Present and future of radiation oncology

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Abstract

Modern advances in computers have allowed parallel advances in imaging technologies. The improvements in imaging have in turn resulted in a higher level of complexity being incorporated into radiotherapy treatment planning systems. As a result of these changes, the delivery of radiotherapy evolved from therapy designed on two dimensional x-ray images and hand calculations to three-dimensional x-ray based images from computerized tomography (CT), incorporating increasingly complex computer algorithms reaching to intensity modulated radiation therapy (IMRT). The incorporation of multimodality imaging (MRI, MR spectroscopy, PET....) is increasingly used for radiotherapy planning. In addition, greater awareness of the challenges to the accuracy of the treatment planning process, such as problems with set-up error and organ movement, have begun to be systematically addressed, ushering in an era of so-called Four-Dimensional Radiotherapy. In this review, we will detail these advances, how they have changed the way cancers are treated now and will be treated in the near future.

Introduction

The greatest challenge for radiation therapy or any cancer therapy is to attain the highest probability of cure with the least morbidity. The simplest way in theory to increase this therapeutic ratio with radiation is to encompass all cancer cells with sufficient doses of radiation during each fraction, while simultaneously sparing surrounding normal tissues. In practice, however, we have been hampered by our abilities to both identify the cancer cells and target them with radiation. The technology of radiotherapy planning and delivery have undergone rapid changes in the last decade due mainly to computer and imaging advances. In this review, we highlight how these new technologies are being used now and are likely to be used in the near future.

Radiotherapy Techniques

The planning of radiotherapy treatment has been revolutionized by the ability to delineate tumors and adjacent normal structures in three dimensions using specialized CT scanners and planning softwares[1].
Two-dimensional (2D) radiotherapy consisted of a single beam from one to four directions. Beam setups were usually quite simple; plans frequently consisted of opposed lateral fields or four-field "boxes". The introduction of three-dimensional (3D) conformal radiotherapy and intensity-modulated radiotherapy (IMRT) has allowed more accurate placement of radiation beams than is possible using conventional X-rays, where soft-tissue structures are often difficult to assess and normal tissues difficult to protect.
Traditionally, the irradiated volume encompasses the gross tumour volume (GTV) and the area at risk for microscopic spread : the clinical target volume (CTV). To assure a proper coverage of the CTV, a margin is added to compensate for daily positioning errors and internal motion of organs, resulting in the planning target volume (PTV), to which the radiation dose is prescribed.

> 3D CRT and IMRT

An enhancement of virtual simulation is 3-Dimensional Conformal Radiotherapy (3DCRT), in which the profile of each radiation beam is shaped to fit the profile of the target from a beam's eye view (BEV) using a multileaf collimator (MLC) and a variable number of beams. When the treatment volume conforms to the shape of the tumour, the relative toxicity of radiation to the surrounding normal tissues is reduced, allowing a higher dose of radiation to be delivered to the tumor than conventional techniques would allow.
Intensity-Modulated Radiation Therapy (IMRT) is an advanced type of high-precision radiation that is the next generation of 3DCRT [2;3] Computer-controlled x-ray accelerators distribute precise radiation doses to malignant tumors or specific areas within the tumor. The pattern of radiation delivery is determined using highly-tailored computing applications to perform optimization and treatment simulation. The radiation dose is consistent with the 3-D shape of the tumor by controlling, or modulating, the radiation beam's intensity. IMRT also improves the ability to conform the treatment volume to concave tumor shapes, for example when the tumor is wrapped around a vulnerable structure such as the spinal cord or a major organ or blood vessel or salivary glands. The

radiation dose intensity is elevated into the gross tumor volume while radiation dose among the neighboring normal tissue is decreased or avoided completely. The customized radiation dose is intended to maximize tumor dose while simultaneously protecting the surrounding normal tissue.

3DCRT is still used extensively for many body sites but the use of IMRT is growing in more complicated body sites such as brain, head and neck, prostate, breast and lung. Unfortunately, IMRT is limited by its need for additional time from experienced medical personnel. This is because physicians must manually delineate not only the tumors on one CT image at a time through the entire disease site but also absolutely all organs at risk which can take much longer than 3DCRT preparation. Then, medical physicists and dosimetrists must be engaged to create a viable treatment plan. And before starting treatment, quality control on the accelerators is much more complex than with 3D CRT. Also, the IMRT technology has only been used commercially since the late 1990s even at the most advanced cancer centers, so radiation oncologists who did not learn it as part of their residency program must find additional sources of education before implementing IMRT.

Proof of improved survival benefit from either of these two techniques over conventional radiotherapy (2DXRT) is growing for many tumor sites, but the ability to reduce toxicity is generally accepted. Both techniques enable dose escalation, potentially increasing usefulness. There has been some concern, particularly with 3DCRT, about increased exposure of normal tissue to radiation and the consequent potential for secondary malignancy. Overconfidence in the accuracy of imaging may increase the chance of missing lesions that are invisible on the planning scans (and therefore not included in the treatment plan) or that move between or during a treatment (for example, due to respiration or inadequate patient immobilization). New techniques are being developed to better control this uncertainty—for example, real-time imaging combined with real-time adjustment of the therapeutic beams. This new technology is called image-guided radiation therapy (IGRT) or four-dimensional radiotherapy – see paragraph 4.

The first works on IMRT were aimed at irradiating patients with head and neck cancer particularly nasopharynx cancer who have a high rate of cure but, due to salivary glands irradiation, were enduring definitive dry mouth, a reduction in taste, and poor dental health. Before IMRT we were unable to reduce these side effects without risking a compromise in cure. The IMRT technique allowed to avoid salivary glands while delivering the same dose to the clinical target volume. Figure 1 displays the previsional dosimetry for a patient with head and neck cancer; figure 1a displays the usual conformationnal treatement, the parotid glands (in purple and blue) receive most of the total dose; on figure 1b, with IMRT, the parotid glands receive a media dose inferior to 26 Gy that keeps them functioning. On figure 1C, the different fields for IMRT are displayed, they are composed by the addition of several subsegments, therefore each beam has a modulated intensity.
IMRT indications are now broadened to all other types of cancer, but mainly to cancers where there is a need for concave tumor shapes of irradiation and steep doses, therefore it is used for
- prostate tumors in order to protect the rectum and increase dose
- in brain tumors when fragile structures as the optic pathways are close to the target volume
- in paediatric tumors when IMRT can avoid late neurological or musculo-squelettal sequelaes
- in mesotheliomas, as it is the only way of irradiating the whole pleura and avoiding lung.

IMRT can be performed either
- on a new generation linear accelerator (Elekta®, Varian® or Siemens®) equipped with multi-leaf collimators and an IMRT software.
- on a special device dedicated only to IMRT : the TomoTherapy® Hi·Art® treatment system The treatment is based on the concept of slice therapy. By mounting the linear accelerator (linac) on a ring gantry, tomotherapy allows a 360° fan-beam delivery of IMRT and fully-integrated, megavoltage CT imaging. This device is equipying around 100 cancer centers worldwide, among them four centers in France, of the federation of comprehensive cancer centers (federation national des centres de lutte contre le cancer FNCLCC) : Bordeaux, Nantes, Paris and Toulouse.
The possibility to acquire rapid daily in-room CT imaging (CBCT) allows adaptive dose guided radiotherapy as shown in figure 2.

> High precision radiotherapy
High precision radiotherapy has to be delivered when the dose needed for a small tumour control exceeds the limiting tolerated dose of the surrounding tissues.
Its technical application requires a stereotactic coordinate system, highly accurate patient repositioning (usually fixed), and multiple convergent beams of photon radiation. Radiosurgery provides no benefit for infiltrative tumors. Moreover the hypofractionation or the use of single dose is more harmful for the surrounding tissue, therefore its use is very limited.
Radiosurgery can be delivered
- with a Gamma Knife® device, but exclusively for brain radiosurgery, and contrarly to all radiotherapy devices now that are linear accelerators using X rays, this device has permanent radioactive sources of Cobalt-60. These 201 sources of radioactive cobalt direct gamma radiation to the center of a helmet, where the patient's head is inserted.
- with a new generation linear accelerator equipped with on-board imaging and a micro-multileaf collimator, for any type of tumor.
- with a CyberKnife®, which is a compact linear accelerator mounted on a robotic arm. For small lung cancer : it allows

to deliver precisely an ablative radiation dose with surgical precision when surgery is not possible. As the robotic arm of the accelerator can follow breathing movements through implanted markers or through markers placed on the surface of the thorax[4]. For example, it can be used too for prostate cancer, small intracerebral tumors, or irradiation at high dose around the spine (initial treatment or reirradiation).

Hadrontherapy: protontherapy and light ions therapy

The particle or hadron beams deployed in radiotherapy (protons and light ions as carbon) have physical and radiobiological characteristics which differ from those of conventional radiotherapy beams (photons) and which offer a number of theoretical advantages over conventional radiotherapy. They deposit their maximum energy density in the Bragg peak at the end of their range, where they can produce severe damages to the cells while sparing both traversed and deeper located healthy tissues.

> Protontherapy

A beam of protons allows highly conformal treatment of deep-seated tumours with millimetre accuracy, giving minimal doses to the surrounding tissues. The result is a smaller treatment volume and therefore a lower incidence and frequency of treatment-related morbidity. Moreover, the reduction in treatment volume permits a higher dose to the tumor. This means an improved local control probability and lower normal tissue complications. The indications for protontherapy are pediatric tumors[5;6], uveal melanomas, base of skull/spinal chordomas and chondrosarcomas and prostate tumors[7]. Although the construction and running costs of hadrontherapy units are considerably greater than those of conventional facilities, a comprehensive analysis that considers all the costs, particularly those resulting from the failure of less effective conventional radiotherapy and the late sequelae induced, might indicate that hadrontherapy could be cost effective. To date, there are only 32 protontherapy centers in operation in the world, and at least 20 others centers proposed. The growing interest in this form of treatment seems to be fully justified by the results obtained to date, although more cost-effectiveness, efficacy and dosing studies are required.[8-10]

> Light ions beams

Other charged particles therapy with carbon ions for example are under evaluation and used for the moment in only a handful of centers around the world.

Quality assurance

Great technical and tools advances in external radiotherapy oblige consequently centers to perform a complete quality control and security control. Methods and appropriate procedures are either imposed by legislation[11] or registered by learned societies or reference organisms[12].

The first step of quality assurance consists in proving the constant performances of linear accelerators and software during acceptance tests or major changes (breakdown, fault, new software version etc). The second step of quality assurance controls the dose applied to the patients (pre-therapeutic measurements with water phantom and ionization chamber, in vivo dosimetry[13] etc...) in order to detect possible systematic or unpredictable errors in process.

Besides, beyond standard and conformational radiotherapy, innovative particular techniques such as intensity modulated radiotherapy, radiosurgery or Tomotherapy® amplified the necessity of more specific total quality control[14] due to the potential greater danger linked to their wrong uses.

Finally, it is important to stress the fact that beyond any control, human error remains the first reason of undesirable events in external radiotherapy[15] and that the human factors (trainings, communication, etc) cannot be excluded from these steps.

Image guided radiotherapy (IGRT)

These radiotherapy techniques have shown to reduce normal tissue toxicity and to allow radiation dose escalation, thus increasing tumor control probability[1;16-18]. On the other hand, the dose distributions delivered to the site of interest can be highly conformal with steep dose gradients. Any variation in organ volume or position during treatment may significantly alter the actual dose delivered to both the target and surrounding normal tissue. This argues for image-guided radiation therapy. Namely, image-guided radiation therapy uses :

- the incorporation of multimodality imaging for treatment planning in order to delineate accurately the target volumes
- then the use of in-room imaging for patient repositioning maximum accuracy.

Image registration is now becoming central to every step of the radiotherapy planning and delivery process. It can improve the ease and accuracy with which multimodality images can be incorporated into a single model of the patient[19], by resolving the geometric discrepancies that exist between the images.

> Multimodality imaging for radiotherapy planning

> CT and MRI

As all patients undergo a CT scanner with their immobilization device on, a good quality CT is helpful to delineate tumors. But the registration of MRI scan data sets with the treatment-planning CT scan is essential for accurate definition of tumor and surrounding organs at risk, in case of brain tumors[20] and prostate tumors[21].

> Metabolic and functional imaging for radiotherapy planning

Integrating additional metabolic and functional imaging studies that reflect the biologic characteristics of tumors is an area of active research.

> Positon Emission Tomography (PET)

2-[18F]fluoro-2-deoxyglucose (FDG) – PET imaging is useful, not only in characterizing disease extent in many tumors of which particularly Lung, Head & Neck and Hodgkin tumors but also in helping target volume definition. It will not be of similar utility across all tumor sites.
It has been now proved that nodal involvement can not be only predicted on the size of the node on the CT[22]. Therefore the addition of PET for planning allows to improve the coverage of nodal extent in lung and head and neck tumors, by either increasing or diminishing the nodal target volume.
For primary lung tumors, recent papers have shown that the use of the registration of PET images on the planning CT diminishes significantly the interobserver variability of tumor delineation when the tumor is close to large vessels, mediastinum of when there is a part of atelectasia[23-25].

For Head and neck tumors[26], the definition of the tumor contours depends on the display windowing that strongly influences the visual rendering of the tumor leading to intra and interobserver variability. Research is still focusing on a reliable segmentation method. As an example, Paulino et al showed that tumor delineated with FDG-PET were larger than those delineated with a CT in 25% of the cases[27].As a whole, PET-FDG is useful for nodal determination[26;28] and is promising for primary tumor definition but it remains a challenging task and an incompletely resolved issue.

Other types of markers are subjects to research too for radiotherapy planning: F-Misodinazole (F-Miso), 11C-methionine (MET) and O-2-18F-fluoroethyl-L-tyrosine (FET).

> Functional Magnetic resonance (MR) imaging

MR spectroscopy, the example of glioblastoma
Proton MR spectroscopy is a technique which is able to characterize biochemical, metabolic, and pathologic changes of tissues, it has been extensively used to date for prostate and brain tumors[29-33]. It was recently suggested that MRSI would be a valuable diagnostic tool for defining the sites of metabolically active tumor[34;35] among and outside MRI abnormalities[36] and for the assessment of residual disease after surgical resection in high-grade gliomas (HGG)[37].
It is, as well, a helpful modality in characterizing suspicious MRI lesions in irradiated gliomas[38-41].

For example, the patients with Glioblastoma Multiforme (GBM) have a poor prognosis and although adjuvant RT increases overall survival, the predominant pattern of failure continues to be within the irradiated volumes[42-44]. As a result, there is a growing interest in increasing the dose to certain portions of the tumor while sparing normal tissue with new technologies such as Radiosurgery (RS)[45] and intensity-modulated radiation therapy (IMRT)[46-48]. T1-weighted images (T1WI) with gadolinium show a heterogeneous, irregular, contrast-enhancing lesion that usually underestimate tumor volumes, as contrast enhancement is more a reflection of blood-brain barrier disruption than actual tumor extent. Conversely, T2-weighted images tend to overestimate tumor volumes due to the high signal intensity resulting from surrounding edema as well as microscopic tumor extension[49]. Since diagnosis and planning for surgical, chemotherapy and radiotherapy treatment utilize MR methods, increased information describing tumor extent and functional regions within the heterogeneous environment would be useful. We reasoned that MRSI might be a valuable tool for helping target definition for radiotherapy.

We recently published the results of a prospective longitudinal study[50] that found a strong predictive value of metabolically abnormal region seen on MR spectroscopy imaging (MRSI) before RT for the site of onset of progression or recurrence. In our study, all patients were included in a prospective phase I clinical trial associating a farnesyltransferase Inhibitor with radiotherapy[51] and underwent MRI/MRSI before RT and every two months thereafter. Among the 23 MRS studied and 1207 voxels analyzed, we observed that metabolically abnormal regions represented a small percentage of MRI lesions before RT, and that without MRSI data; the imaging abnormalities do not predict the site of relapse. We showed that MRSI either alone or associated with T1 and T2 weighted images has a highly statistically significant predictive value for the site of relapse. Our opinion it that the incorporation of MRSI data in the definition of radiotherapy target volumes may be a promising avenue leading to increased local control of glioblastoma. Figure 3 is an example of our results[50].

> Other MR functional imaging
- Prostate MR spectroscopy: the addition of MR spectroscopy to MRI improves the sensitivity and specificity for identifying sites of predominant intraprostatic lesion and therefore has been used for targeting radiotherapy boosts, particularly with IMRT or with brachytherapy[52]. MR prostate diffusion is under evaluation.
- Brain MR perfusion and diffusion: these modalities may give additional information on the localization of radio-resistant areas and are under evaluation in prospective clinical trials

> In room imaging for patient repositioning accuracy
To account for geometric uncertainties during radiotherapy, safety margins are applied. In many cases, these margins overlap organs at risk, thereby limiting dose escalation. The aim of image-guided radiotherapy is to improve the accuracy by imaging tumors and critical structures on the machine just before irradiation. The availability of high-quality imaging systems and automatic image registration

on the machine leads to many new clinical applications, such as high-precision hypofractionated treatments of brain metastases and solitary lung tumors with online tumor position corrections. IGRT makes use of many different imaging techniques, using modalities ranging from planar imaging to fluoroscopy to cone-beam CT, and following procedures as simple as using a single set-up image or as complex as intra-fraction tumor tracking. Figure 4 and 5 display the examples of use of in-room imaging.

Respiratory gating

Respiration-gated radiotherapy improves significantly the irradiation of tumor sites affected by respiratory motion such as lung, breast and liver tumors. Reduction of respiratory motion can be achieved by using either breath-hold techniques or respiration synchronized gating techniques. Breath-hold techniques can be achieved with active techniques, in which airflow of the patient is temporarily blocked by a valve, or passive techniques, in which the patient voluntarily holds his/her breath. Synchronized gating techniques use external devices to predict the phase of the respiration cycle while the patient breathes freely[53].

Summary

In summary, there have been recently many exciting advances in radiation therapy including IMRT, functional imaging for RT, and in-room imaging. These modalities are more commonly finding their way into clinical practice and early data are emerging on their effectiveness. The next decade is likely to yield more advances regarding the role of radiotherapy in an increasingly multidisciplinary oncology environment.

FIGURES

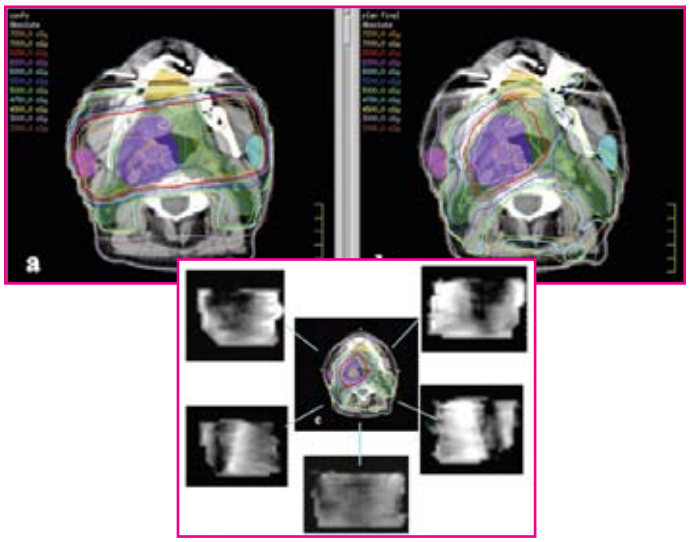

Figure 1 displays the previsional dosimetry for a patient with head and neck cancer; figure 1a displays the usual conformational treatment, the parotid glands (in purple and blue) receive most of the total dose. Dose delivered to tumor is 70 Gy, to nodal areas is 50 Gy and the dose that stops parotid glands from functionning is 26 Gy, the dose received with conformal treatment is superior to 65 Gy; on figure 1b, with IMRT, tumor receives a more conformal dose of 70 Gy, nodal areas receive 50 Gy and the parotid glands receive a much lower median dose that keeps them functioning. On figure 1C, the different fields for IMRT are displayed, they are composed by the addition of several subsegments, therefore each beam has a modulated intensity.

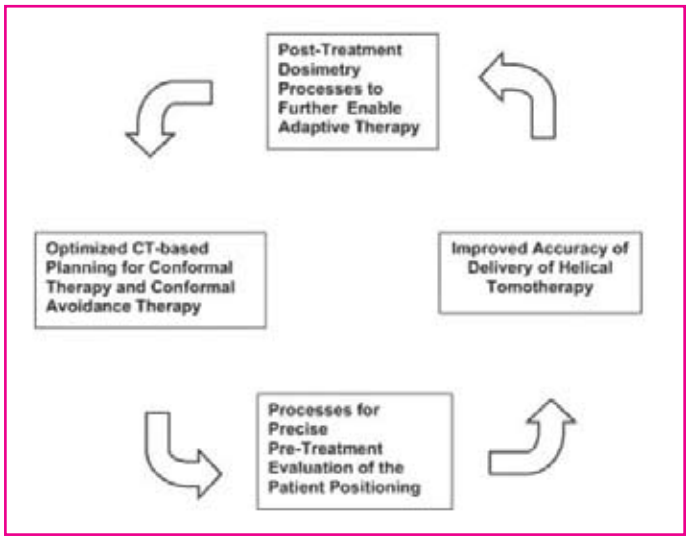

Figure 2 The possibility to acquire rapid daily in-room CT imaging (CBCT) allows adaptive dose guided radiotherapy.

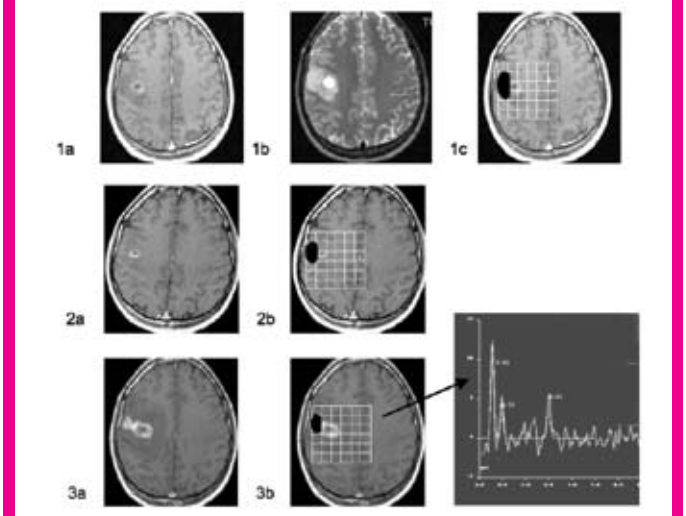

Figure 3 MR spectroscopic follow-up of a 31 years old patient with an unresecable glioblastoma
1- before radiotherapy:
Axial T1WI post contrast
Axial T2WI
MRSI volume, the black region is metabollicaly active and was situated on the T2 hyperintensity (HyperT2), outside contrast enhancement (CE) on T1 weighted sequences (T1).
At 4 months: HyperT2 regions outside CE on T1 kept metabolically active despite lesion regression.
At 6 months:. The initial lesion was growing and a new CE appeared exactly on the site of the initial and persistent metabolically active region. The choline on NAA ratio of this voxel was greater than 2.0 suggesting it was recurrent tumor rather than radiation necrosis. The patient died one month after the six-month scan.

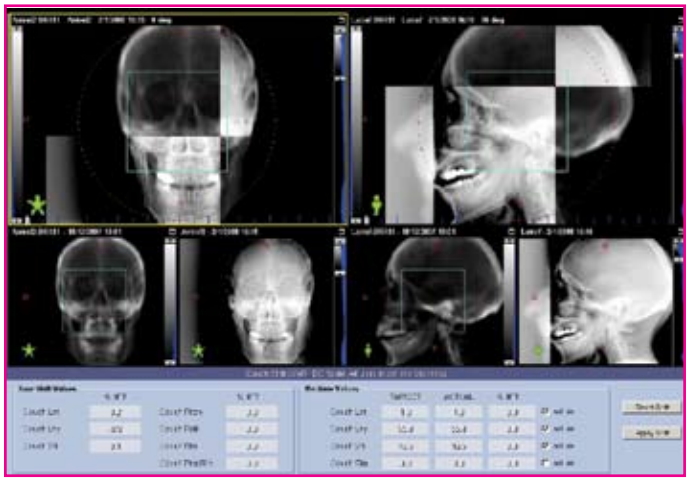

Figure 4 Combined kilovoltage orthogonal images : exemple of an overlay of digitally reconstructed radiographs (from the planning CT scanner) and daily kilovoltage imaging after adjustement. The necessary adjustements required for registration of both imaging sets yield information on the corrections that are required for patient set-up.

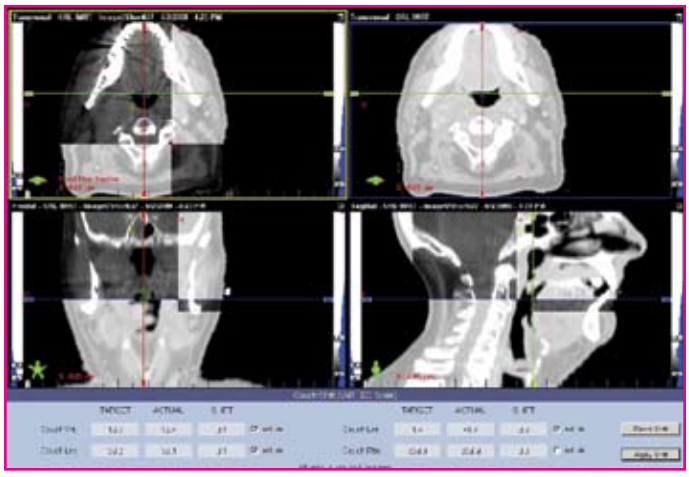

Figure 5 combined computed tomography and daily MVCT image data. Example of an overlay (axial and sagittal cross-sections are shown) of planning computed tomography data and daily Megavolt computed tomography (MVCT) data, after adjustment. The necessary adjustments required for registration of both imaging sets yield information on the corrections that are required for patient set-up.

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