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# Radiation Therapy with a Simultaneous Integrated Boost

Despina Katsochi

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## Abstract

Radiotherapy has an established role in the treatment of cancer and represents a definitive, less invasive approach for various cancer types. Its main aim is to deliver the maximum dose to the tumor with minimal toxicity on neighboring healthy tissues. Therefore, the precise determination of the target and its spatial relation to critical surrounding organs is of main importance. New imaging modalities such as the CT, MRI, and PET/CT offer more anatomical detail and facilitate the accurate delineation of the target volume and the organs at risk. The recent advances in 3D-CRT and IMRT radiation techniques offer high accuracy in tumor targeting and ensure safe dose escalation. Moreover, the introduction of IGRT offers the opportunity to safely apply a supplementary dose to the macroscopic tumor. In trials conducted, a simultaneous integrated boost (SIB) has proved to be feasible in various cancer localizations, to safely increase the total delivered dose, shorten the total treatment time and results in increased tumor control while keeping the side effects low at the same time. However, more trials need to be conducted to establish an acceptable protocol.

**Keywords:** radiation therapy, simultaneous integrated boost, fractionation, radiation dose escalation, image guided radiotherapy

## 1. Introduction

Radiation therapy is the core treatment strategy with curative intent and organ preservation for many inoperable cancer types. The main aim of radiation therapy is the local control of the tumor.

With open field conventional 2D RT, both healthy tissue and tumors are irradiated with a similar dose per fraction of 1.8–2 Gy. Now, the 3D-CRT is the new standardized procedure. The target volumes are defined on CT or PET-CT or other high-definition imaging such as

the MRI. During the treatment planning, a 3-D projection of the area of interest provides the opportunity to match the high-dose radiation region to the target volume while minimizing the radiation dose to the surrounding healthy tissue. More refined radiation techniques, which lead to enhanced conformity, can be performed with the use of these generation machines. 3-D techniques have given way to IMRT or volumetric modulated arc therapy (V-MAT) [1–4].

High conformity is generally accepted as a way to reduce toxicity and allows dose escalation to produce better results and long-term tumor control. This is only possible through IGRT, which involves real-time imaging of the treatment target and normal organs during each treatment, in order to avoid uncertainty about patient positioning and tumor targeting and to also reduce the irradiated volumes without missing any of the targets [5].

Trials have investigated different fractionation schedules to also increase local control, which has become of high importance in clinical oncology patient management. Randomized clinical trials have established equivalent outcomes between radical surgery and organ-preservation treatment with an RT backbone for appropriately selected patients.

The radiation oncologist's main concern is local recurrence after definitive radiation therapy. The combined chemo-radiation protocols have led to the increased tumor control and survival rates, but the results have remained unchanged for a long time. All eyes are now on radiation therapy for a more targeted improvement of local tumor control and diminishment of the odds of local recurrence [6].

The newly developed approach of applying different radiation doses to different areas in one single session is called SIB or simultaneous integrated boost-intensity-modulated radiotherapy (SIB-IMRT). By increasing the dose per fraction focally to the tumor itself while maintaining lower dose to the elective areas of interest, a more accurate dose distribution can be achieved, in order to improve local tumor control without putting the neighboring organs at risk. The advances, improvements and clinical usage of this technique will be expanded in full detail [7].

## 2. Simultaneous integrated boost–radiation therapy strategy and procedure

The radiation therapy strategy is an evidence-based treatment, personalized to the particular needs of each individual patient. The 3D-CRT is the minimum standard for the delivery of a radiation dose that conforms to the target volume and controls the exposure to surrounding tissue (**Figure 1**). The evolution of the 3D-CRT is the IMRT technique. It optimizes the radiation intensity distribution within each beam in order to achieve a higher rate of conformity and target coverage especially for irregularly shaped tumors, using nonuniform radiation beam intensities to maximize the delivery of radiation to the planned target volume while minimizing irradiation of normal tissue outside the target. It requires a precise definition of anatomy, a treatment planning system that can calculate the dose in three dimensions, and a treatment device that can deliver the specified dose. Randomized studies demonstrate reduced side effects with IMRT (particularly that of xerostomia in patients with head and neck tumors) in comparison with older 3D-CRT techniques even in the setting of concurrent chemotherapy.

The delivery of each dose to the tumor has become much faster with the introduction of the VMAT where the gantry moves around the patient as the beam is being modulated (**Figure 2**). Typically, IMRT plans require 20–25 min for delivery of the daily treatment while a VMAT plan can now be delivered in approximately 3–5 min (approximately 1.5 min per gantry rotational arc), which is easier on patients (**Figure 3**) [8–10].
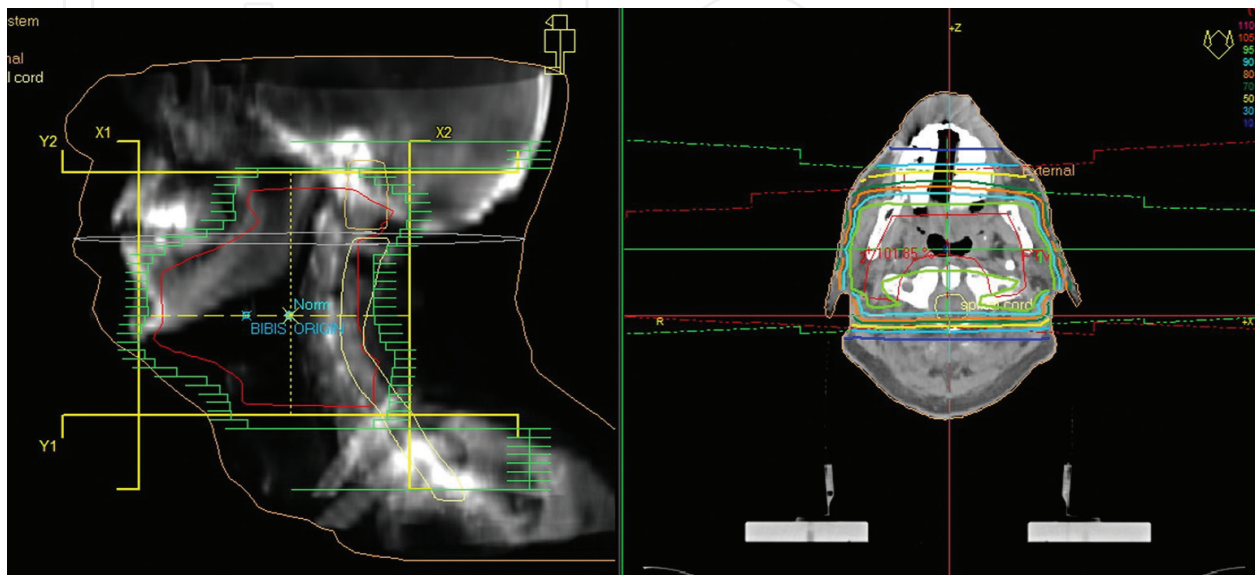


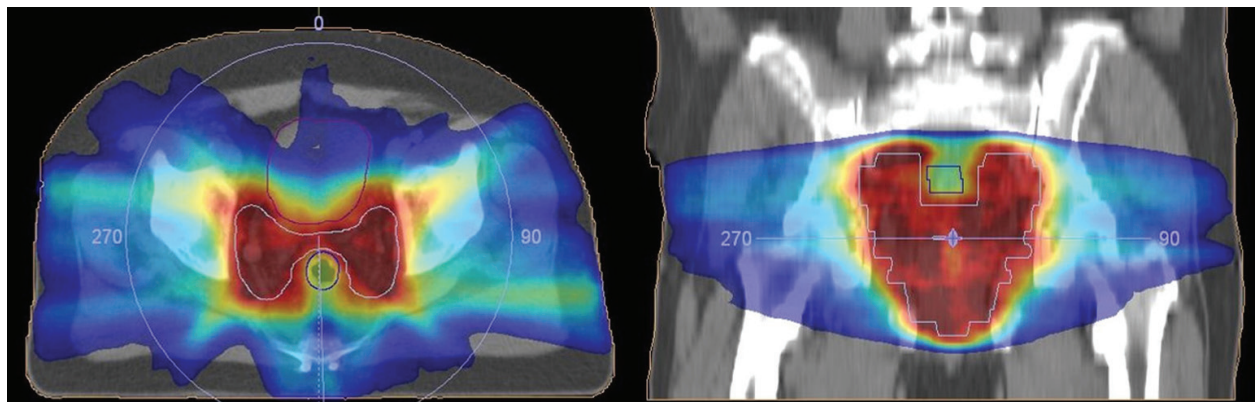**Figure 1.** 3D-CRT RT with multileaf collimator shielding.



**Figure 2.** IMRT: Gradient dose distribution is achieved in the different parts of the target volume, and the surrounding healthy tissue is less exposed to the total radiation dose.

Treatment planning is the most important procedure. Target delineation is the main concern of the radiation oncologist. The definition of the extension of the infiltrated tissue is often an interdisciplinary procedure where the surgeon, pathologist, radiologist and radiation oncologist have to collaborate in order to decide on the most appropriate treatment plan. The precise determination of the target and its spatial relation to critical surrounding organs is of main importance. The reference imaging modality for RT treatment planning is the CT with which we can

fuse additional medical images (MRI PET/CT scans) for accurate treatment planning, dosimetric calculations and ensure safe dose escalation. The PET/CT images can change gross tumor volume (GTV) delineation in 35–60% of patients treated and show a better treatment outcome (31 months vs. 16 months) and can increase the 1-year survival rate from 8 to 17% (**Figure 4**) [11–15].
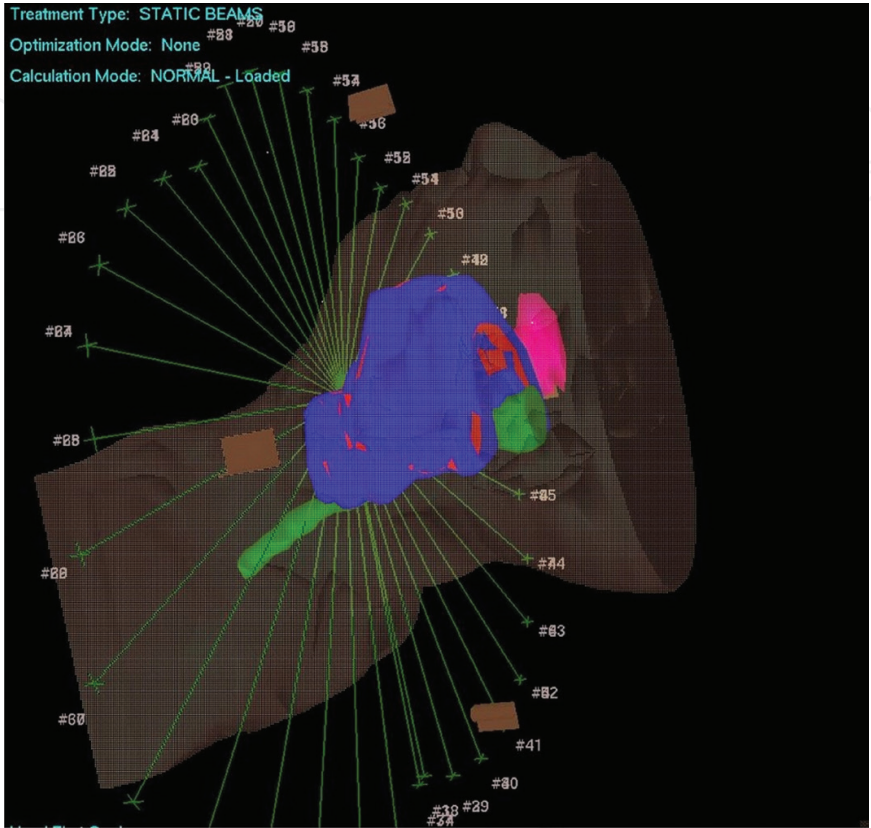


**Figure 3.** VMAT where the gantry moves around the patient as the beam is being modulated.
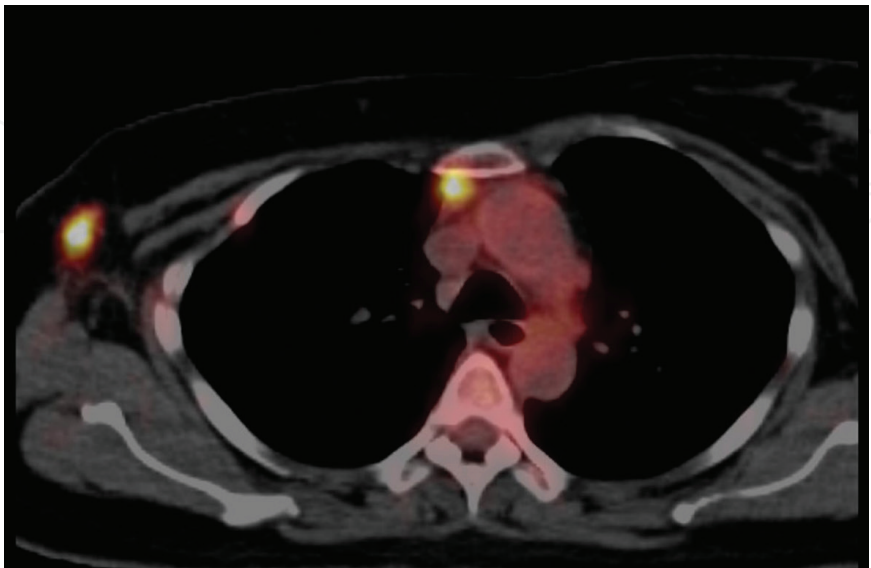


**Figure 4.** PET/CT gives information about the metabolic tumor activity.

For accurate 3D-CRT and IMRT delivery, every day patient set up and verification systems are required, i.e., CBCT scanners, which produce 3-D images of the treatment area (**Figure 5**) [10, 11].
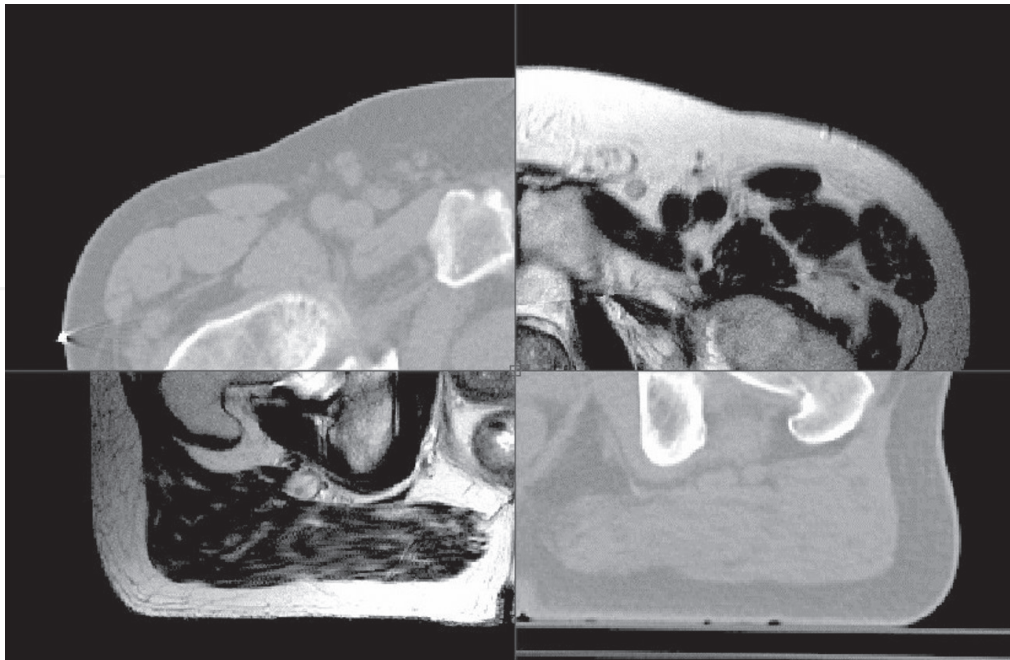


**Figure 5.** IGRT real-time imaging of the treatment area fused with the computer tomography image used for the planning.

According to ICRU-83, the GTV represents the palpable or visible (on imaging) tumor, whereas the so-called clinical target volume (CTV) is an additional volume with a certain probability of microscopic (subclinical) malignant disease. The irradiated planning target volume (PTV) is a geometrical concept. The PTV is defined according to the ICRU 62 report and includes GTV, CTV and takes into account the internal organ motion and set up errors [16, 17].

In the past, radiation therapy was applied using a shrinking field approach or sequential boost, starting with large fields and shrinking gradually depending on the pre-planned total dose to each region. Inevitably, the high-risk target volume or GTV, the intermediate risk target volume or CTV and the low risk volume or PTV were exposed to different total doses, which have been delivered sequentially (SeqB-IMRT intensity-modulated radiotherapy sequential boost). This risk adaptive strategy now is modified to deliver a single efficient treatment plan with dose levels and intensities appropriate for each elected region. The SIB-IMRT is more conformal and potentially enables a slightly higher dose escalation to high-risk volumes compared to the SeqB-IMRT. Higher conformity in combination with smaller PTV allows 25% RT dose escalation and increases the effectiveness of therapy. A dose escalation of 10 Gy to lung cancer patients treated with 3D-CRT is correlated with 36% decrease in local failure rates [18–20].

The concomitant boost technique is a variant of accelerated fractionation, whereby the boost is delivered as a second daily fraction during the basic treatment course to reduce the total duration of treatment. The incorporation of boost at the same session of RT is the SIB, which involves the CTV with a prophylactic dose and the GTV with a curative dose.

Simultaneous accelerated radiation therapy (SMART) boost technique initially was described by Butler in 1999 [21]. The GTV was treated with large fractions of 2.4 Gy, while conventional fractions of 2 Gy were delivered to the PTV, which represent the regions at risk for microscopic disease up to a total dose of 60 and 50 Gy, respectively. The total treatment time was moderately shortened than previously. The term "simultaneous integrated boost" was introduced later to define such treatment, delivering different doses per fraction in different target regions, by Mohan, 2000 [22]. The initial proposed dose delivery was either the conventional 2 Gy per fraction to the lower or intermediate dose volumes, thereby enabling a higher dose per fraction to be delivered to the GTV, with as much as 2.4 Gy for gross disease. The SIB technique offers the biological advantage of shortened treatment duration, i.e., 70 Gy over 6 weeks, which has been shown to significantly increase the loco-regional control compared to the same dose delivered in 7 weeks. According to the literature provided, an increase in the biological dose of 7.5% could be translated into an increase in loco-regional control in the order of 15%. In this context, the gain resulting from an increase in the equivalent dose can be achieved without any further increase in late normal tissue complications compared to standard treatment. Only the normal tissues embedded in the tumor volume and thus included in the PTV will be irradiated with a dose per fraction similar to that of the tumor itself. Provided that the dose per fraction to the organs at risk is limited to a maximum of 2 Gy per fraction, this increase in dose intensity will be achievable without undue damage to normal tissue (**Figure 6**) [23, 24].
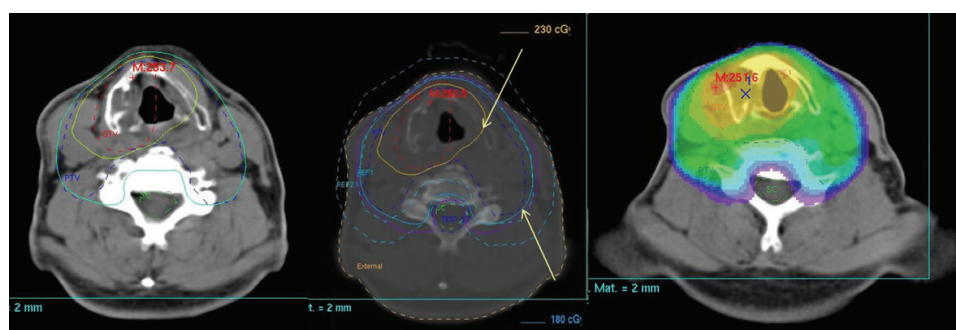


**Figure 6.** SIB-IMRT gradient dose distribution in the different parts of the target volume and the surrounding healthy issue in one single session.

In the following paragraphs, there are detailed examples of different cases where the SIB technique has been applied.

It is a fact that the treatment of **head and neck cancers** is influenced by fraction size, total dose and overall treatment time regarding the tumor control and toxicity. The total radiation dose has demonstrated a direct impact to the tumor response as well as to the acute or late adverse events.

The SIB-IMRT approach may be used to deliver a fraction size of 2.2 Gy to the boost volume and a fraction size of 1.8 Gy to the elective volume in the same treatment session. As a result, the high-risk volume is treated with fewer fractions compared to conventional protocols and leads to reduction in the overall treatment time (6 weeks compared to 7 weeks) (**Figure 7**).
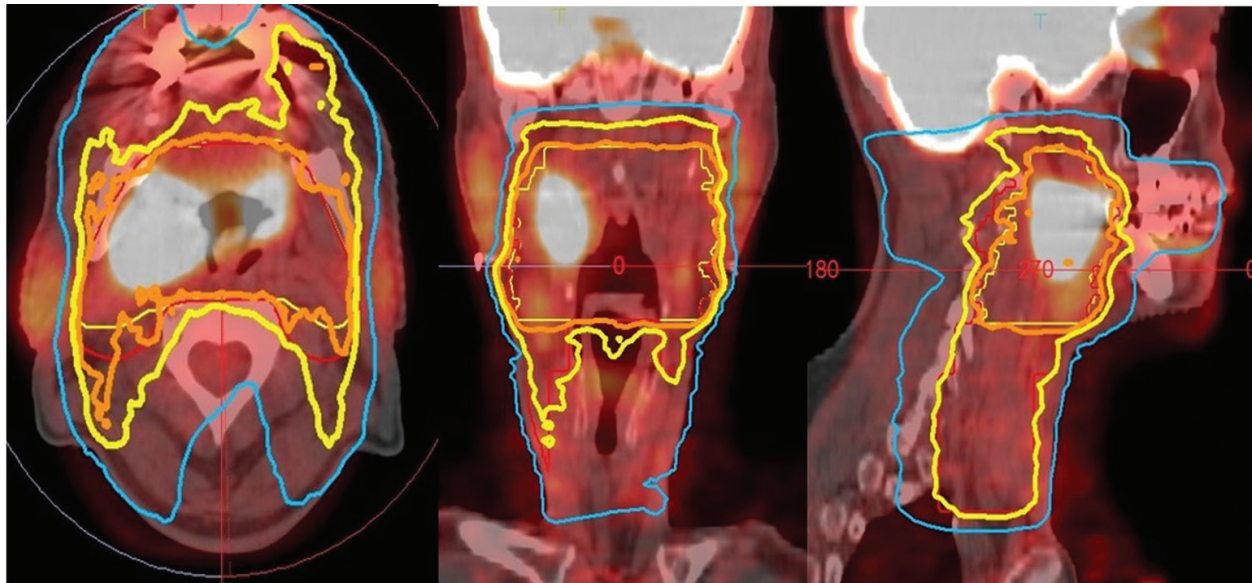
**Figure 7.** Head and neck tumor, metabolic image activity for better targeting of GTV gross tumor volume.

According to the RTOG H-0022 trial for oropharyngeal carcinomas SIB-IMRT in head and neck cancer, the use of 2.0, 2.11 or 2.2 Gy per session is highly effective and safe with respect to tumor response and tolerance. However, SIB with 2.2 Gy is not recommended for large tumors involving laryngeal structures [25–32].

Before the arrival of IMRT, the SeqB method was mostly used, within the 3D conformal irradiation technique to treat **high-grade gliomas**. With the SIB method, the dose per fraction to the PTV is lower when compared with the SEB, delivers an enhanced dose to the gross tumor volume and has a greater potential of sparing of organs at risk (**Figure 8**) [33–37].

Whole brain radiotherapy is the most common palliative treatment and has always been considered the standard treatment for patients with **brain metastases**. As opposed to surgery which was used in the past decades, today neurosurgical techniques such as radiosurgery have been combined with whole brain radiotherapy and have allowed for using more aggressive local treatment with the goal to increase local control probability and potentially overall survival. The literature reports a statistical advantage on overall survival probability in patients with a single brain metastasis treated with a combination of whole brain radiotherapy and radiosurgery compared with whole brain radiotherapy alone.

According to RTOG, the use of 20 Gy in five fractions to the WBRT can be considered an acceptable fractionation and is equivalent to 30 Gy in 2 weeks. Median survival (15–18 weeks) and overall response rates probability (75–80% for symptom palliation) are similar. The SIB together with this hypofractionated schedule in WBRT (20 Gy in five fractions) (40 Gy in five fractions) has proven to be feasible. This schedule offers the advantage of shorter treatment time, which could be very useful in oligometastatic patients that need systemic therapy (**Figure 9**) [38–43].
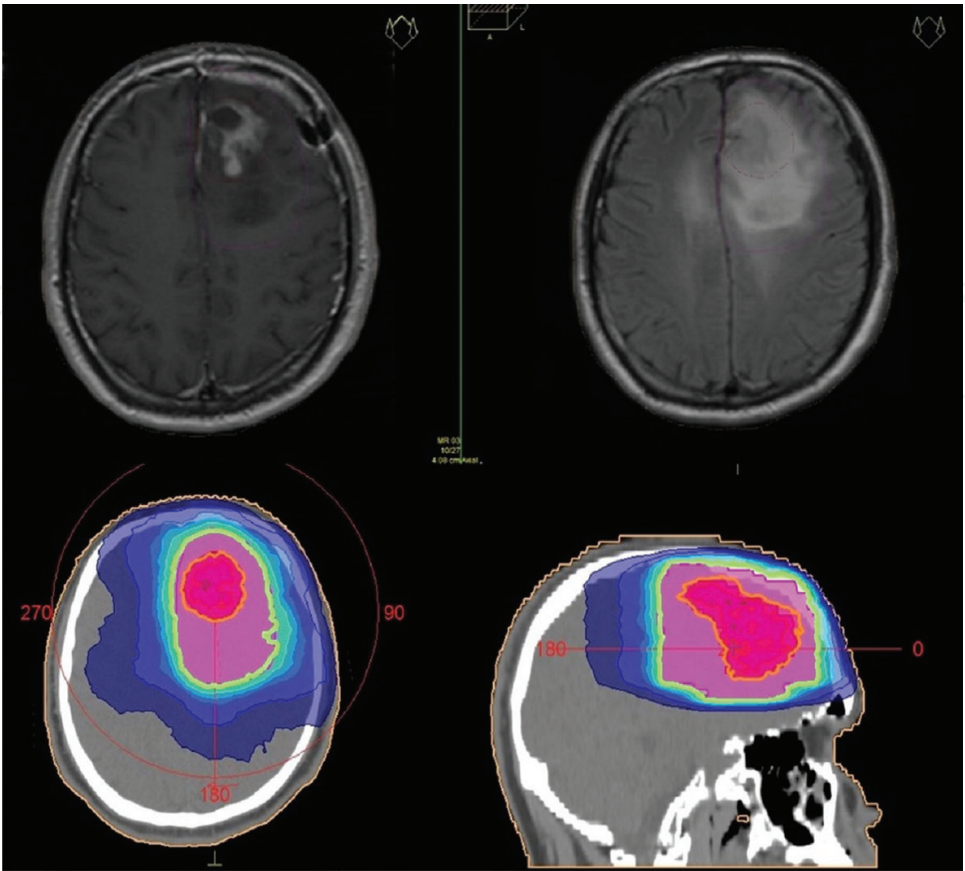
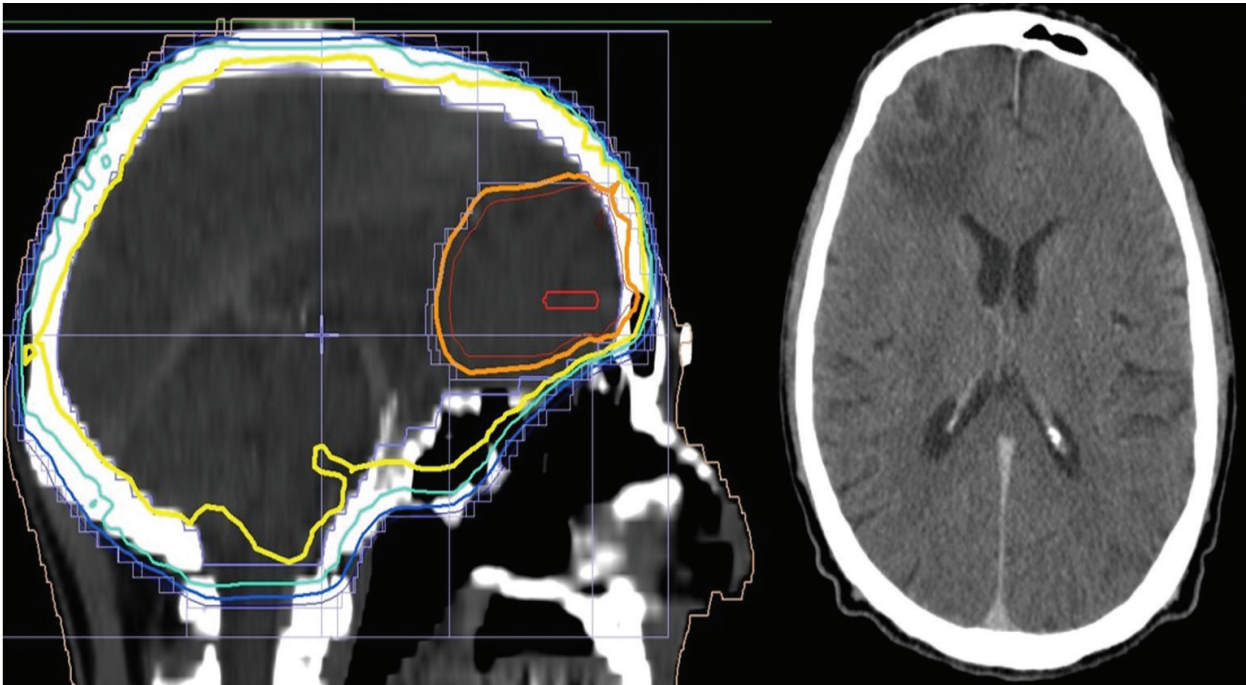**Figure 8.** CT after excision of a brain tumor, SIB-IMRT.



**Figure 9.** Single brain metastasis treated whole brain VMAT and SAB.

The true value of radiotherapy confined to the thorax is indisputable in the treatment of locally advanced **nonsmall cell lung cancer**. However, even with standard chemo-radiation, it is difficult to achieve durable local control, and this contributes to the high morbidity and mortality of patients with NSCLC. Results of RTOG 0617 clinical (Phase III) trial showed that the overall survival of stage III NSCLC patients given a high-dose (74 Gy) conformal radiation therapy with concurrent chemotherapy was no better than that of patients given the standard dose (60 Gy) [44–46]. The new idea is, instead of escalating the dose to the whole PTV, to selectively increase the treatment dose using SIB-IMRT to deliver a higher dose to the GTV and a relatively lower dose to the subclinical disease PTV [47–51].

Clinical outcomes of patients with NSCLC treated with SIB-IMRT have been retrospectively analyzed to evaluate the feasibility of this technology and to provide evidence in support of future clinical studies. The results so far should, at the very least, be considered encouraging (**Figure 10**).
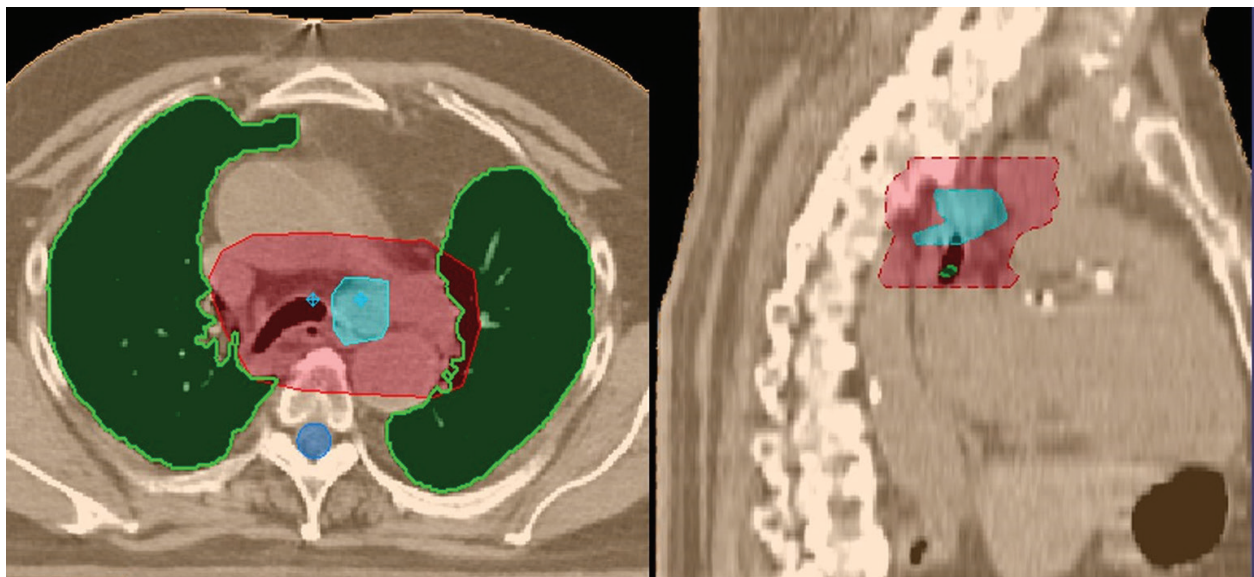


**Figure 10.** SIB treatment plan in lung cancer nodal recurrence.

Breast-conserving surgery followed by whole breast radiotherapy has become the standard approach for early stage **breast cancer** since the survival rates have proved to be similar to those with radical surgery. Local control can be improved by an additional boost of 16 Gy to the lumpectomy cavity after administration of 50 Gy to the whole breast. Breast irradiation with a boost to the tumor bed provides significantly higher local recurrence rates than whole breast irradiation alone, namely, 93.8% vs. 89.8% at 10 years. In the EORTC study 22881–10882, the absolute benefit of a boost in terms of local control was most pronounced in young patients [52–55].

A new technical perspective is to apply SIB to the whole breast 3D-CRT plan, in one integrated treatment schedule throughout the entire course of treatment. In this case, the whole breast represents the PTV and is exposed to a daily fraction of 1.8 Gy for 28 days, a total dose of 50,

40 Gy. Additionally, the tumor bed CTV is delineated, guided by the presence of the surgical clips, hematoma, seroma and/or other surgery-induced changes and is irradiated with a daily dose of 2.3 Gy (76.2%) or 2.4 Gy (23.8%) adding up to a total dose of 64.4 Gy or 67.2 Gy. These fractionation schemes are biologically equivalent to the sequential boost technique [56, 57].

The SIB technique is proposed for standard use in breast-conserving radiation therapy, because it can be easily implemented to reduce excess volumes of normal tissue irradiated, shorten the treatment course, decrease the dose per fraction for the breast, and increase the dose per fraction for the boost, with a relatively low incidence of acute skin toxicity (**Figure 11**).
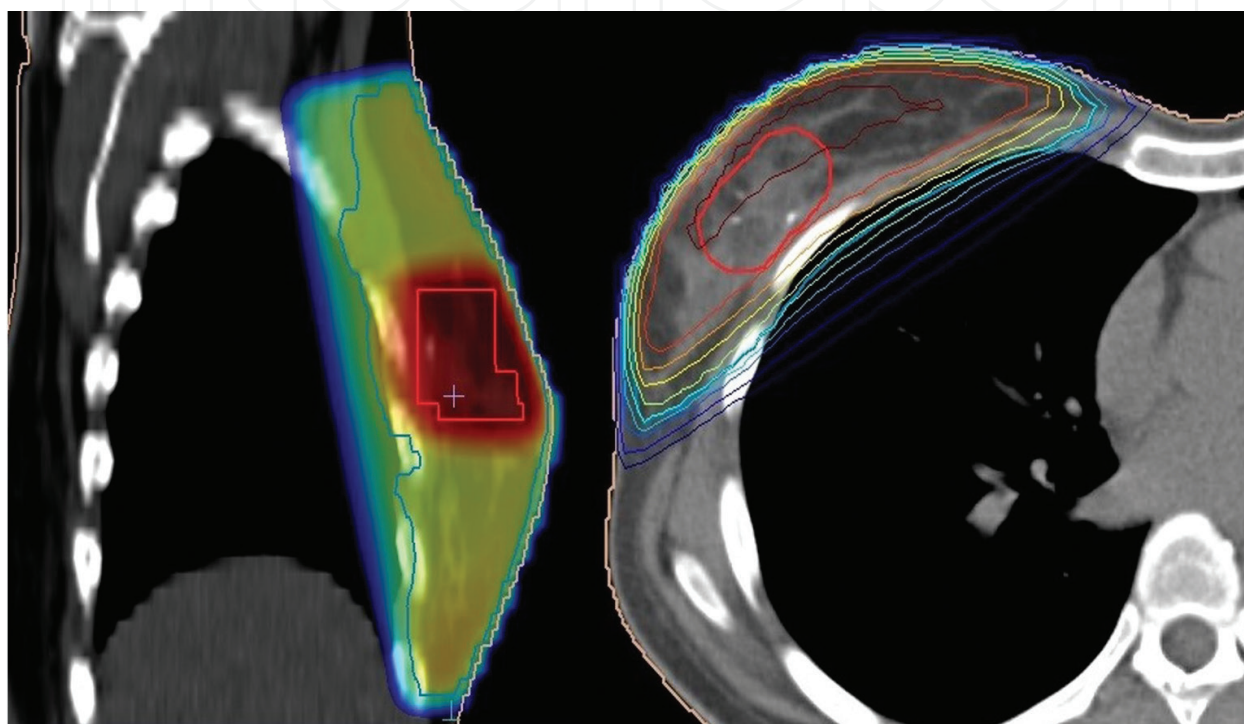


**Figure 11.** SIB breast cancer-tumor bed guided by the presence of the surgical clips.

The prospective RTOG 0529 phase II trial investigated the utility of IMRT in **anal cancer**. The two-year loco-regional control rate was 80%. In comparison with the results of RTOG 98–11, the use of IMRT reduced early G3 or higher gastrointestinal toxicity from 36 to 22%, and G3 or higher skin toxicity from 47 to 20%. However, until long-term control rates become available, concerns remain regarding potential compromise of tumor control rates using more conformal radiotherapy.

Several different SIB-IMRT schedules are described in various literatures. In the RTOG trial, the total dose varied according to T stage, in which 45 Gy/50.4 Gy was given to T1/T2 and 55–59 Gy/54 Gy to T3/4 tumors (RTOG 98–11, RTOG 0529). In contrast to tactics used in many US centers, where 59 Gy were administered regardless of T stage, with very few exceptions for very small primary tumors [58–62].

A new SIB-IMRT schedule is presented to treat patients with anal cancer in two series using moderate single doses from 1.5 to 2.0 Gy with a total dose of 59 Gy in combination with

mitomycin and 5FU 5FU/MMC. The results, in terms of loco-regional control and toxicity, are comparable to the results of other studies. Remarkably, the incidence of treatment interruptions was very low. Therefore, this regimen appears to be safe and favorable for clinical use.

The optimal technique of IMRT with or without SIB is still under debate, and up to date no standard SIB-IMRT schedule has been established.

The overall radiation therapy treatment time plays an important role, since every single one day prolongation of treatment beyond 30 days leads to 1% loss of tumor control in patients with **cervix carcinoma**. The presence of lymph node metastases in cervical cancer patients is a significant risk factor for disease recurrence. Currently available data showed that [18]FDG-PET\CT detects more favorable results as far as regional disease when compared with the CT or MRI. PET/CT contributes to better disease control as far as better diagnosis of local and regional disease spread with consequent better delineation based on molecular data [63–66].

IMRT with simultaneous integrated boost (SIB) improves the therapeutic ratio and delivers different doses to different parts of the irradiated volume through dose painting. Further trials are needed in order to optimize the treatment procedure (**Figure 12**).
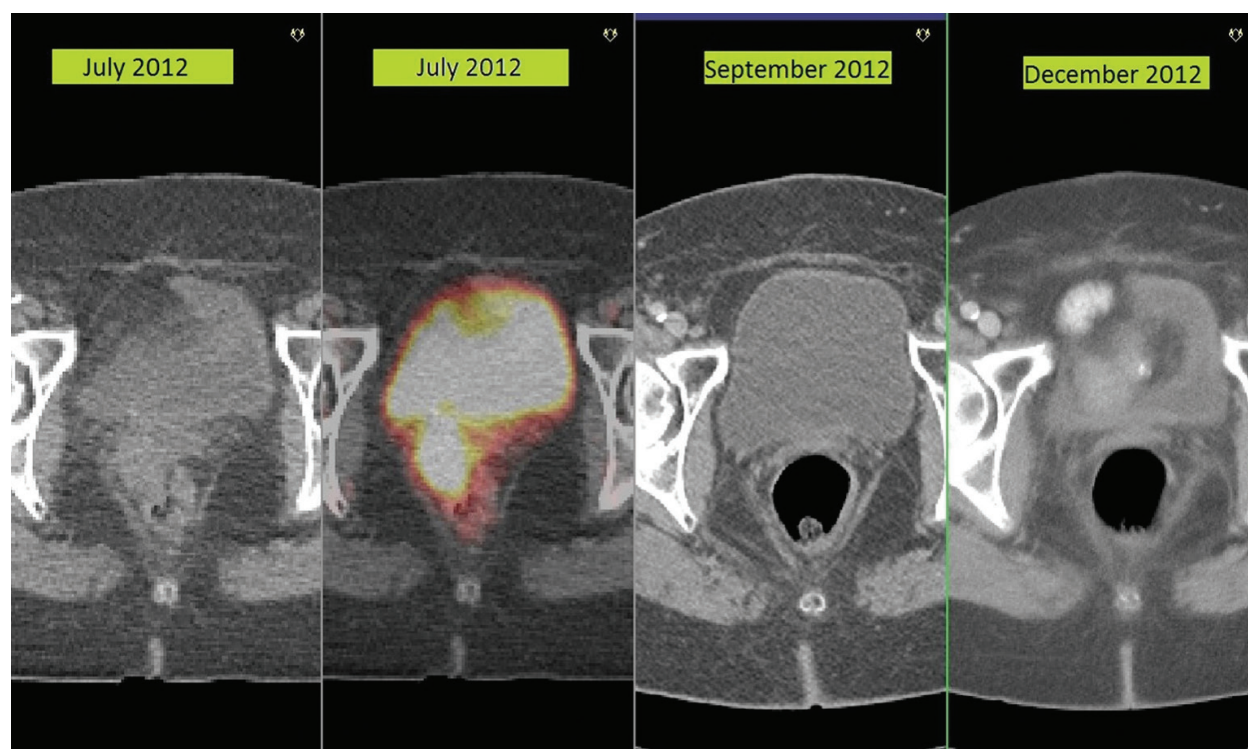


**Figure 12.** Follow-up of a patient treated with SIB-IMRT.

Local recurrences after external beam radiotherapy for **prostate cancer** are dose-dependent and mainly occur in the dominant intraprostatic lesion, i.e., the initial tumor site. Trials published demonstrated the feasibility and safety of delivering a SIB to the dominant intraprostatic lesion. No increase in acute and late GU or rectal toxicity was observed when performing a SIB up to an eight-year follow-up. The impact on outcome of focal boosting to the dominant

intraprostatic lesion is currently evaluated in an ongoing phase 3 trial randomizing intermediate and high-risk prostate cancer patients to receive either 77 Gy (35 fractions) or 77 Gy to the prostate with an additional boost to the macroscopic tumor up to 95 Gy [67–71].

## 3. Conclusion

The SIB-IMRT or SMART is feasible and time sparing with encouraging loco-regional results and controlled side effects. From a radiobiological point of view, it appears to be an effective RT strategy for the primary treatment of H&N cancers, and also for various other cancer types. Many different SIB schedules have been employed so far, but a standard regimen has not yet been defined. Based on the available published studies on the SIB-IMRT, the short-term clinical outcome is very promising. However, very few data on late effects are available as of yet, due to the short follow-up time in the majority of the reported studies. However, further data are awaited shortly from ongoing clinical trials in order to determine the most efficient protocol.

For the past 5 years, our department has been using the SIB method where it is applicable. All images shown in this chapter are actual images of patients we personally have treated.

## Acknowledgements

## Conflicts of interest statement

Nothing to declare.

## Author details

Despina Katsochi

Address all correspondence to: dkatsochi@aktinotherapeia.com
Hygeia Hospital, Athens, Greece

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