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ARTYKUŁ POGLĄDOWY / REVIEW ARTICLE

Modern radiation techniques for treatment of head and neck cancers

Nowoczesne techniki napromieniania w leczeniu nowotworów rejonu Głowy i Szyi

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ABSTRACT: Alongside surgery, radiation therapy remains the mainstay of treatment for head and neck cancers. Because the head and neck contain a number of critically important structures, it is crucial to try to curtail the adverse effects of radiation therapy by increasing its precision. Such precise radiation techniques include the three-dimensional conformal as well as highly conformal radiotherapy. The latter includes, for instance, intensity modulated radiation therapy (IMRT), stereotactic radiation, and proton-beam therapy. All of the above-mentioned techniques are available in Poland and give the opportunity of a more aggressive treatment that lead to improved outcomes, curtailment of adverse effects, and by that, a better quality of life.

KEYWORDS: positron emission tomography, radiotherapy, throat, apoptosis

STRESZCZENIE: Radioterapia (obok chirurgii) stanowi niezmiennie podstawową metodę leczenia chorych na nowotwory narządów Głowy i Szyi. Ze względu na istnienie w rejonie Głowy i Szyi wielu struktur krytycznych, w celu ich oszczędzenia i zmniejszenia odczynów popromiennych konieczne jest stosowanie precyzyjnych technik napromieniania takich jak: technika konformalną 3D oraz techniki wysokokonformalne. Do technik wysokokonformalnych zaliczamy: technikę modulacji intensywności wiązki napromieniania IMRT (IMRT – ang. intensity modulated radiation therapy), napromienianie stereotaktyczne oraz napromienianie wiązka protonową. Wszystkie te techniki są już dostępne w Polsce i dają możliwość stosowania bardziej agresywnej terapii w celu poprawy wyników leczenia i zmniejszenia jego skutków ubocznych, co przekłada się na poprawę komfortu życia chorych.

SŁOWA KLUCZOWE: pozytonowa emisyjna tomografia komputerowa, radioterapia, gardło, apoptoza

Alongside surgery, radiation therapy remains the mainstay of treatment for head and neck cancer. In radiation therapy, the therapeutic effect is achieved by damaging the susceptible structures of cancer cells, which is assumed to induce cell death. The ionizing radiation causes cell death either directly or indirectly. The direct effect is the result of the damage to essential cellular structures, including the DNA, which leads to cell death after several divisions. In the case of photon radiation, characterized by a low linear energy transfer ratio, the direct effect concerns less than 10% of cancer cells. Therefore, cell death is mostly the result of indirect damage. The ionizing radiation causes intracellular hydrolysis, which induces free radical formation. Subsequently, free radicals damage the intracellular structures including DNA - this causes sublethal or potentially lethal defects leading to apoptosis (Fig. 1, 2). Some of these defects are reversed by intracellular repair systems. Moreover, the efficiency of cell damage through the indirect effect is dependent on the state of oxygenation of the tumor (oxygen is essential for free radical generation) and on the susceptibility of the tumor to radiation, which is in turn associated with the degree of cellular differentiation. These factors restrain the efficacy of radiation therapy, and at the same time, provide molecular targets for targeted therapy that is supposed to overcome resistance to radiation, and consequently, lead to an improved therapeutic index.

The ionizing radiation exerts its effects not only on the cancer cell, but also, albeit to a lesser degree, on the surrounding tissue that has been enfolded within the radiation volume. Inevitably, this leads to adverse reactions in the healthy tissue, which determines the maximal dose of radiation that can be used. Consequently, there is a tradeoff between the efficacy of radiation therapy and the severity of adverse reactions. There are early and late radiation therapy reactions. The early reactions unfold during therapy and remain for several weeks after its discontinuation. The late reactions are those reactions that are observed more than 6 months after treatment. In the case of the head and neck radiotherapy, early and late reactions in the mucous membranes as well as late reactions in the salivary glands, spinal cord, optic nerves, intraorbital structures, cartilage, and bones are of particular importance (1, 2, 3).

Because the head and neck contain a number of critically important structures, it is crucial to try to curtail the adverse effects of radiation therapy by increasing its precision. Due to the technological advancements in the last three decades, we are now able to use modern radiation techniques that enable an efficacious protection of the healthy tissue, which results in higher doses of radiation being used, and by that, in improved outcomes. The three-dimensional conformal radiation therapy is one of those techniques, which is now a standard treatment in every institution in Poland. The three-dimensional conformal radiation therapy is planned based on three-dimensional reconstructions derived from imaging studies such as computerized tomography, magnetic resonance imaging, and positron emission tomography. The following techniques are regarded as highly conformal radiation techniques:

- Intensity modulated radiation therapy (IMRT)
- Stereotactic radiation
- Proton beam radiation

Intensity modulated radiation therapy (IMRT)

Having such a precise means of radiation therapy as the IMRT (4,5) or other highly conformal radiation techniques, a key issue is to ensure the patient's stability in order to eliminate potential errors associated with routine treatment plan implementation. To that end, the patient is stabilized in a most comfortable position with an orfit mask attached to the table. Then, the reproduction of patient position and movability of less than 3 millimeters of the patient within

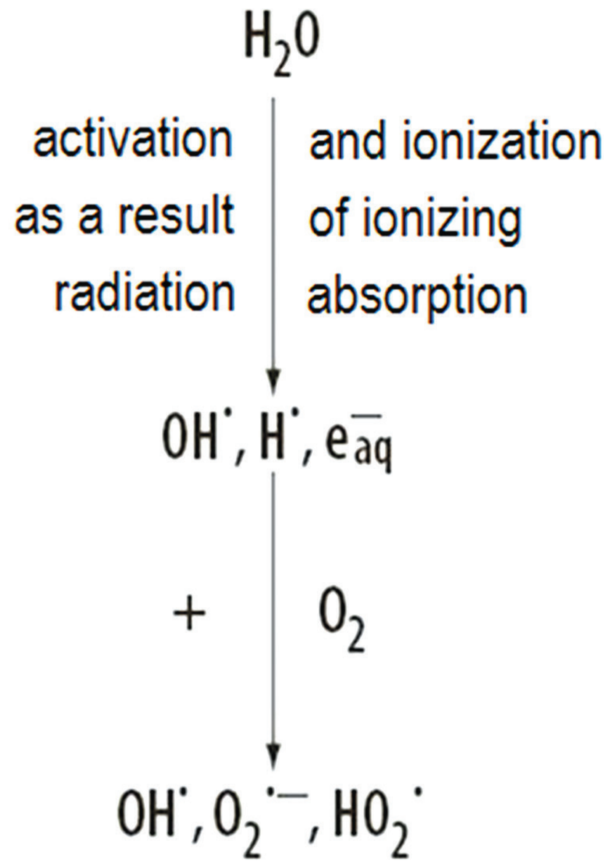

Fig. 1. Free radical generation

the mask should be achieved. If the deviation is less than 3 millimeters, a contrast-enhanced computerized tomography is performed for further treatment planning in the therapeutic position.

The IMRT requires a radiation oncologist to precisely determine the therapeutic areas (based on CT scans) and thereafter to choose an appropriate dose of radiation. Moreover, the critical organs in the vicinity of the therapeutic are described, and the radiation dose for each of them is estimated

GTV (*gross tumor volume*) – macroscopically visible tumor, palpable on physical examination, and seen on CT, MRI, or PET (used for the primary tumor and lymph node metastases)

CTV (*clinical tumor volume*) – the area of high-risk subclinical infiltration (a margin of 10-15 mm around the GTV in the soft tissues; in the vicinity of naturals barriers, such as bones, the margin is smaller)

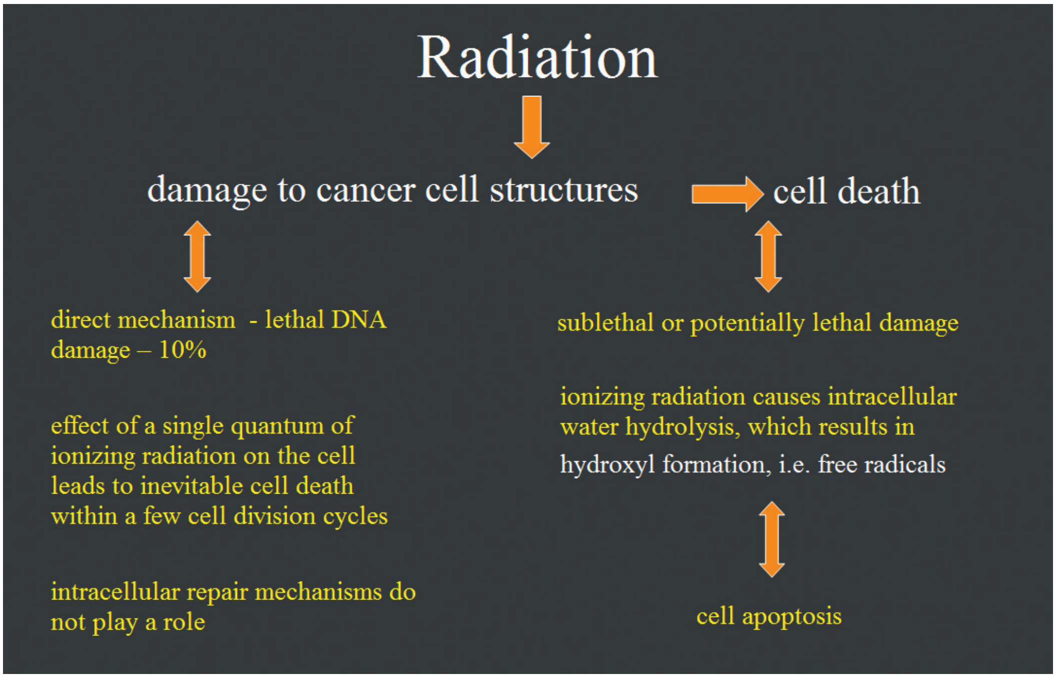

Fig. 2. Radiation-induced cancer cell damage

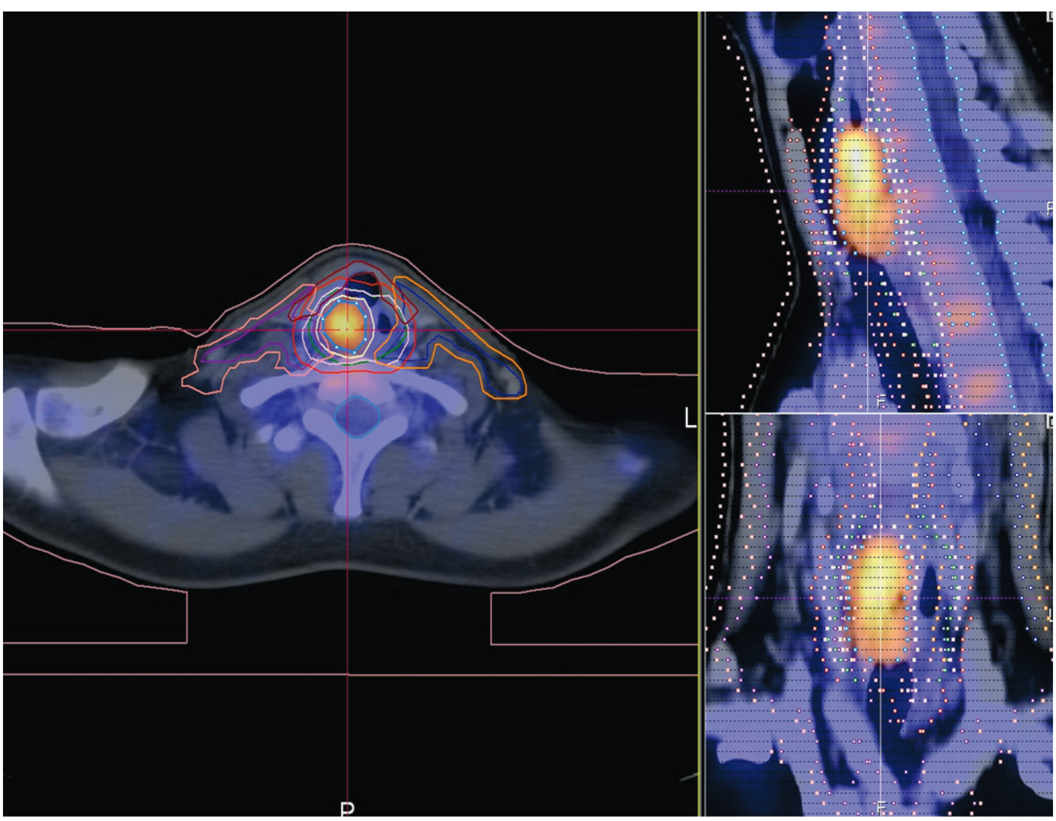

Fig. 3. Differences in radiation volume estimation between CT and PET-CT

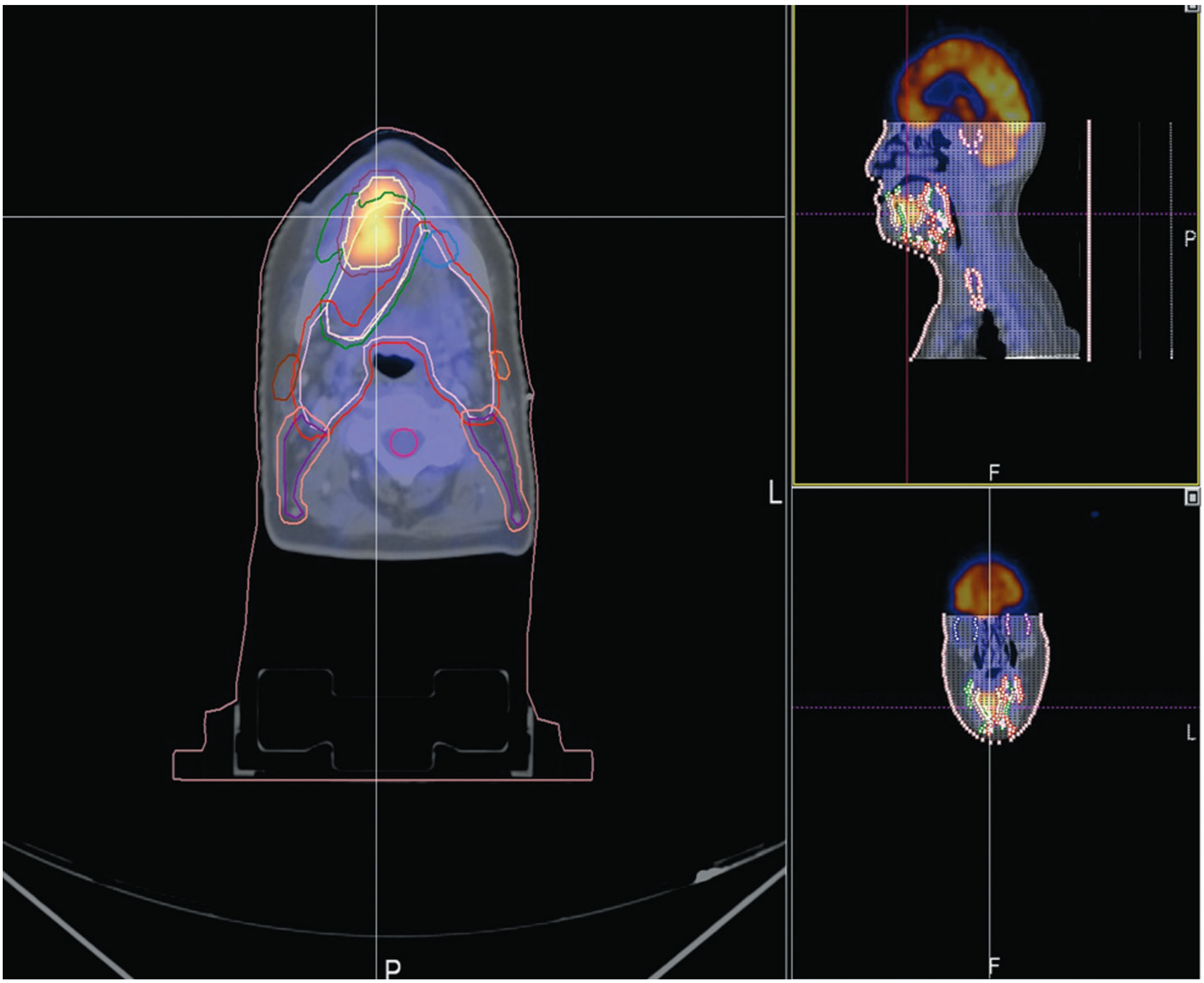

Fig. 4. Delineation of radiation areas based on PET-CT

CTV – it encompasses also the elective lymph nodes in the neck (the range of elective radiation is always dependent on the N and T scores, and on the degree of cellular differentiation.

CTV 1 – it encompasses the area of a lower risk of subclinical infiltration and the remaining lymph nodes.

PTV(*planning tumor volume***)** – it encompasses **CTV** with a margin of 3 millimeters that takes into account the movability of the patient and potential deviations in patient position.

Routinely, the radiation areas are determined by radiation oncologists based on anatomical information derived from contrast-enhanced CT or MRI, and more recently also PET-CT studies, performed in the therapeutic position. A combined use of CT with FDG-PET allows for a more precise treatment planning, which is based on the molecular and biological activity of macroscopically infiltrated areas – both primary and metastatic. (Fig. 3, 4). Consequently, we now know more about the biologically active areas, which is very important for SIB-IMRT (*simultaneous integrated boost – IMRT)* – a technique which enables the use of higher radiation doses in areas of increased FDG uptake with a concomitant reduction of radiation in the surrounding tissue. It is likely that a more precise GTV estimation with subsequent dose escalation in that area will result in better outcomes of SIB-IMRT.

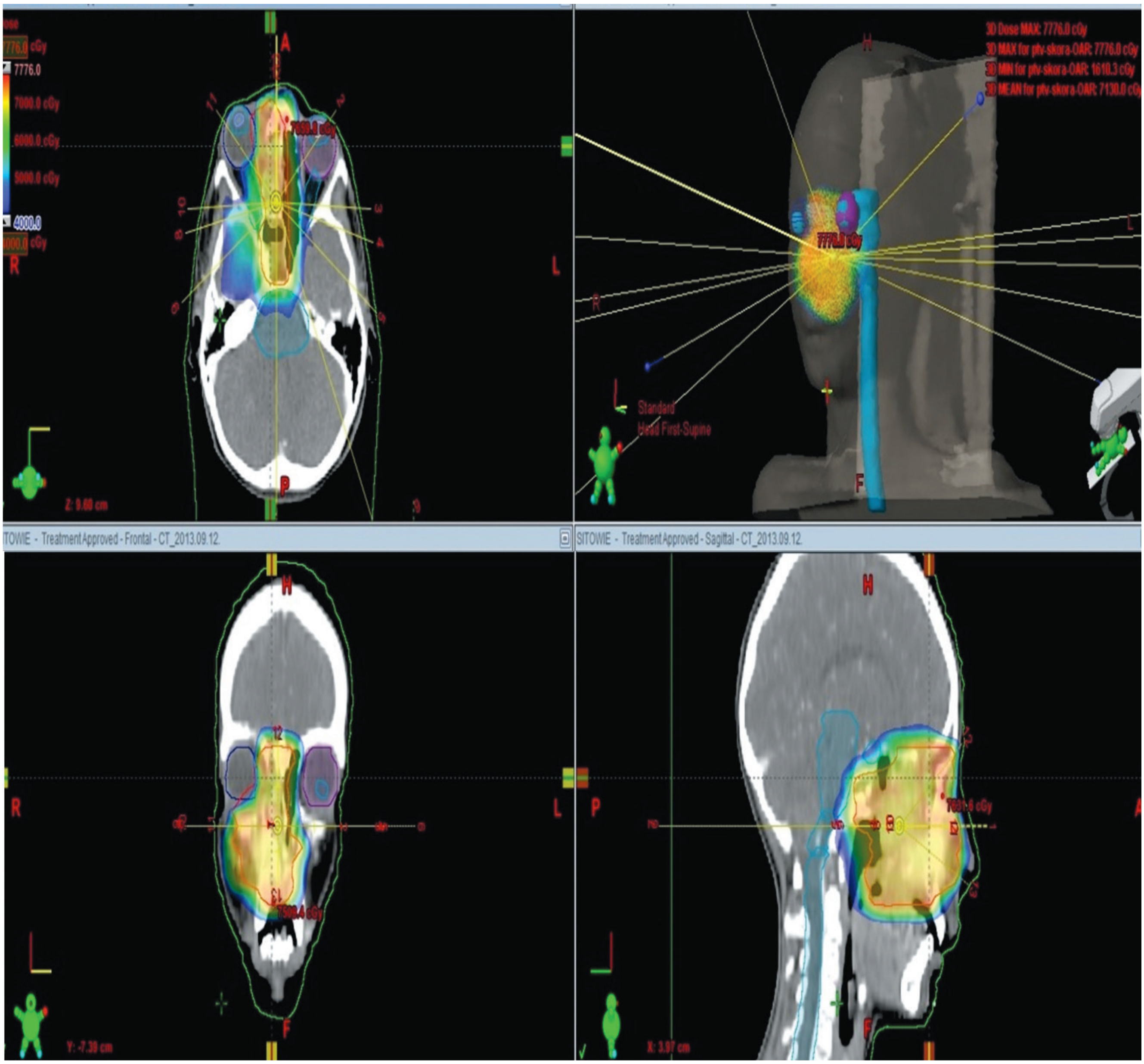

Fig. 5. Dose distribution for IMRT of a non-operable lesion of the paranasal sinuses

The application of IMRT-type techniques that use standard radiation doses, i.e. 2 Gy within the tumor, has led to a reduction in radiation reactions but not to an improved outcome (Fig. 5). Owing to the simultaneous modulation of both the shape and dose of radiation, the IMRT enables the use of increased radiation doses within the tumor and at the same time of lower fractional doses in other areas, which spares the critical structures surrounding the tumor. Therefore, this technique has been termed the simultaneous integrated boost IMRT (SIB-IMRT) [7, 8]. During each fraction of SIB-IMRT, a dose greater than the standard dose of 2 Gy is administered within the tumor area, whereas electively radiated areas receive lower doses. There are two potential benefits of SIB-IMRT. Firstly, in comparison to standard IMRT, SIB-IMRT requires a shorter time period for the administration of a given radiation dose to the

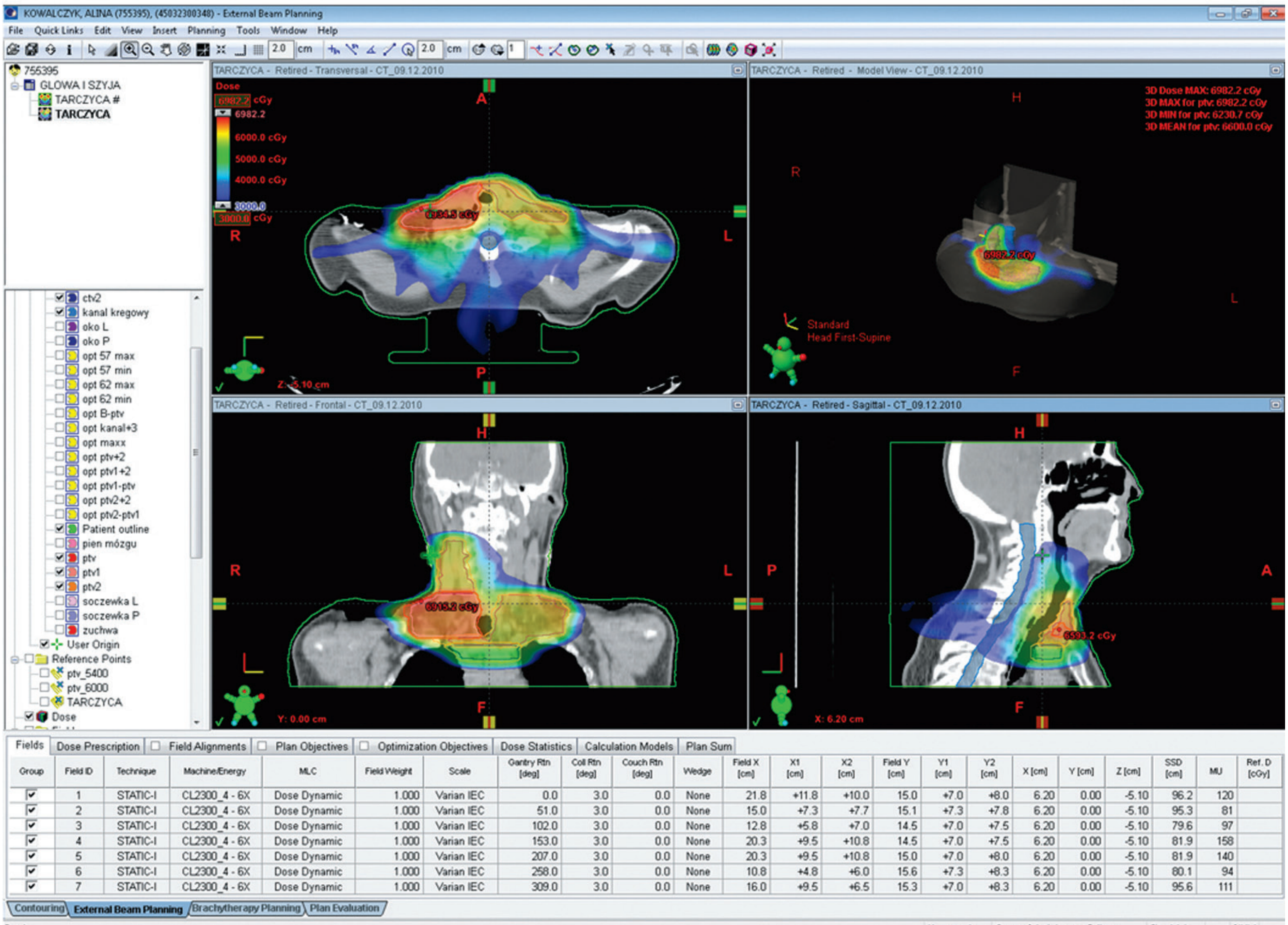

Fig. 6. Radiation dose distribution for SIB-IMRT following a non-radical surgery for thyroid cancer

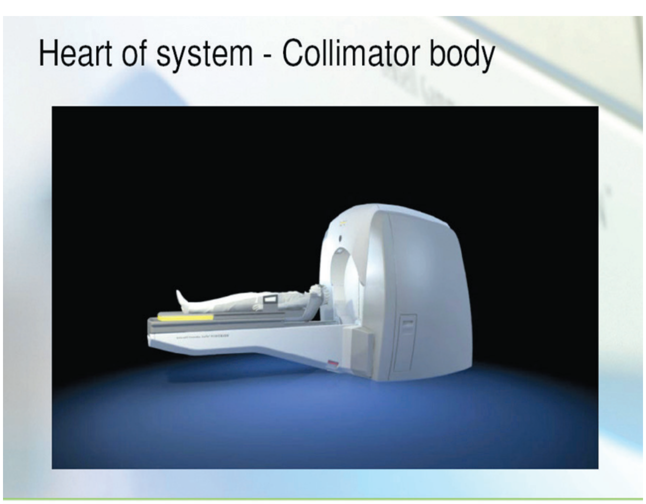

Fig. 7. GammaKnife

ELEKTA NEUROSCIENCE

Fig. 8. True Beam accelerator

Fig. 9. CyberKnife

primary tumor site and/or lymph node metastases as well as the administration of a higher fractional dose to the primary tumor site, which may be associated with a potential improvement of local efficacy leading to a better locoregional outcome. In other words, SIB-IMRT is a new approach to accelerated radiation [9, 10, 11, 12,13]. Secondly, owing to the modulation of radiation beam intensity, the healthy tissue surrounding the tumor receives lower doses of radiation, which is reflected by a more favorable treatment tolerance in such an aggressive treatment approach as radiochemotherapy (Fig. 6).

STEREOTACTIC RADIATION THERAPY

The development of stereotactic radiation therapy in Poland has been very dynamic over the last five years. Stereotactic radiation therapy is a method based on a very precise administration of either a single dose of radiation (radiosurgery) or multiple daily doses that are higher than the standard dose (fractional stereotactic radiation). During stereotactic radiation therapy, the only area to which radiation is administered is the macroscopically visible tumor site with no elective radiation areas. Among head and neck tumors in which stereotactic surgery might be indicated on can include meningiomas or neuromas located on the base of the skull, single brain metastases in patients in a good general condition, hormonally active pituitary

Fig. 10. Attachment of a stereotactic frame for radiosurgery with GammaKnife

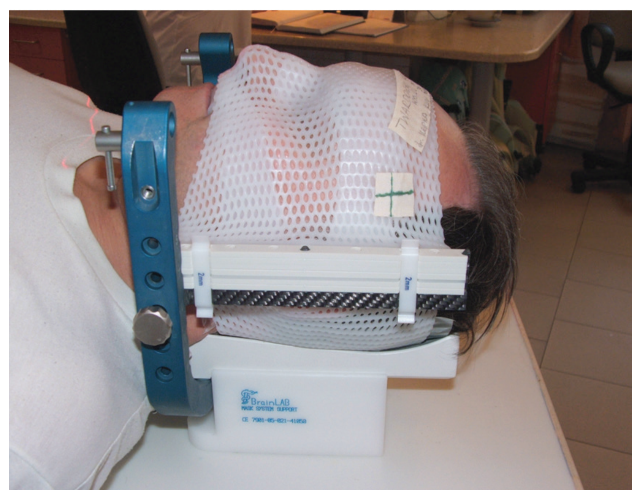

Fig. 11. Stereotactic mask used for head stabilization in fractional stereotactic radiation therapy – CyberKnife, Accelerator

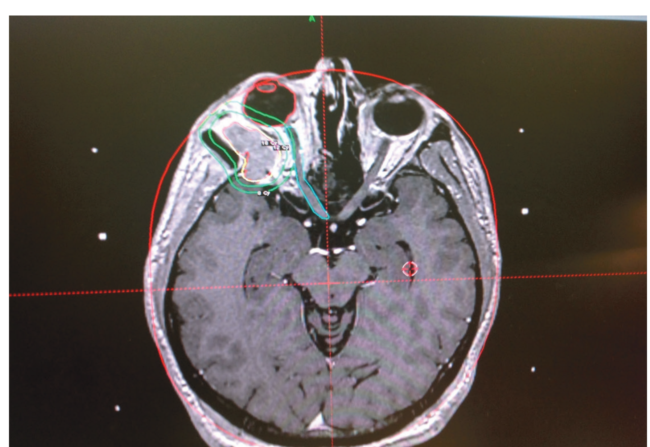

Fig. 12. Distribution of isodoses in radiosurgery – dose of 18 Gy in an 80% isodosis (GammaKnife)

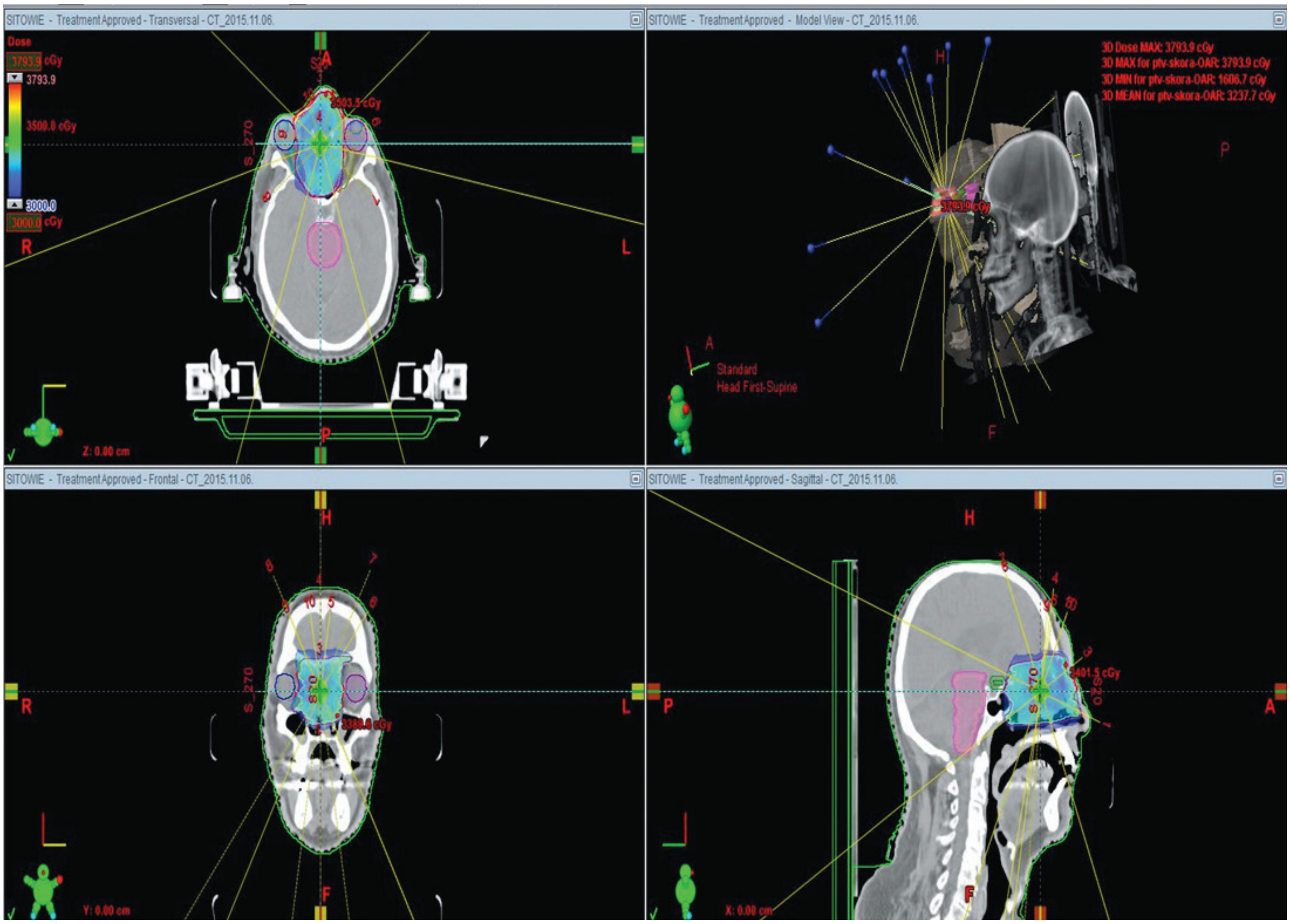

Fig. 13. Distribution of isodoses in fractional sterotacitc radiation for a dose of 30 Gy in 5 fractions

adenomas, tumors neighboring critically important structures (base of the skull, spinal cord), and tumors requiring re-radiation. Stereotactic radiation can be performed with gamma radiation (GammaKnife – 192 cobalt sources, Fig. 8) or with photon radiation (CyberKnife, Accelerator, Fig. 8, 9) [14,15,16,17,18,19]. Because of the need to administer a very high dose of radiation in a single session, it is crucial to reduce the movability of the head as much as possible. There are two methods used for head stabilization – the stereotactic frame and an orfit mask. The stereotactic frame is attached to the head with four fiber carbon screws that have ceramic tips – this method is used primarily for Gammaknife radiation (Fig. 10). The orfit mask, in turn, enables a high repeatability of fractional radiation (Fig. 11). Stereotactic radiation therapy can be performed in a single session – radiosurgery with the use of radiation doses of 12 – 34 Gy (Fig. 12), or as fractional radiation in which the total dose is administered in 3 – 6 session.

Fractional stereotactic radiation is used when the tumor infiltration area is greater than 15 cm3 or abuts critically important structures (Fig. 13).

PROTON BEAM RADIATION

Proton beam radiation, owing to its geometry (Pik Bragga, Fig. 14), allows for tumor site irradiation at a significantly lower rate of adverse reactions in the healthy tissue. It can be used in multiple and neck tumors as a stand-alone treatment or as an adjunctive treatment in photon beam radiation therapy.

The most common indications for proton beam radiation are situation in which the tumor infiltration area is located in the vicinity of vital organs. Then, the administration of radical doses, even when the highly conformal radiation techniques such as IMRT are used, can be associated with the risk serious

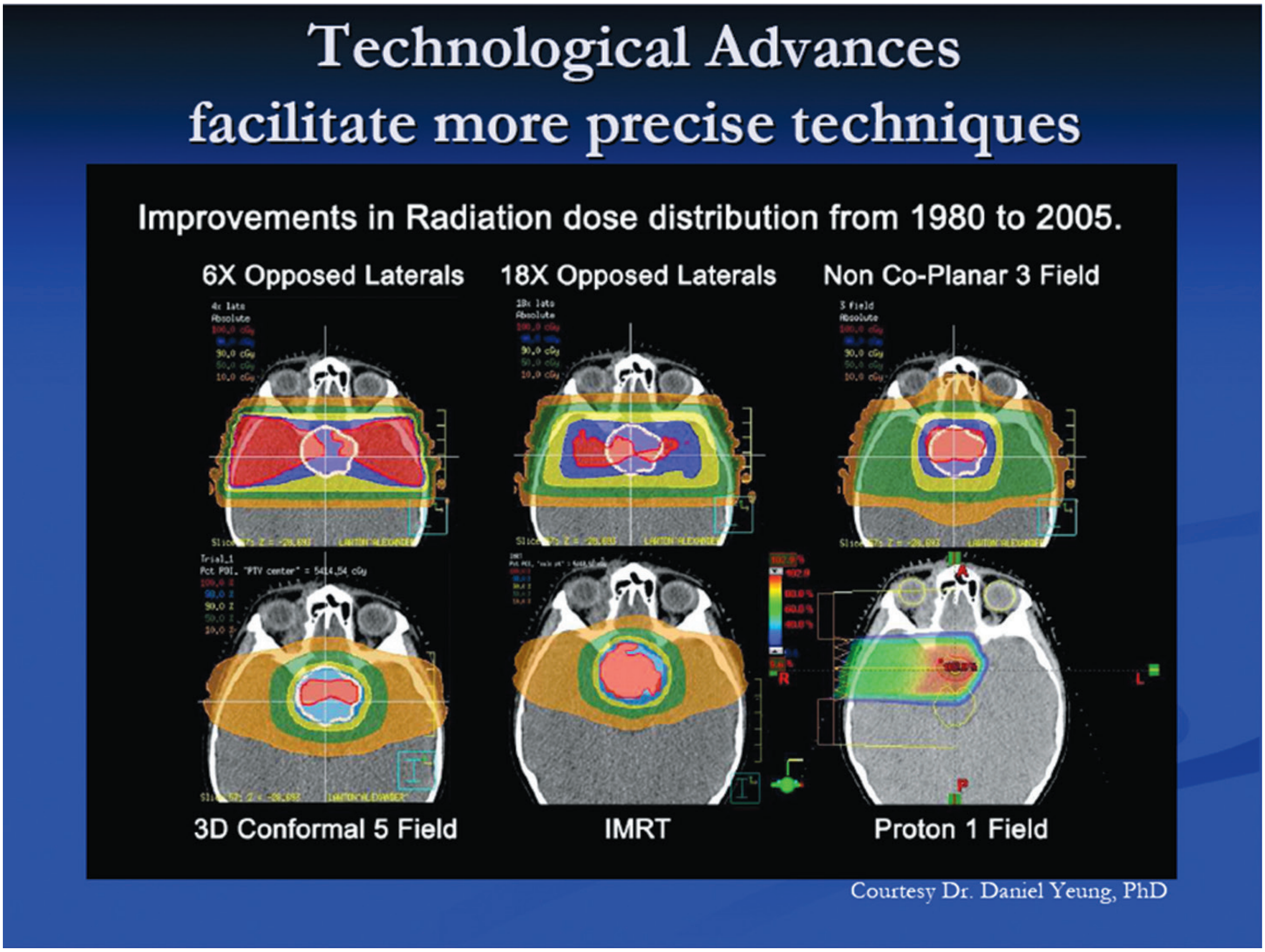

Fig. 14. Comparison of beam geometry for gamma, photon, and proton radiation

adverse effects. The physical properties of the proton beam allow for: (1) precise application of a high (therapeutic) dose within a strictly defined volume, (2) reduction of volume and dose in the healthy tissue and vital organs located in the vicinity of the tumor or on the pathway of the beam, (3) reduction of the total radiation dose. The major benefit of proton beam radiation is the possibility to use high radiation doses with a reduced risk for the healthy tissue and the vital organs neighboring the tumor. This is reflected by an improved locoreginal outcome and a better safety profile (Fig. 15). The indications for proton beam radiation result from the physical properties of this method, which enables the treatment of tumors of, continuous with, or localized in the vicinity of vital organs. Moreover, proton beam radiation is used when the reduction of adverse effects is crucial. The classical indications for proton beam radiation include the melanoma of the eye, tumors localized on the base of the skull and in the paravertebral area, tumors of the paranasal sinuses - maxillary sinuses, nasal sinuses that infiltrate the base of the skull (carcinoma adenoides cysticum, adenocarcinoma, malignant melanoma), and certain tumors in children (e.g. medulloblastoma, sarcomas, CNS tumors)[20,21,22,23,].

Proton beam radiation can be used as a stand-alone treatment or as an adjunctive treatment in photon beam radiation for the treatment of advanced tumors of the nasopharynx that infiltrate the base of the skull, when it is necessary to include the whole lymphatic system of the neck in the radiation volume.

Such a dynamic development of the highly precise radiation techniques in Poland gives the possibility to use more aggressive treatments to achieve better clinical outcomes without an increased risk of adverse effects, which leads to the improvement of the patient quality of life.

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