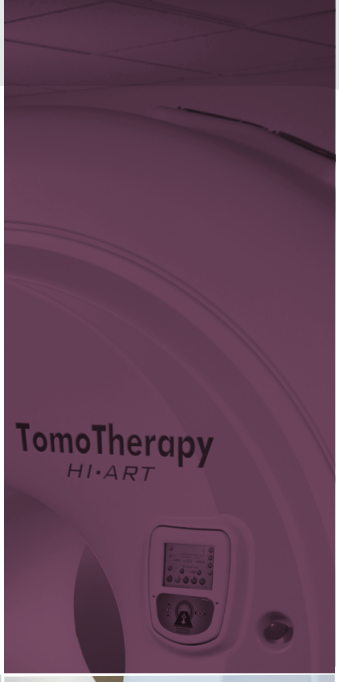
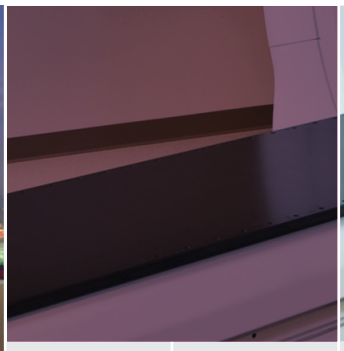
Clinically Proven

Metabolically-Guided TomoTherapy℠ Treatments Advancing Cancer Care





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San Raffaele Hospital, a nationally-recognized Scientific Institute, was the first radiotherapy department in Europe to offer *TomoTherapy* treatments in 2004. We chose the advanced technology to help us take our biomedical and clinical research even further. We demonstrated that hypofractionation and dose escalation can be administered safely and efficiently, especially when *TomoTherapy* is combined with metabolic imaging. Through clinical studies, we continue to demonstrate that combining *TomoTherapy's* advanced IG/IMRT technology with PET/CT imaging allows for highly-advanced treatments that deliver significant patient benefit.

CHOOSING THE MOST ADVANCED TECHNOLOGY TO PURSUE A NEW IDEA

We view *TomoTherapy* as the most sophisticated technology for radiation treatment using external beams. For the past seven years, our patients have benefited from helical treatment delivery and fully integrated megavoltage CT (MVCT) imaging for each of their daily treatment fractions. *TomoTherapy's* design concept for IG-IMRT gives us the advanced technology needed to expand our research interest in the role of PET/CT in radiation oncology.

Our *TomoTherapy* Hi·Art® is used with a PET/CT scanner, creating what we call "Metabolically-Guided *TomoTherapy*." The combination provides excellent tumor definition, highly advanced treatment delivery and improved control of the patient's position. In particular, this gives us the precision needed for hypofractionated treatment regimes.

PROVING THE CONCEPT WITH PROSTATE STUDIES

In 2007, we published our first results on the positive effect of *TomoTherapy* in reducing toxicity of prostate cancer treatment [1, 2]. One of the reasons for our success is that *TomoTherapy* is an excellent planning solution for prostate cancer. Our physics team has shown it to be highly efficient in a simultaneous integrated boost (SIB) scenario [3]. Therefore, we were not surprised that our hypofractionated SIB approach for prostate cancer — delivering 71.4-74.2 Gy in 28 fractions — shows excellent results with regard to acute toxicity [4].

Our experience in prostate cancer patients treated with hypofractionated *TomoTherapy* has demonstrated excellent results in terms of acute and late toxicity. No patients experienced acute rectal or upper intestinal toxicity greater than grade 1, and only 2% had late rectal toxicity. In addition, the three-year biochemical-free survival of 89% seems better than that reported in other studies in the literature.

To learn more about this promising concept, a research project has been started to define molecular profiles indicative of better response to hypofractionated radiation therapy. The goal is greater efficacy and precision in patient selection. To do so, we will correlate semi-quantitative data provided by PET/CT to proteomic data, in order to find a possible relationship between the effects of radiotherapy on [11C]Choline uptake and proteomic characteristics.

ESCALATING DOSES

Because *TomoTherapy* allows us to expand clinical opportunities of radiotherapy, we also conducted a feasibility study to understand whether it is safe to escalate dose to single or multiple highly radio-resistant dominant intra-prostatic lesions (DILs).

Within a feasibility study, we simulated a *TomoTherapy* treatment delivering an SIB to one or two DILs in seven patients and found that safe escalation may be possible to at least 113 Gy without significant increase in the rectal normal tissue complication probability (NTCP). A Phase I–II study will allow us to investigate the clinical possibilities further [5].

Another highlight is the [11C]Choline-PET-guided helical *TomoTherapy* that we perform in patients with abdomino-pelvic lymph nodal recurrent prostate cancer. With a mean follow-up of 26 months, all patients showed significant prostate-specific antigen (PSA) reduction and in many cases (50%) PSA became undetectable. Few cases experienced

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PROSTATE
RECTUM
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LUNG
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HEAD AND NECK

grade 1 or 2 acute toxicity and no late toxicities were recorded. A disease-free survival of 26 months, in the absence of any type of systemic therapy, is uncommon in metastatic prostate cancer [6].

EXPANDING INNOVATIVE TREATMENTS TO MANY DISEASE SITES

Following our successes with prostate treatments, we started studies on many different disease sites with the combination of *TomoTherapy* and PET/CT. Detailed information on our approach for rectal adenocarcinoma, head and neck, lung, malignant pleural mesothelioma, pancreas, gynecological, brain and cranio-spinal irradiation can be found in the appendix.

SUMMARY

TomoTherapy has allowed us to demonstrate the viability of new, highly effective radiation oncology treatments that show real benefits for our patients. We are excited to continue our work collecting clinical outcomes data related to acute and late toxicity. The addition of our third *TomoTherapy* system, the more advanced TomoHD™ with new core technologies, will allow us to treat patients even faster — this will speed our research and potentially help even more patients around the world receive the advanced treatment care they deserve.

APPENDIX

RECTAL ADENOCARCINOMA

Between 2007 and 2009, we enrolled 20 patients in a Phase II study to investigate the effect of preoperative, moderately hypofractionated, image-guided *TomoTherapy* treatment concomitant to oxaliplatin and 5-FU in rectal adenocarcinoma. Preliminary results were promising, particularly in terms of low rate of acute toxicity [7].

In order to further improve the complete pathologic control rate, we explored the possibility of delivering a concomitant boost. A retrospective estimation of rectal volume variations during the *TomoTherapy* treatment was performed (an overall average shrinkage of more than 50% was detected) and a reduced variation of rectal volume in the second half of the treatment suggested an advantage in delivering the concomitant boost during the last six fractions. Moreover, we decided to apply a boost to the residual tumor assessed by an intermediate treatment course CT/MR simulation. Preliminary results are encouraging [8].

HEAD AND NECK

We published our first results on the positive effect of *TomoTherapy* treatments for the toxicity profile of head and neck cancer in 2006 [9]. Due to the capability to spare organs at risk and increase dose delivered to the target, *TomoTherapy* is an excellent solution for head and neck cancer, particularly in a simultaneous integrated boost (SIB) scenario [10] when administered concurrently with chemotherapy.

To identify potentially radio-resistant tumor sub-volumes for head and neck tumors, which could benefit from a dose escalation program, we use multimodality imaging (MRI and PET/CT) for the planning. We found that *TomoTherapy* enables us to achieve low acute toxicity while shortening the overall treatment time in radical treatment of patients with advanced head and neck cancer, and in an adjuvant setting.

LUNG

In 2008 we published the results of a treatment planning comparison between conformal radiotherapy and helical *TomoTherapy*. We found that *TomoTherapy* is an excellent planning solution for locally advanced tumors, which usually involve large volumes [11]. Due to its sophisticated organ at risk sparing capability, *TomoTherapy* also allows the delivery of hypofractionated treatments in patients with inoperable locally-advanced non-small-cell lung cancer (NSCLC). To fully use *TomoTherapy's* capabilities for minimizing side effects, along with improved target definition, for treatment planning we evaluated lung perfusion using PET/CT and SPECT/CT imaging in order to spare functional lung as much as possible. In general we can say that *TomoTherapy* enables hypofractionation with an excellent toxicity profile and a

shortened overall treatment time.

In addition we obtained excellent results in hypofractionated *TomoTherapy* treatment of small lung lesions (primary and metastatic). It is possible to deliver a high dose in a few fractions thanks to a 65% reduction of the irradiated surrounding tissue achieved by considering motion with the help of 4D PET/CT images. None of the treated patients experienced acute or late toxicity.

MALIGNANT PLEURAL MESOTHELIOMA

There is no clear consensus on the optimal treatment of malignant pleural mesothelioma (MPM). Recent developments in the field of intensity-modulated and image-guided radiotherapy have led radiation oncologists to reconsider the role of radiotherapy in treating this disease. The role of FDG-PET/CT in the definition of the target volume in MPM treatment is not mentioned even in the most recent papers. Its prognostic value has been demonstrated however and some publications have shown that PET could play an important role in MPM diagnosis.

Using this evidence we started a feasibility study of dose escalation with *TomoTherapy*, based on FDG-PET/CT images taken for planning purposes, with the patient in the treatment position. A first group of 12 consecutive MPM patients was treated with 56 Gy in 25 fractions to the Planning Target Volume (PTV). FDG-PET/CT simulation was always performed for these patients to include all positive lymph nodes and MPM infiltrations. Subsequently, a second group of 12 consecutive patients was treated with the same dose to the whole pleura while adding a simultaneous integrated boost of 62.5 Gy to the FDG-PET/CT positive areas.

Good dosimetric results were obtained in both groups. No grade 3 (RTOG/EORTC) acute or late toxicities were reported in the first group; three cases of grade 3 late pneumonitis were registered in the second group, with the duration of symptoms being two to ten weeks. Median overall survival was eight months (1.2 to 50.5 months) and 20 months (4.3 to 33.8 months) from the beginning of radiotherapy, for groups I and II respectively (p= 0.19). A significant impact on local relapse from radiotherapy was seen (median time to local relapse of 8 versus 17 months; one-year local relapse-free rate of 16% versus 81%, p=0.003). In the second group, distant relapses were dominant, reproducing to some extent the result found in post-extra-pleural pneumonectomy radiotherapy with high-dose IMRT.

PANCREAS

For unresectable pancreatic cancer, contrast enhanced 4D-PET/CT is helpful in definition of target volumes. The first results of our Phase I-II dose escalation trial on hypofractionated image-guided radiation therapy, in both radical and adjuvant pancreatic cancer, indicate an acceptable grade-3 acute toxicity rate, while providing stabilization or improvement of local control [12, 13].

GYNECOLOGY

An exciting gynecology project will start shortly. We will investigate *TomoTherapy* versus RapidArc™ and static IMRT in gynecologic cancers, and also the use of *TomoTherapy* for brachytherapy substitution. Two protocols will be followed:

- Protocol I: whole pelvis irradiation, comparing static IMRT with RapidArc™ and helical *TomoTherapy* to determine the dosimetric differences among the three techniques, and the impact on acute and late toxicity in all cases.

- Protocol II: SIB for PET/CT-positive lymph nodes in the pelvic or lomboaortic region, while treating the whole pelvis with or without the lomboartic region. For this approach, RapidArc™ and helical *TomoTherapy* will be compared. Our hope is that the treatment-related mortality rate due to toxicity with standard radiotherapy can be reduced.

BRAIN

Helical *TomoTherapy* has been a useful tool in treating skull base tumors. Since June 2005, we have treated 23 patients, all evaluated with computer-based perimetry for assessing

their visual field. This was done prior to treatment and every six months after treatment, for the first two years of follow up, then on a yearly basis. In addition, MRI imaging was performed for treatment planning and every three months after treatment for evaluation during the first two years of follow up. After that, MRI imaging was performed every six months or yearly.

In all cases, good PTV coverage was achieved (average V95% = 96%) with an acceptable sparing of critical structures. Twenty-one patients showed stable disease at their last follow-up with only one extra-field recurrence for a patient with meningiomatosis, who was scheduled for a salvage re-irradiation with *TomoTherapy*. Visual function was evaluated with computerized campimetric assessment in 15 of the 23 patients treated. In 11 of these 15 patients visual function was stable, while in four patients it improved. In one instance, a patient with a recurrence of atypical meningioma experienced vision loss the week before treatment. After *TomoTherapy* treatment and high-dose dexamethasone, her vision improved, being able to see 4/10 diopters in the eye contralateral to the recurrence. Furthermore, no moderate or severe acute or late toxicities have been reported. These promising results will be presented at the International Course of Neurosurgery for skull base tumors that will be held in San Raffaele Hospital in 2011.

CRANIO-SPINAL IRRADIATION

Another field of interest is the capability of helical *TomoTherapy* in cranio-spinal irradiation (CSI) for patients with primitive brain tumors at risk for spine seeding. Our series includes seven patients treated for disseminated ependymomas and medulloblastomas. All patients were adults. The advantage of helical *TomoTherapy* in performing CSI is the ability to remove the need for junctions in the treatment field and junction shifts used to avoid beams overlapping in the spine. Moreover, patients can be treated in the supine position and the daily MVCT allows the best setup check for these treatments. The preliminary results of our work were presented at the 2009 International Conference on Translational Research and Pre-Clinical Strategies in Radiation Oncology (ICTR) in Geneva, Switzerland.

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