alcanza un máximo de 5 mm. Para lesiones que superen estas dimensiones se debería elegir otra técnica más adecuada. La superficie de la lesión además debe ser plana o al menos depresible por compresión, ya que la superficie del aplicador es rígida y necesita mantenerse completamente en contacto con toda la lesión a tratar sin dejar aire entre ambas superficies.

Este estudio se llevó a cabo de manera secuencial. Inicialmente se incluyeron 20 pacientes con 37 lesiones que se trataron a 36,6 Gy (6 fracciones de 6,1 Gy), dosis resultante del cálculo teórico de la efectividad radiobiológica (RBE) tomando como referencia la dosis biológica efectiva (BED) utilizada en la HDR-BT con los aplicadores Valencia (BED=71,4-78,8 según α/β 10-8) por sus

excelentes resultados en eficacia y cosmesis. Teniendo en cuenta que los fotones de la BTE tienen menos energía que los de la BT con Ir-192 y que una menor energía conlleva una mayor RBE, teóricamente una dosis menor debería obtener resultados clínicos similares. Así, si la RBE de Esteya = 1,15, 7/1,15 = 6,1 Gy/fracción. De este cálculo teórico obtenemos la dosis de 36,6 Gy (6 x 6,1 Gy). Durante los 6 primeros meses de seguimiento de este primer grupo de tratamiento detectamos dos casos de recurrencia (10% de los pacientes), uno a los 3 y otro a los 6 meses tras la BTE. Debido a este porcentaje no admisible de respuestas parciales decidimos incluir un segundo grupo de tratamiento de 20 pacientes, en este caso con 23 lesiones. Este segundo grupo fue tratado con una dosis total de 42 Gy (6 fracciones de 7 Gy). Esta dosis es ligeramente superior a la del primer grupo y fue tomada por equivalencia a la utilizada en la HDR-BT con los aplicadores Valencia (sin el cálculo de la dosis equivalente). Entre los dos grupos se trataron a 40 pacientes con 60 CBCs.

El margen lateral propuesto para el estudio fue de 5 mm tras la revisión de la literatura, en la que encontramos tasas altas de RC utilizando márgenes entre 5-10 mm[82,36]. Debido a que el tratamiento con Esteya es más preciso que con otros equipos de BT y a que usamos la dermatoscopia para la delimitación del margen lateral, decidimos elegir el margen más estrecho posible (5 mm) e irradiar así menor cantidad de tejido sano circundante.

La edad media de los pacientes fue elevada (superior a 70 años) como debe corresponder a sujetos que van a recibir tratamiento ionizante, con el fin de evitar la aparición de segundas

neoplasias a largo plazo. Desgraciadamente, esto también conlleva una mayor pérdida en el seguimiento a largo plazo de los pacientes, que fallecen o dejan de acudir a las consultas por otros motivos no relacionados con la enfermedad. De entre las características basales de los pacientes destacan el alto porcentaje de cardiopatía y de tratamiento antitrombótico (casi el 19%). También destacar que más de la mitad de los pacientes corresponde a un fototipo III. Estas características basales están relacionadas con el hecho de tratarse de sujetos caucásicos españoles de edad avanzada, como corresponde a la mayoría de la población visitada en las consultas de dermatología con CCNM.

La mayoría de las lesiones estaban localizadas en cabeza y cuello, tenía diámetros comprendidos entre 8 y 20 mm, profundidades medias de 1,44 mm con HP y 1,23 mm con ECAF y la inmensa mayoría correspondían a estadios T1 de la AJCC. Estas características de las lesiones tratadas también son superponibles al grueso de CBCs que llegan a la consulta para tratamiento.

Dentro de los parámetros usados en el tratamiento hay que destacar que los aplicadores más usados fueron por orden de frecuencia los de diámetros de 25, 30 y 20 mm, lo que significa que el diámetro de la lesión por orden de frecuencia estaba comprendido entre 11-15, 16-20 y 6-10 mm. Por otra parte, la dosis en profundidad más utilizada con mucha diferencia (más del 95% de los casos) fue de 3 mm. El tiempo de tratamiento depende de estas dos variables y es calculado directamente por el equipo, aunque en todos los casos varía entre 2 y 3 minutos, por lo que siempre es corto.

Sabemos que pautas de tratamiento con mayor fraccionamiento suponen una mejor tolerancia por parte del paciente y un mejor resultado cosmético, pero a la vez suponen un mayor número de tratamientos y por tanto de visitas al centro sanitario. Asumiendo que tratamos a pacientes de edad avanzada con dificultades para el desplazamiento y que la dosis por fracción recibida en la superficie cutánea debe de ser inferior a 10 Gy (dosis tolerada), decidimos realizar seis fracciones en todos los casos, en contraposición con otros autores que realizan un mayor fraccionamiento (en general 8 fracciones).

La eficacia del tratamiento está analizada en los capítulos 3, 4 y 5 en función del tiempo de seguimiento que se había alcanzado en cada momento (6 meses, 1 año y 2 años respectivamente). En el capítulo 3 se muestran únicamente los datos a 6 meses del segundo grupo de tratamiento con 23 lesiones tratadas a 42 Gy. En el capítulo 4 se muestran los resultados de ambos grupos de tratamiento con las distintas dosis con seguimiento a un año, aunque sólo se analiza una lesión por paciente (lesión principal de mayor tamaño), con un total de 40 pacientes y 40 lesiones (20 por brazo de tratamiento). En el capítulo 5 se analizan los resultados a los 2 años de seguimiento (largo plazo). Debido a la alta tasa de pérdidas en el seguimiento y por tanto al bajo número de pacientes que alcanzar la visita de los dos años, decidimos incluir todas las lesiones tratadas durante este periodo que alcanzaron los dos años de seguimiento. En total 44 CBCs correspondientes a 26 pacientes fueron analizados.

Encontramos 3 respuestas parciales de todos los tumores tratados; dos casos de persistencia tumoral tratados con dosis de 36,6 Gy, uno detectado a los 3 meses y otro a los 6 meses tras el tratamiento. El tercer caso corresponde a una recidiva tumoral en un paciente del grupo 2 tratado a 42 Gy y detectado al año de tratamiento. Si medimos la eficacia en función de la dosis utilizada observamos una RC en el 90% de los pacientes tratados a 36,6 Gy y del 95% a 42 Gy, aunque esta diferencia no resulta estadísticamente significativa. Si en cambio medimos la eficacia global teniendo solamente en cuenta a aquellos pacientes que alcanzan un seguimiento de dos años encontramos una tasa de RC del 95,5 %, similar aunque ligeramente inferior a otras series publicadas.

Los tres casos de respuesta parciales fueron nuevamente analizados en busca de posibles fallos en el protocolo. Se revisó la historia clínica de los tres pacientes y todas las pruebas y tratamientos realizados. No encontramos errores en la inclusión de pacientes, medidas histopatológicas ni ecográficas ni en las pautas de tratamiento que justificaran el fallo en el tratamiento. Revisando la literatura sobre la valoración de la respuesta a la RT en el CCNM, nos llama la atención la falta de criterios al respecto. Sabemos que la mayoría de neoplasias sometidas a RT no desaparecen de forma rápida tras finalizar el tratamiento, pudiendo perdurar restos tumorales inactivos durante meses incluso años antes de reabsorberse[11]. Esto conlleva a una discordancia clínico-patológica, ya que podrían observarse restos tumorales pero que éstos no fueran viables por su incapacidad de

entrar en ciclo. Se ha determinado que una valoración de la respuesta definitiva es prematura antes de los 3 meses[11], y que es aconsejable adoptar actitudes prudentes y no abusar de biopsias repetidas o cirugías tempranas[12,13]. Pero más allá de estas afirmaciones no está determinado el momento a partir del cual biopsiar o extirpar la lesión en caso de duda sobre una posible recidiva tumoral. Durante nuestra experiencia, el primer caso de duda lo biopsiamos a los 3 meses. En la histología se observaron pequeños nidos tumorales con células poco cohesionadas y presencia de un infiltrado inflamatorio peri e intratumoral. Aunque el diagnóstico patológico fue de persistencia de CBC, probablemente estos restos tumorales fueran inactivos y todavía no habrían tenido tiempo de desaparecer tras el tratamiento. Por este motivo y a partir de este momento decidimos esperar como mínimo 6 meses antes de biopsiar una lesión clínicamente sospechosa.

La toxicidad aguda del tratamiento la hemos observado en todos los casos a partir de la cuarta dosis, y de manera más intensa entre la segunda y la sexta semana tras el tratamiento. En todos los casos ha sido leve (G1-G2), sin observarse en ningún caso toxicidad de grado G3 o G4. Los efectos más frecuentes han sido la aparición de eritema, ulceración y alopecia, en general tolerables por ser poco molestos para el paciente y fácilmente manejables con medidas básicas (fotoprotección, hidratación y oclusión). Si comparamos la toxicidad en función de la dosis total no encontramos diferencias estadísticamente significativas entre ambos grupos de tratamiento. Sí que hemos encontrado mayor

frecuencia de ulceración en aquellos casos de CBC nodular y aquellos localizados en tronco y extremidades comparados con cabeza y cuello (resultando este último grupo estadísticamente significativo).

Los resultados cosméticos a los dos años tras el tratamiento han sido excelentes en la mayoría de los casos (88,6%) y buenos en el resto. No se ha observado ninguna alteración cutánea en el 61% del grupo 1 y en el 55% del grupo 2. En el resto de casos la alteración ha sido leve. Destacan por orden de frecuencia las alteraciones de la pigmentación (habitualmente hipopigmentación central con hiperpigmentación periférica) en el 66,7% de los casos, la alopecia en casi el 19% y las telangiectasias en un 9,1%. Hemos observado una mejor cosmesis en aquellos casos localizados en cabeza y cuello, aunque esta diferencia no ha resultado estadísticamente significativa probablemente por un "n" bajo. De estos efectos a largo plazo, la alopecia es un fenómeno previsible si se tratan zonas pilosas y por tanto evitable, por lo que se debería seleccionar otro tipo de tratamiento si la alopecia fuera *a priori* un efecto indeseable.

Somos conscientes que nuestro trabajo tiene una serie de limitaciones que se deben de tener en cuenta a la hora de interpretar los resultados:

1- Se trata de un estudio descriptivo que analiza el efecto de la BTE en pacientes consecutivos. Nuestro trabajo por lo tanto carece de un grupo control en el que se haya aplicado la terapia estándar (cirugía).

2- Por su naturaleza de estudio piloto, el número de lesiones incluidas en el presente estudio es bajo. El pequeño tamaño muestral así como el hecho de que las variables no se distribuyeran de forma normal en la muestra de estudio nos obligó a emplear tests estadísticos no paramétricos, limitando la potencia de las observaciones.

3- El seguimiento de los pacientes a dos años sigue siendo insuficiente ya que, aunque la mayoría de recidivas aparezcan en este intervalo de tiempo su pueden encontrar recurrencias tras 5-10 años de tratamiento, por lo que el seguimiento debería ser más prolongado[8].

4- Por último, destacar que la avanzada edad de los pacientes y sus múltiples comorbilidades conllevan un porcentaje importante de pérdidas durante el seguimiento, disminuyendo el número de casos evaluables al final del estudio.

Por todo ello consideramos que sería conveniente diseñar un estudio prospectivo aleatorizado en el que se incluyera un mayor número de pacientes (teniendo en cuenta la pérdida de pacientes durante el seguimiento por comorbilidad) y cuyo seguimiento se prolongara durante, al menos, 5 años.

Como hemos expuesto, la BTE tiene ventajas respecto a otros tipos de BT; es un tratamiento rápido, no doloroso y cómodo para el paciente. No utiliza isótopos radioactivos (y por tanto no precisa sistema de almacenamiento). Tampoco requiere el uso de

moldes ni bolus, y el uso de aplicadores estandarizados simplifica mucho el procedimiento. Tiene una menor penumbra (caída de dosis lateral más acusada) y por tanto se recibe menor dosis en periferia, irradiando menor tejido sano circundante. Es por ello que el tratamiento es más preciso y por tanto se podrían usar márgenes más estrechos. Por último, el aparato es pequeño, móvil y requiere menos blindaje. Dentro de los sistemas actualmente comercializados de BTE, Esteya® destaca en que su fuente es más estable, tiene una mejor protección, el procedimiento es más sencillo y la sobredosis en la superficie cutánea es más reducida.

Con los resultados expuestos y la información que tenemos hoy en día sobre la BTE en el CBC podemos aventurar posibles indicaciones de este tipo de terapia. Sería de elección en sujetos de edad avanzada, lesiones múltiples, contraindicación para la cirugía por motivos médicos (múltiples comorbilidades) o quirúrgicos (tratamiento anticoagulante o antiagregante), por rechazo a la cirugía o comodidad del paciente o por ser esperable un resultado cosmético superior a la cirugía en aquellos casos en los que ésta suponga un mayor desfiguramiento.

Todavía sigue habiendo debate en el posicionamiento de esta nueva técnica para el tratamiento del CCNM. Ha sido criticado el elevado reembolso por parte del sistema americano Medicare y la sobreutilización que podría suponer en algunos casos. Las mayores críticas han ido dirigidas básicamente al poco seguimiento de los estudios publicados hasta la fecha y a la ausencia de estudios randomizados. Estas dudas en el conocimiento quedarían solventadas en caso de realizarse

estudios de calidad, prospectivos, comparativos y randomizados con cirugía en los que se incluyeran un número de casos elevado y se realizara un seguimiento a largo plazo. La elección de un tratamiento u otro depende de cada facultativo y se basa en el uso de guías de práctica clínica. El reembolso de cada técnica utilizada depende de los diferentes sistemas de salud que tiene cada país y su legislación. Es por ello que en muchos países de Europa no supondría un problema.

El sistema sanitario en nuestro país es público y universal, por lo que el reembolso no supone un problema o una ventaja. El médico que mejor conoce la historia natural del CBC y que se encarga de su manejo es el dermatólogo. El tratamiento de esta patología en cada caso estará determinado por las guías de práctica clínica, los medios disponibles en cada centro, la experiencia personal del profesional y las preferencias del paciente. El coste del los tratamientos no deberían suponer una barrera si es la mejor opción para el paciente. En términos generales el coste de la RT es mayor que el de la cirugía para el tratamiento del CBC. Además, el número de visitas al centro sanitario es inferior en el caso de optar por la cirugía. Este desequilibrio en el coste del tratamiento es menos acusado en el caso de la cirugía de Mohs, donde el tiempo de quirófano, el aumento de la plantilla, la necesidad de un patólogo y el tiempo de trabajo en el laboratorio incrementan considerablemente el coste de la técnica. Otra desventaja de la RT desde el punto de vista dermatológico es la necesidad derivar al paciente a otro servicio por no poder realizar él mismo el tratamiento en un tumor cuyo

tratamiento siempre ha realizado el dermatólogo. Como hemos comentado, esta barrera sería menos rígida en el caso de mantener una buena comunicación y participación de ambos servicios en el proceso.

Hasta la fecha, como se ha expuesto, existen publicadas pocas series de pacientes tratados con BTE. Hasta donde llega nuestro conocimiento, han sido publicadas series de 4 grupos estadounidenses[9596,97,98] que tratan CCNM con un predominio del CBC (entre 147 y 275 CBCs por grupo) con Xoft-EBT®. Todos utilizan la misma pauta de tratamiento, 40 Gy divididos en 8 fracciones de 5 Gy. Las tasas de RC son iguales o superiores al 98% con seguimientos inferiores a dos años (entre 12 y 16 meses) y con buenos resultados cosméticos. No hemos encontrado datos clínicos de pacientes tratados con Intrabeam® ni otras series de pacientes tratados con Esteya®.

CONCLUSIONES

CONCLUSIONES

Depth determination of skin cancers treated with superficial brachytherapy: ultrasound vs. histopathology

Tras la comparación de la medida de profundidad tumoral usando dos técnicas distintas (biopsia punch y ECAF) no hemos encontrado una correlación estadísticamente significativa entre el uso de ambas técnicas. Seguimos pensando que aunque la ecografía no sustituye a la biopsia, puede ser de utilidad para el diagnóstico de invasividad y determinación de márgenes previa a un tratamiento con radioterapia. Más estudios con un mayor tamaño muestral serían necesarios para poder encontrar diferencias estadísticamente significativas. Probablemente, la introducción de mejoras tecnológicas ecográficas y de sondas de mayor resolución, ayuden también a equiparar estas dos técnicas en la determinación de márgenes.

Dermoscopy margin delineation in radiotherapy planning for superficial or nodular basal cell carcinoma

La dermatoscopia ha demostrado ser de utilidad para delimitar el margen lateral del tumor con la intención de tratar toda la lesión subclínica preservando el mayor tejido sano posible y por tanto la funcionalidad. No hemos encontrado ningún caso de recidiva en el margen lateral. El uso de la dermatoscopia en RT puede ser de utilidad en el diagnóstico del tumor, en la delimitación del margen lateral y en el seguimiento para poder detectar recidivas de manera temprana.

Efficacy and safety of electronic brachytherapy for superficial and nodular basal cell carcinoma

Electronic brachytherapy for superficial and nodular basal cell carcinoma: a report of two prospective pilot trials using different doses

2 year results of electronic brachytherapy for basal cell carcinoma

La BTE ha demostrado eficacia en el tratamiento del CBC superficial y nodular con tasas de respuesta completa superiores al 95% con un seguimiento a dos años, usando dosis de 36,6 o 42

Gy en 6 fracciones (2 fracciones semanales durante 3 semanas consecutivas).

La toxicidad ha sido leve en todos los casos (G1-G2). Las manifestaciones más frecuentes han sido eritema, ulceración y alopecia. Aparece a partir de la cuarta sesión y es máxima entre la segunda y sexta semanas tras el tratamiento. En todos los casos se ha resuelto antes de los tres meses, ha sido bien tolerada por el paciente y no ha requerido la toma de ninguna medida ni procedimiento extraordinario.

Los resultados cosméticos han sido buenos o excelentes en todos los casos. Las alteraciones permanentes presentadas más comunes han sido por orden de frecuencia: alteraciones en la pigmentación, telangiectasias y alopecia. Se han observado peores resultados cosméticos en localizaciones distintas de cabeza y cuello y en subtipos nodulares.

Por todo ello la BTE ha demostrado su utilidad como herramienta en el tratamiento del CBC superficial y nodular.

Este es un estudio piloto con un número limitado de pacientes y un seguimiento a medio plazo. Serían necesarios más estudios con un mayor tamaño muestral, seguimientos más largos y en comparación con el tratamiento estándar (la cirugía) u otros tipo de tratamiento. A partir del presente estudio se ha diseñado un estudio multicéntrico, prospectivo, comparativo y randomizado entre BTE y cirugía en el tratamiento del CBC. Se han propuesto 6 equipos europeos de referencia (Jean Jacques Grob en Marsella,

Katty Peris en Roma, Eggert Stockfleth en Bochum, John Lear en Manchester, Reinhard Dummer en Zürich y Rafael Botella en Valencia), con la intención de incluir 300 pacientes, 150 pacientes por rama de tratamiento.

A pesar de la elevada incidencia del CBC y del gasto sanitario que supone existen muy pocos estudios prospectivos de calidad que evalúen y comparen las distintas opciones terapéuticas. Es necesario un esfuerzo por parte de la comunidad científica y especialmente de los dermatólogos para que nuestra práctica clínica asiente sobre los principios de la medicina basada en la evidencia.

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