White Paper

Esteya® Electronic Brachytherapy

A Dedicated Solution for Improving Skin Cancer Patient Care

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Executive Summary

- The global incidence of skin cancer is extremely high, an estimated 4 million new lesions arise every year in the USA alone
- The incidence rate has increased at roughly 3-6% per year and continues to rise as the population ages
- Skin cancer is a disease of the elderly, more than half of new patients are 65 years or older
- About half of the skin cancer patients will develop a new unrelated primary lesion within 5 years after the initial diagnosis
- Lesions mainly affect cosmetically sensitive areas due to sun exposure such as the face, nose, eyelids, ears, scalp and lips
- Lesion size is usually less than 20 millimeter in diameter and a few millimeters thick (<5-mm)
- Skin cancer and its treatment-related side effects can have a dramatic impact on self-image and body image, causing anxiety and depression
- According to the American NCCN guidelines, surgery or radiation therapy are the first line treatment options; topical therapies should be reserved for those patients where surgery or radiation therapy is contraindicated or impractical
- Radiation therapy as primary therapy can result in excellent control rates, cosmesis, and quality of life
- Currently radiotherapy is being underutilized; less than 2% of skin cancer patients in the USA receive radiotherapy as primary therapy
- When multidisciplinary teams include radiation oncologists in addition to dermatologists in the treatment of non-melanoma skin cancer (NMSC) patients, radiotherapy is recommended significantly more often in approximately 20% of cases
- Brachytherapy offers the most conformal radiation therapy option to patients
- Electronic brachytherapy involves the placement of a high dose rate (HDR) X-ray source directly in a skin applicator close to surface, thereby combining the benefits of brachytherapy with those of low energy X-ray radiotherapy
- The Esteya® electronic brachytherapy system is specifically designed for surface brachytherapy procedures
- Compared to existing brachytherapy modalities, Esteya electronic brachytherapy provides a more homogeneous dose distribution within the area to be treated
- Robust and simple machine QA and reliable X-ray source minimize downtime and improve user-experience and clinic efficiency
- Several safety features, based on Elekta's many years of experience with brachytherapy, were implemented in this treatment system
- With the tungsten shielding, unnecessary collateral radiation damage to healthy tissue is minimized
- The Esteya electronic brachytherapy system is engineered for improved patient comfort for treatment via comfortable, easy and quick surface applicator positioning, short treatment times and an aesthetically pleasing design
- Electronic brachytherapy allows expansion of advanced skin cancer radiation therapy to be delivered outside of radiation oncology centers due to minimal shielding requirements and mobile machine solutions

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Introduction Non-melanoma Skin Cancer

Over the past decade, an alarming increase in incidence rate of skin cancer has been reported worldwide, especially in countries with a predominantly Caucasian population[1, 2]. With 4 million new lesions per year, skin cancer is the most common malignancy and affects 2-3 million people each year in the United States[3, 4]. Skin cancer can be categorized into 2 major groups: melanoma and non-melanoma skin cancers (NMSC). The latter group consists primarily of basal cell carcinomas (BCC) and squamous cell carcinomas (SCC).

BCC is a slow-growing, locally invasive epidermal tumor with a metastatic rate of <0.1%[5, 6]. It accounts for approximately 75% of all skin cancers (reviewed by[7]).

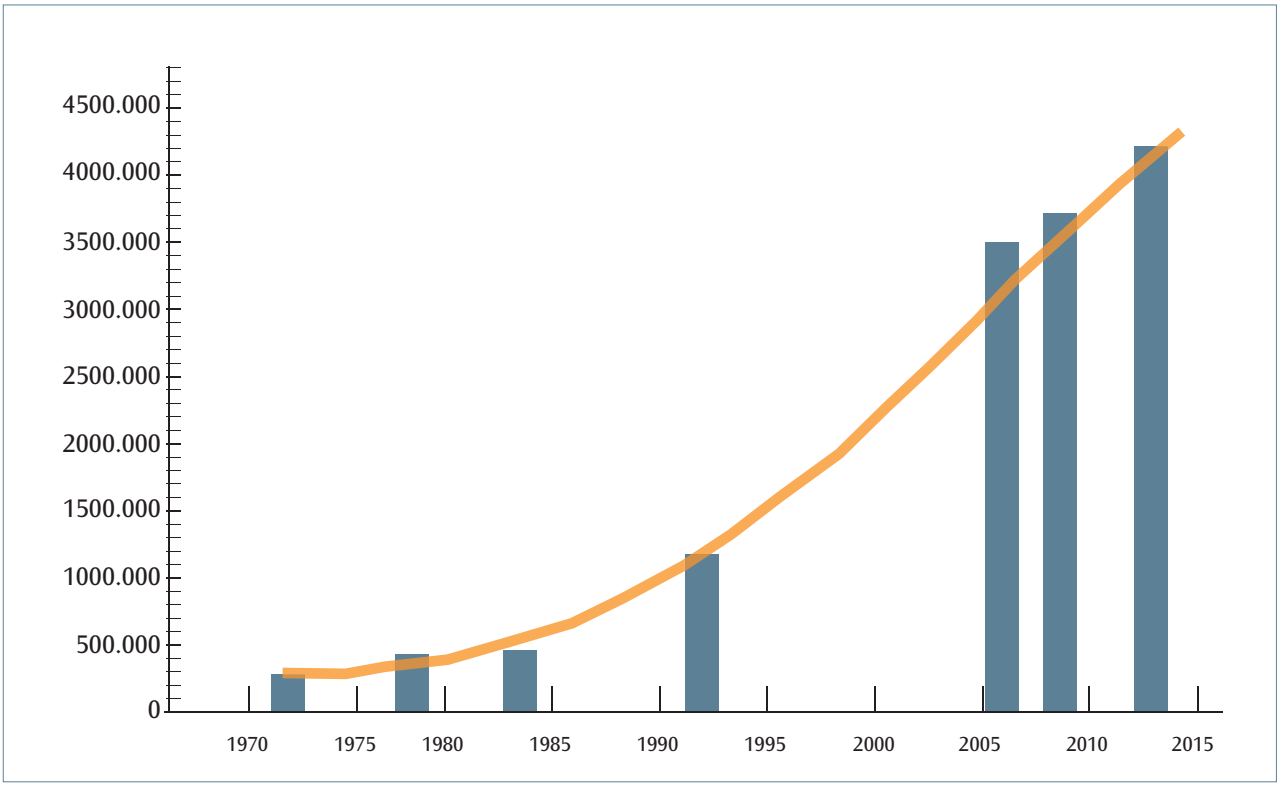
Cutaneous SCC arises from dysplastic epidermal keratinocytes[8]. Approximately 20% of all skin cancers consists of this type[6]. In contrast to BCC, SCC has a low but significant recognized rate of metastasis (0.3–3.7%), the majority of which occur from within a subgroup of high-risk SCC[7].

BCCs and SCCs tend to occur in areas of chronic sun exposure and therefore a large proportion, around 80%, occur on the head and neck[9,10]. Typically, NMSCs affect quality of life but not survival[11]. Although rarely metastatic, basal and squamous cell cancers can produce substantial local destruction along with disfigurement due to the disease itself or the treatment, and may involve extensive areas of underlying soft tissue, cartilage, and bone[12].

Picture 1 and 2: Typical examples of BCC of the nose and ear

NMSC: Magnitude of the Problem

In the USA, NMSC has become an epidemic[1]. Rates have increased markedly and are expected to keep rising with an estimated 3-6% per year, with the largest absolute increase in the most common type of skin cancer, basal cell carcinoma[4]. NMSC is by far the most common human malignancy, in fact, the incidence of NMSC exceeds the cumulative incidence of all other cancers combined[13]. Nearly 30% of Caucasians living in areas of exposure to high ultraviolet radiation will develop a NMSC in their lifetime[14].



Picture 3: Published NMSC incidences per year in the USA [1,3,13,14,15,16]

Ultraviolet light exposure is the principal pathogenic environmental factor for development of NMSC[17]. In the absence of marked changes in current ultraviolet radiation exposure, incidence will probably continue to grow after 2015[18].

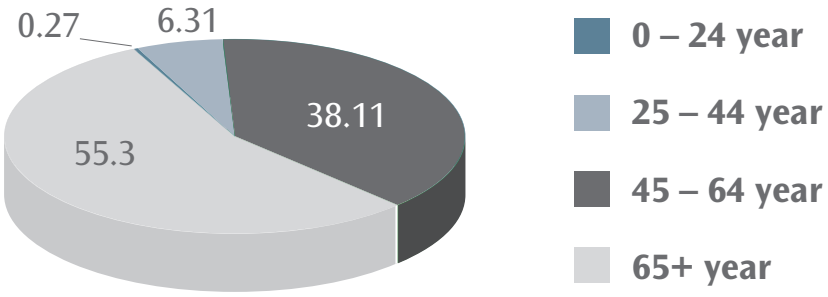
Key Messages

1. The global incidence of skin cancer is extremely high, an estimated 4 million new lesions arise every year in the USA alone.
2. The incidence rate has increased at roughly 3-6% per year and continues to rise as the population ages.

The Typical NMSC Patient

Between 40 and 50 percent of Americans who live to age 65 will have either BCC or SCC at least once[19]. According to a study in 2009 nearly 50% of people routinely treated for BCC developed multiple primary BCCs during 10 years of observation[20]. This is consistent with earlier reports showing that 43% of people affected by BCC developed a subsequent BCC within 4.5 years of active surveillance in the same population[21] and those of a meta-analysis of seven independent studies which showed a mean 3 year risk of BCC of 44% after an initial diagnosis of BCC in North America[22].

Historically, basal cell carcinomas were found almost entirely in middle-aged or older people. However, it is more recently also being reported in younger people, likely attributed to increased and prolonged sun exposure[23]. Regardless, greater than 90% of newly diagnosed patients are over 45 years of age and more than half are at least 65 years or older[24].



Picture 4: Age distribution of NMSC in the USA[24]

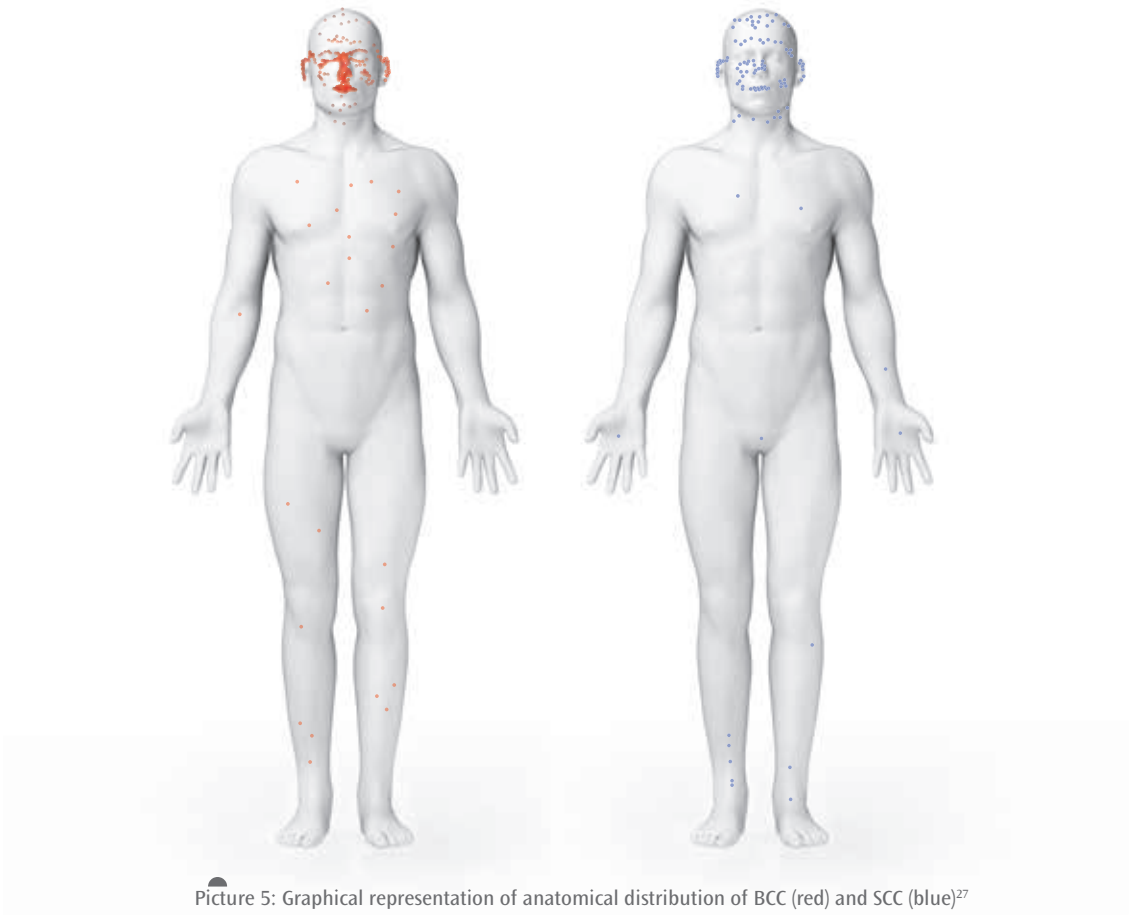
Since the population is aging and skin cancer incidence is on the rise in the younger population, the age window of risk of developing new and multiple skin cancers is widening[23].

Key Messages

3. Skin cancer is a disease of the elderly, more than half of new patients are 65 years or older.
4. About half of the skin cancer patients will develop a new unrelated primary lesion within 5 years after the initial diagnosis.

The Lesion Characteristics

Over 80% of non-melanoma skin cancers occur in the head and neck region, especially the scalp, nose, eyelids, ears and lips[25, 26, 27]. The nose is the most common in this region representing about 30% of all lesions[27, 28].



Picture 5: Graphical representation of anatomical distribution of BCC (red) and SCC (blue)[27]

Since most skin cancers grow slowly and develop in regions of the body that are usually highly visible, tumors are usually detected early in their evolution. The majority (~90%) of lesions are small (<20 mm) and superficial[29-32]. Thickness is often confined to only a few millimeters but with time the tumor can extend along for example nerves or hair follicles, and deep invasion can occur[33-35].

Key Messages

5. Lesions mainly affect cosmetically sensitive areas due to sun exposure such as the face, nose, eyelids, ears, scalp and lips.
6. Lesion size is usually less than 20 millimeter in diameter and a few millimeters thick (<5-mm).

Skin Cancer Impact and Treatment Goals

Having a diagnosis of cancer can evoke many emotions within a person[36]. Although non-melanoma skin cancers are typically not fatal, they can potentially disrupt or destroy facial sensory structures such as the nose, eyes, ears and lips[37]. Skin cancer can have a dramatic impact on self-image and body image, causing anxiety and depression[38].

The location of the lesion is important, as treatment decisions and the consequential side effects for tumors that arise in cosmetically or functionally important areas may differ significantly to those that would be made for BCCs arising elsewhere[39]. Special attention must be paid to the location of the skin cancer on the face as there are many areas of functional and cosmetic importance for example the peri-ocular, peri-oral, and peri-nasal areas[39].

The treatment goals for NMSC are to remove the tumor and achieve a high cure rate, preserve the maximal amount of normal surrounding tissue for form and function, and provide an optimal cosmetic outcome[40, 41]. Given that BCC, contrary to other malignant neoplasms, is rarely responsible for patient's death, 5-year survival as an outcome measure is not justified. For that reason, in order to assess the efficacy of BCC treatment the local control rate during a 5-year follow-up period is preferred. Moreover, it is necessary to take cosmetic, functional, comfort and quality of life measures into account[42].

Skin Cancer Treatment Options

Treatment options include surgery, radiation therapy, and topical therapies such as 5-fluorouracil, imiquimod, photodynamic therapy (PDT) or cryotherapy. According to the American NCCN guidelines for skin cancer treatment the topical therapies should be reserved for those patients where surgery or radiation therapy is contraindicated or impractical[43].

The treatment approach must be individualized based on specific risk factors and patient characteristics in order to achieve the most acceptable cosmetic and functional outcome[44]. Factors such as cosmetic outcome, patient age, comorbidities, costs and treatment time, wound care and patient preference should all be taken into consideration for patient selection in order to achieve optimal overall results[45,46].

Key Messages

7. **Skin cancer and its treatment-related side effects can have a dramatic impact on self-image and body image, causing anxiety and depression.**
8. **According to the American NCCN guidelines surgery or radiation therapy are the first line treatment options; topical therapies should be reserved for those patients where surgery or radiation therapy is contraindicated or impractical.**

Radiation Therapy for NMSC

Radiotherapy has been used for the treatment of skin cancers since 1899 and continues to be a highly effective and non-invasive alternative to surgery[11, 43, 47].

According to the NCCN radiation therapy as primary therapy can result in very good cure rates and excellent cosmesis when applied properly, especially for the majority of small (up to 20 mm) and relatively shallow lesions[11, 43]. Radiotherapy can also be delivered adjuvantly after surgery to improve local control rates in cases of higher risk pathologic features such as positive margins, or perineural invasion or in recurrent lesions when repeat surgery may be rendered more difficult[43].

Potential reasons to select radiotherapy instead of surgery, or in combination with surgery for a patient with a non-melanoma skin cancer are suggested in the following table:

Patient related	Tumor related	Anatomical location related
Elderly/fragile, not able to undergo surgery	Perineural invasion	Cosmetically or functionally sensitive areas (e.g. nose, ears, lips eyelids)
Use of blood thinners	Positive margins after surgery	
High risk of post-operative wound complications (i.e; diabetes, smokers, peripheral vascular disease)	Recurrent tumors after surgical excision	
Multiple cancerous lesions	Moderately or poorly differentiated tumors*	
Refusal of surgery		
Prone to keloid formation	Advanced lesions where complex surgery (graft or local flap) under general anesthesia is required	

Table 1: Reasons to select (adjuvant) radiotherapy for NMSC patients[11, 30, 48, 49, 50, 51]

The choice for radiotherapy for a particular BCC or SCC depends less on the likelihood of tumor control, which are excellent with surgery and radiation therapy, than on the anticipated cosmetic and functional results. Currently radiotherapy is being used in only a small percentage of patients in the USA (1-2%) and Europe (1-8%)[52, 53] (Elekta data on file). According to the American Osteopathic College of Dermatology, radiation therapy as treatment choice for skin cancer is used less often than it should be[54]. The reason that radiation therapy is underutilized therapy is multi-factorial; however, a significant influence is that dermatologists are often the gatekeepers for identifying and treating the vast majority of skin cancer patients[49]. Data suggest that when multidisciplinary teams including dermatologists and radiation oncologists are involved in the treatment of NMSC patients that the rate of radiotherapy utilization increases approximately 20%[55].

In addition to an excellent cosmetic and functional outcome, radiation therapy has the advantage that it is non-invasive and thus does not require any anesthesia or analgesia, and that patients can continue with anticoagulants[56]. It has the great advantage of avoiding reconstructive procedures and eliminating the need for skin grafts or skin flaps[57], for example on critical sites such as around the lacrimal system and on the nose and ears[49]. This results in less need for bandaging and wound care. Radiotherapy does not limit physical activity during patient recovery—a frequent requirement following surgery, which often can lead to joint pain in patients with arthritis or other bone/joint abnormalities[50]. Radiation allows the patient to continue taking prescribed medications, and poses minimal long-term side effects. Radiation treatment is painless and may be preferred in both elderly and debilitated patients[40, 58].

Key Messages

9. Radiation therapy as primary therapy can result in excellent control rates, cosmesis, and quality of life.
10. Currently radiotherapy is being underutilized; less than 2% of skin cancer patients in the USA receive RT as primary therapy.
11. When multidisciplinary teams include radiation oncologists in addition to dermatologists in the treatment of NMSC patients, radiotherapy is recommended significantly more often in approximately 20% of cases.

Brachytherapy for NMSC

Several therapeutic modalities exist to deliver radiotherapy for skin cancer. Radiation therapy can be applied using teletherapy, also named external beam radiation treatment, in which an external source of radiation generates photons or electrons aimed from a distance at the target lesion on the body. Alternatively, brachytherapy involves accurate placement of the radiation source directly onto or into the target tissues using specialized applicators.

Several clinical considerations are required from the radiation oncologist when selecting the specific RT treatment modality. Although external beam therapy and surface brachytherapy can be used interchangeably in some situations, there are cases where there are clearly defined advantages of High Dose Rate (HDR) brachytherapy. Brachytherapy, derived from the Greek root "brachos", or "at short distance", enables the most conformal radiation therapy to be delivered to the tumor, while minimizing collateral irradiation of adjacent healthy tissue[59, 60]. In selected cases, however, electrons may be indicated such as larger diameter or thicker lesions and treatment of irregular surfaces where placement of a flat applicator may be rendered more challenging[61].

Picture 6: Graphical representation of electronic brachytherapy source placed on skin tumor

The most experience with HDR brachytherapy for skin lesions is with a 6 to 8 fraction course (one per day, at least 48 hours interval) for a total dose around 40-48 Gy delivered over the course of 2-4 weeks[44, 62]. For comparison, the external beam treatment equivalent is to deliver 2 Gy per fraction (once per day, 5 days a week) with a total treatment time of 4 to 6 weeks[63]. The overall shortened treatment time, targeted delivery and straightforward patient setup procedures makes brachytherapy an attractive treatment methodology, especially when the average age (70+ years) of the skin cancer patient population is considered[63].

Since its discovery, there have been significant advances that have revolutionized radiation therapy technologies via two primary goals. First, by conforming the dose distribution more closely to the target volume, dose escalation becomes feasible. A higher dose to the tumor could result in an improved probability of local tumor control. Second, by conforming the dose more tightly to the target volume, normal tissues may be spared of radiation exposure, decreasing morbidity[64]. Brachytherapy as a modality allows both of these tenets to be maximally addressed.

Recent developments in the field of radiotherapy for skin cancer have included the introduction of electronic brachytherapy. Electronic brachytherapy involves the placement of HDR X-ray sources directly in skin applicators combining the benefits of brachytherapy (accurate placement, conformal delivery and rapid dose fall off) with the reduced shielding requirements and targeted energy of low energy X-rays. This offers an even more refined approach to treating skin cancer and further improves conformity of radiation dose to the skin lesion yet sparing the unnecessary irradiation of normal tissue so reducing toxicity[65]. The better dose distribution and more accurate dose delivery should ultimately yield better outcomes for patients.

Key Messages

12. **Brachytherapy offers the most conformal radiation therapy option to patients.**
13. **Electronic brachytherapy involves the placement of a HDR X-ray source directly in a skin applicator close to surface, thereby combining the benefits of brachytherapy with those of low energy X-ray radiotherapy.**

Esteya® Electronic Brachytherapy System at a Glance

The Esteya® electronic brachytherapy system is specially designed for surface brachytherapy procedures. The Esteya electronic brachytherapy system consists of a treatment unit, a user interface with planning software and a treatment control panel. The treatment unit is a moveable unit with four swiveling wheels and has the applicator that holds the X-ray source that is connected via an adjustable positioning arm. This arm has freedom of movement which allows for accurate positioning of the applicator on virtually any body location. The treatment unit in turn delivers the radiation dose conforming to the treatment plan.

Picture 7: Laptop with treatment planning system

Picture 8: Treatment control panel

Picture 9: Esteya treatment unit

The output field of the X-ray source is limited to the tumor size using a surface applicator that functions as a radiation dose collimator. There are different sizes of surface applicators available to fit to the desired target size and required margin. Before treatment the X-ray source is inserted in the surface applicator.

Picture 10: Automated applicator detection reduces possibility of human errors

Using the graphical user interface, treatment patient and lesion date can be entered and treatment can be planned. The treatment unit delivers treatment based on the customized treatment plan.

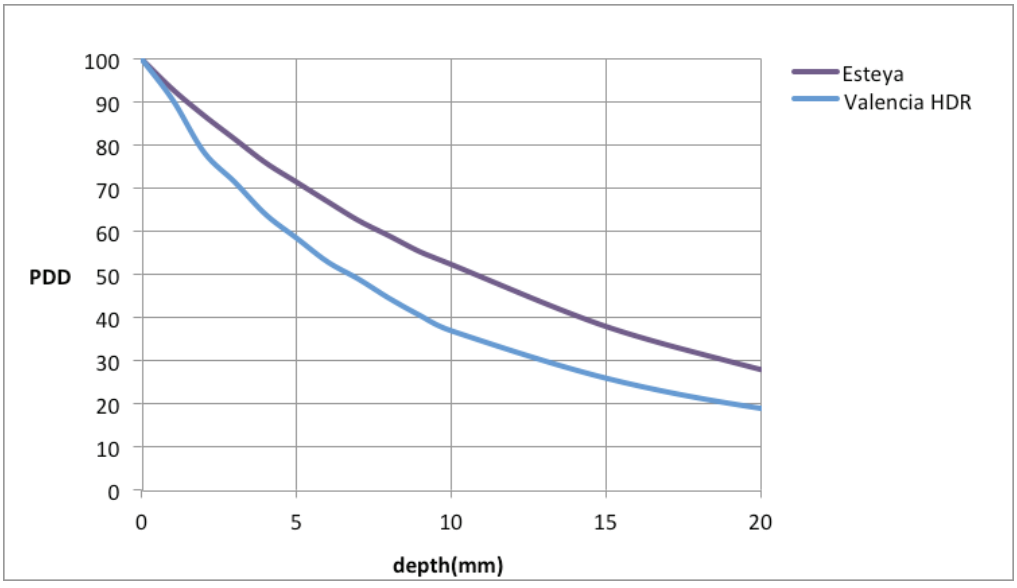
Key Messages

14. **The Esteya electronic brachytherapy system is specifically designed for surface brachytherapy procedures.**

Esteya® Electronic Brachytherapy Clinical Benefits

The depth of penetration of X-rays into tissue is determined by the accelerating potential, applied filtration and the source to skin distance (SSD).

The Esteya electronic brachytherapy system was designed such that the ideal percentage dose depth for the majority of skin lesions would be the delivery of 80% of the dose at the surface to a depth of 3 millimeters. As a result, the inherent typical overdose to more superficial tissue would be minimized, while dose drop off would be sufficient to minimize potential damage to deeper structures. In addition at a depth of 5 mm still 70% of the surface dose would be delivered enabling a hypofractionated schedule with the electronic brachytherapy equivalent of isotope based Ir-192 HDR brachytherapy without the dose at the surface exceeding 10 Gy. Ten Gy has been published to be the threshold that some permanent side effects of radiation occur such as epilation, radiation induced telangiectasia and dermal atrophy[66]. For certain clinical situations such as larger lesion size or those adjacent to sensitive critical structures, alternative fractionation schedules with an increased number of fractions and lower dose per fraction may be preferred to decrease late effects.



Picture 11: Relation between dose fall off and depth in tissue for the 30 mm Esteya surface applicator and the Ir192-Valencia 30 mm applicator.

With the above mentioned criteria the percentage dose depth curve of the Esteya electronic brachytherapy unit resembles the PDD curve of Ir-192 brachytherapy with the Valencia applicator, but with a more homogeneous dose distribution within the area to be treated.

The Esteya electronic brachytherapy applicator is designed in such a way that leakage of radiation to the environment is minimized. With the tungsten applicator shielding in combination with an extremely sharp penumbra the amount of collateral radiation exposure to healthy tissue is further minimized, thereby further reducing risks of toxic side effects.

Key Messages

15. **Compared to existing brachytherapy modalities Esteya electronic brachytherapy provides a more homogeneous dose distribution within the area to be treated.**

Esteya® Electronic Brachytherapy Ease of Use

Esteya was designed for a user friendly and time efficient treatment delivery. The password protected user interface contains treatment planning and delivery software, thus there is no need for transfer of patient data which saves time and prevents loss of personal data.

The small X-ray source was constructed in such a way that it is stable and reliable, with a guaranteed lifespan of at least 4000 fractions. This reduces the downtime and risk of source malfunction during fraction delivery. Because of source robustness and stability of voltage and current a QA check of source output is only required once per day compared to other systems where the QA procedure must be repeated for every source, every patient, every lesion prior to delivery. The QA procedure only lasts 2 minutes, which further increases availability of the system for actual treatment delivery. All of these features translate to improved clinic efficiency and safety.

Key Messages

16. Robust and simple machine QA and reliable X-rays source minimize downtime and improve user-experience and clinic efficiency.

Esteya® Electronic Brachytherapy Safety

System safety was an important design criterion for the Esteya® electronic brachytherapy system.

Several safety features, based on Elekta's many years of experience with brachytherapy, were integrated into this novel treatment system. First of all, permissions to use specific functions such as approving a treatment plan or start of therapy can be restricted to specific users preventing unauthorized use. The intuitive patient data management software that contains options to enter pictures of patient and lesion helps prevent treatment of wrong sites, but also reduces risk of future re-irradiation of previously irradiated sites. Automated applicator detection assures that the correct applicator is in place before commencing treatment.

Built-in sensors continuously measure X-ray tube voltage, current and timing of a fraction thereby ensuring accurate dose delivery. The temperature of the applicator and temperature and flow of cooling fluid is also monitored and if it deviates from pre-defined margins the device will not deliver radiation. Audible and visual signals indicate when radiation is generated.

The treatment control panel contains treatment start interrupt and emergency stop buttons similar to conventional HDR systems. The skin applicator is fitted with tungsten shielding along the entire length of the applicator thereby limiting scatter radiation that is not aimed at the lesion. A biocompatible sterilizable and replaceable surface applicator cap helps prevent cross contamination between lesions and patients.

Key Messages

17. **Several safety features, based on Elekta's many years of experience with brachytherapy, were implemented in this treatment system.**
18. **With the tungsten shielding unnecessary collateral radiation damage to healthy tissue is minimized.**

Esteya® Electronic Brachytherapy Patient Comfort

When developing Esteya special emphasis was placed on the smooth aesthetically pleasing design. This design in combination with the low shielding requirements and mobility capability make it possible to use the device virtually anywhere patients are seen and help mitigate patient anxiety when being treated with the Esteya® electronic brachytherapy system.

With the high dose rate that automatically adjusts for larger fractions, treatment duration is always limited to a maximum of three minutes. Duration of patient set up and actual treatment is therefore limited and in experienced hands the patient can leave the facility within 10 minutes thereby minimizing the impact on a patient's daily schedule and quality of life.

The positioning arm freedom of movement in combination with the LED guided applicator allows for accurate and reproducible positioning of the applicator on virtually any body location without requiring patients to adopt an uncomfortable body position during treatment.

Key Messages

19. The Esteya electronic brachytherapy system is engineered for improved patient comfort for treatment via comfortable, easy and quick surface applicator positioning, short treatment times and an aesthetically pleasing design.
20. Electronic brachytherapy allows expansion of advanced skin cancer radiation therapy to be delivered outside of radiation oncology centers due to minimal shielding requirements and mobile machine solutions.

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