Rationale for adding a non invasive robotic radiosurgery system in a multi-platform radiotherapy department

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San Raffaele Scientific Institute Radiation Therapy Department

• 1st TomoTherapy® System in Europe installed in 2004 (substituted in 2013 with Tomotherapy H)

• 2nd TomoTherapy® System installed in 2007

• 3rd TomoTherapy® System installed in 2012

Simulator: “Varian Acuity”

CT simulator: “GE Hi Speed”

Rapid Arc “Clinac iX” Varian

Gamma knife “Perfexion”

TomoTherapy “Hi-Art® II System”

TomoHD™ System

TomoH™ System

CyberKnife® System
New patients/year : 2000
IMAGING

- Precise localization of the tumor and/or target volume and sensitive structures
- Reduce the uncertainty of microscopic extension
- Reduction of safety margins

IGRT

- Reduce the uncertainty in the set-up, identify and reduce organ motion
- High selectivity in radiation dose administration
- Increase of radiation dose and dose per fraction

IMPROVEMENT IN LOCAL CONTROL

- Reduction of collateral damage to OARs
How does the CyberKnife® System fit with the main diseases treated in our department?

1) Prostate Cancer
2) CNS malignancies
3) Breast Cancer
4) Metastases
5) ADAPTIVE RT Rectal Cancer
Prostate cancer


**Table 1**

<table>
<thead>
<tr>
<th>Volumes</th>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose/fraction</td>
<td>Total dose</td>
<td>Dose/fraction</td>
</tr>
<tr>
<td>PTV1 (lymph nodes)</td>
<td>1.85</td>
<td>51.8</td>
<td>1.85</td>
</tr>
<tr>
<td>PTV2 (cranial)</td>
<td>2.2</td>
<td>61.6</td>
<td>2.34</td>
</tr>
<tr>
<td>PTV3 (caudal)</td>
<td>2.34</td>
<td>65.5</td>
<td>2.65</td>
</tr>
<tr>
<td>Prostate</td>
<td>2.65</td>
<td>74.2</td>
<td>2.65</td>
</tr>
<tr>
<td>Overlap</td>
<td>2.34</td>
<td>65.5</td>
<td>2.65</td>
</tr>
</tbody>
</table>

**Di Muzio et al, Clin Oncol 2016**

**RTOG 5y TOXICITY**

**LAST FOLLOW UP TOXICITY**

**GU:**
- G 2-4: 20.2% (± 2.8)
- G 3-4: 5.9% (± 1.7)

**GI:**
- G 2-3: 17.0% (± 2.7)
- G 3: 6.3% (± 1.7)

**Table 5**

Five year outcome results (± standard deviation) for biochemical relapse-free survival, overall survival and cancer-specific survival.

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 211)</th>
<th>Low risk (n = 78)</th>
<th>Intermediate risk (n = 53)</th>
<th>High risk (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 year biochemical relapse-free survival</td>
<td>93.7% (± 1.9)</td>
<td>94.6% (± 2.6)</td>
<td>96.2% (± 2.6)</td>
<td>91.1% (± 4.0)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>88.6% (± 2.4)</td>
<td>90.5% (± 3.4)</td>
<td>87.4% (± 4.9)</td>
<td>87.0% (± 4.5)</td>
</tr>
<tr>
<td>Cancer-specific survival</td>
<td>97.5% (± 1.3)</td>
<td>98.7% (± 1.3)</td>
<td>95.0% (± 3.5)</td>
<td>94.3% (± 3.9)</td>
</tr>
</tbody>
</table>
“Extremely hypofractionated image-guided IMRT/SBRT regimens (6.5 Gy per fraction or greater) are an emerging treatment modality with single institutional and pooled reports of similar efficacy and toxicity to conventionally fractionated regimens. They can be considered as an alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise.” (NCCN Guidelines Version 2.2017, Prostate Cancer)


King CR, et al. Radiother Oncol 2013

Calculations of the dose distributions in SRS radiotherapy for VMAT and CyberKnife® System techniques shows, that stereotactic radiosurgery of prostate cancer can be carried out on CyberKnife® System accelerator as well as on the classical accelerator with the use of VMAT technique


- 53,841 IMRT patients & 1,335 SBRT patients with at least 6 months of follow-up
- Statistically significant higher GU toxicity at two years with SBRT
- No statistically significant difference in the incidence of fistulas between IMRT and SBRT at any point in time
- The majority of symptoms resolved with conservative management
- But...SBRT current techniques may be able to minimize dose to adjacent tissues (prostate targeting) → CyberKnife® System
- SBRT preferable for both patients and Institutions (insurers)

TABLE 4. Complications and Use of ADT Within 2 Years of Therapy

<table>
<thead>
<tr>
<th></th>
<th>SBRT n=176</th>
<th>Brachytherapy n=3885</th>
<th>IMRT n=9148</th>
<th>Proton Beam Therapy n=306</th>
<th>Combination Therapy n=2172</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>69 (39.2%)</td>
<td>1493 (38.4%)</td>
<td>3433 (37.5%)</td>
<td>124 (40.5%)</td>
<td>859 (39.5%)</td>
<td>.37</td>
</tr>
<tr>
<td>Urinary nonincontinence</td>
<td>26 (14.8%)</td>
<td>1191 (30.7%)</td>
<td>1405 (15.4%)</td>
<td>33 (10.8%)</td>
<td>737 (33.9%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>42 (23.9%)</td>
<td>1501 (38.6%)</td>
<td>1824 (19.9%)</td>
<td>44 (14.4%)</td>
<td>906 (41.7%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>41 (23.3%)</td>
<td>729 (18.8%)</td>
<td>1129 (12.3%)</td>
<td>33 (10.8%)</td>
<td>384 (17.7%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>NR</td>
<td>25 (0.6%)</td>
<td>104 (1.1%)</td>
<td>NR</td>
<td>30 (1.4%)</td>
<td>.02</td>
</tr>
<tr>
<td>ADT</td>
<td>13 (7.4%)</td>
<td>301 (7.7%)</td>
<td>2701 (29.5%)</td>
<td>29 (9.5%)</td>
<td>542 (25.0%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Median costs | $27,145 | $17,183 | $37,090 | $54,706

2) CNS malignancies

- First Gamma Knife installed in our institution in **1993**.
- Collaboration with the Neurosurgery.
- **9700 patients** treated up to the end of 2016 (2nd European centre after Marseille).

Leksell Gamma Knife® Perfexion™, version in use
Brain metastases
A 41 year-old woman with multiple metastases from lung adenocarcinoma, in treatment with Gefitinib, presented 10 brain metastases at MRI diagnosis. Sixteen lesions identified on volumetric MRI were treated in March 18, 2016. The patient is alive one year later, without brain PD.

A 52 year-old woman with brain metastases from breast cancer, already treated in 2013 with WBRT, presented a PD in March 2016, with 10 metastases at MRI. At stereotactic MRI 18 lesions were diagnosed and treated with GammaKnife.
Identical clinical results, but CyberKnife® System better tailored to target than GK for single brain metastases (Wowra B, et al. J Neurooncol 2009)

-Good CI, as GK for stereotactic radiosurgery of arteriovenous malformations and acoustic neuromas
-More homogeneous plans, because of inverse planning,
-Lower dose spread.
(Gevaert T, et al. Radiother Oncol 2013)
Lesions close to optic chiasma are not manageable with SRS, but SRT with Gamma knife is not tolerated by the patients, because of the stereotactic frame, which requires anesthesia to be positioned, and cannot be worn for more than one day.

GammaKnife can treat lesions up to C2, thus spinal lesions (meningiomas, schwannomas, metastasis), which need the same precision and the same reduced margins, can be treated with CyberKnife® System.


3) Breast cancer

- Our protocol for breast conserving therapy: whole breast hypofractionated (40 Gy/15 fr) adjuvant radiotherapy with forward planned intensity modulation (~1500 patients treated).

- 2.25% local failure at a median follow up of 68 months, with low acute (5 G3/442 pts) and late toxicity (2 G3/442 pts).
PBI good local control

ELIOT trial: better than expected results with EBRT in selected low-risk

TARGET A: reduced deaths for other causes (cardiovascular).


Table 3. Treatment-related toxicities (N = 75, n (%))

<table>
<thead>
<tr>
<th>Finding</th>
<th>Grade 0</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>62 (83)</td>
<td>12 (16)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>49 (65)</td>
<td>20 (27)</td>
<td>6 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Breast edema</td>
<td>52 (69)</td>
<td>18 (24)</td>
<td>5 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Breast pain</td>
<td>56 (75)</td>
<td>15 (20)</td>
<td>2 (2.5)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>65 (87)</td>
<td>6 (8)</td>
<td>4 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>41 (55)</td>
<td>28 (37)</td>
<td>6 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fat necrosis</td>
<td>69 (92)</td>
<td>3 (4)</td>
<td>3 (4)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Asymptomatic Symptomatic


Table 5. Cosmetic score with follow-up ≥6 months (n = 43)

<table>
<thead>
<tr>
<th>Cosmetic result</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>38</td>
</tr>
<tr>
<td>Good</td>
<td>58</td>
</tr>
<tr>
<td>Fair</td>
<td>4</td>
</tr>
<tr>
<td>Poor</td>
<td>0</td>
</tr>
</tbody>
</table>


Table 3
Incidence of first events.

<table>
<thead>
<tr>
<th>Event</th>
<th>Study population (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence</td>
<td>4 (8.9%)</td>
</tr>
<tr>
<td>TR/MM</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>EBF</td>
<td>4 (8.9%)</td>
</tr>
<tr>
<td>Regional recurrence</td>
<td>2 (4.4%)</td>
</tr>
<tr>
<td>Axillary failure</td>
<td>2 (4.4%)</td>
</tr>
<tr>
<td>Others</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>5 (11.1%)</td>
</tr>
<tr>
<td>Any first relapse*</td>
<td>11 (24.4%)</td>
</tr>
<tr>
<td>Contralateral breast cancer</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Second primary malignancy</td>
<td>4 (8.9%)</td>
</tr>
<tr>
<td>Non-breast cancer death</td>
<td>1 (2.2%)</td>
</tr>
</tbody>
</table>

(TR/MM = true recurrence/marginal miss; EBF = elsewhere breast failure.
* Any first relapse = local, regional, or distant failure, whichever came first.

APBI with HDR BT (Polgar C, et al. Radiother Oncol 2010)

CK APBI (Obayomi-Davies O, et al. FrontOnc 2016)
All the dosimetric parameters for the target and critical structures met the NSABP B39/RTOG 0413 protocol.

With advanced real-time tracking capability, CyberKnife® System should provide better target coverage and spare nearby critical organs for APBI treatment.

4) METASTASES

20–25 Gy per fraction, for 3 fractions did not evidence any considerable toxicity in inoperable liver tumor (Goyal K, et al. HPB Surgery 2010)

SBRT with and without fiducials

Radicular pain has been relieved in 25–85% of patients with 5 fractions CK SBRT approach (Gill B, et al. Front Oncol 2012)
Prostate Cancer Oligometastases:

- 72 patients not previously irradiated in the same area were treated at pelvic and/or LA lymph nodes at a total dose of 51.8 Gy/28 fr, and with SIB up to 65.5 Gy (BED 167.73 Gy for α/β 1.5) on + LN
- 9 re-irradiated patients were treated without SIB at 50-65.5 Gy/25-30 fr.
- Prostatic bed was always treated when not previously irradiated.

- 91.4% of patients had a PSA reduction 3 months after salvage HTT
- OS 3 y = 80%, LRFS 3 y = 89.8%, CRFS 3 y = 61.8%


Uni and multivariate analysis showed no impact of ADT on these patients!

- Multi-institutional evaluation of SBRT

- Pts with diagnosis of up to 3 positive LN (73 LN/60 pts), or bone (43 mts/36 pts), or visceral (1 lung/1 pts, 1 liver/1 pts) mts at choline (92 pts) or FDG PET/CT (24 pts); 2 pts had bone/LN and visceral mts for a total of 163 mts /119 pts treated with SBRT

- Median PSA at first documented metastases= 4.0 (1.6-8.8) ng/ml, median interval from diagnosis to mts: 4.7 (2.7-6.6) years

- DPFS= 21 (15-26) months; LPFS 3 years = 79% for biologically effective dose ≤100 Gy and 99 % for >100 Gy; DPFS 3 years= 31%, DPFS 5 years= 15%
RPM Respiratory Gating™ System

Increase Treatment Time by X 3.8 (26% Duty Cycle)

- Inspiration: 1.6 Sec.
- Phase Interval: 40% - 70%
- Expiration: 1.9 Sec.
- Breathing Period: 3.5 Sec.

- Gated Motion 3.5 mm
- INHALE
- EXHALE
- Beam Enable
- Beam Hold

330 335 340 3 Sec. Seconds
4D Data Sorting

Patient Breathing Curve

X-ray ON
PET acquisition

CT or PET Images Phases
Goal:
Define the target volume and the volume of space that encompasses tumor motion.
4D-PET/CT CONTOURING
4D-PET/CT CONTOURING

ITV
4D CT

Cine Review

ITV
28 USA Centers (+1 Australian +1 Germany)
702 Patients: 577 evaluable

Median dose: 50 Gy (range 25/75% 48–54) delivered in 3Fr

Median LC for all patients: 53 ms no difference by primary histologic type
5) Adaptive RT rectal cancer @ San Raffaele: the approach of boosting the shrinking tumour

**Background:** 2007-2009 moderately Hypo (2.3 Gy/fr, 18 fr, 41.4 Gy + oxaliplatin/5FU). Daily IGRT Tomo; based on LQ-model to be equivalent to bi-fractionation (45Gy, 2.5Gy/day)

**Reported results for the first 100 pts:** G3 GI:9%; pcR:28%. Compares well with historical experience with bi-fractionation (reduced tox with Tomo)
Adaptive Radiation Therapy: RECTAL CANCER

- The rectum was retrospectively contoured on the daily Megavoltage images (MVCT) of six patients previously treated with TomoTherapy® System. The variations of rectum volume during TomoTherapy® System were examined.

- Rectal volume shows a linear decrease of 58.2% between the start and end of the treatment (range: 28.6%-75.4%); most of the rectum volume variation was observed in the first half of the treatment with an average reduction of 50%.

- A first estimate of optimized margins for adaptive RT with concomitant boost to the tumor was achieved by expanding the rectal contouring during the initial MVCTs and subsequently during the second half of the treatment with different margins (0.5, 0.7, 1, 1.5, 2 cm).

- In the second half of the treatment, more than 90% (range: 82.4%-100%) of the rectal volume union was contained within a margin of 0.5 cm, while a margin of at least 1 cm is necessary to obtain the same coverage in the first part of the treatment.

- Based on the results of this investigation, a pilot adaptive approach was started in which a concomitant boost is delivered on the last 6 treatment fractions.
DOSE DISTRIBUTION WITH TOMOTHERAPY® SYSTEM

**PTV1**

**PTV2**

<table>
<thead>
<tr>
<th>ACUTE TOXICITY</th>
<th>G1-2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>25 (50%)</td>
<td>9 (18%)*</td>
</tr>
<tr>
<td>Proctitis</td>
<td>27 (54%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>7 (14%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Cistitis</td>
<td>7 (14%)</td>
<td>-</td>
</tr>
<tr>
<td>Skin erythema</td>
<td>11 (22%)</td>
<td>-</td>
</tr>
</tbody>
</table>

*All G3 in the first phase, only in women; No G4 toxicity occurred

First phase no boost 100% 2,3Gy/f

Adaptive phase 100% 3Gy/f
### Adaptive radiotherapy for rectal cancer

<table>
<thead>
<tr>
<th>Pathological Responses</th>
<th>Nº pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRG4 (pRC)</td>
<td>13 (28%)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>TRG3</td>
<td>22 (48%)</td>
</tr>
<tr>
<td></td>
<td>(pts with viable cells &lt;=5%: 28% and with 6-10% viable cells: 13% of pts)</td>
</tr>
<tr>
<td>TRG2</td>
<td></td>
</tr>
<tr>
<td>76% of Pts : near Complete response</td>
<td></td>
</tr>
<tr>
<td>TRG1</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>TRG0</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

2 pts achieved cRC (1 pt is still cCR after 54 months and 1 had local relapse and underwent transanal resection 1 year after treatment; 1 pt was lost and one pt died before surgery)
CONCLUSIONS

• Invaluable solution to the treatment of selective tumours/lesions located close to critical structures and/or subject to organ motion

• Salvage of recurrent and metastatic lesions

• Opportunity to treat selective early stage malignancies like the prostate and lung carcinoma

• Management of intractable trigeminal neuralgia.

• Arteriovenous malformation for patients who are not suitable for invasive surgery

• Currently innovative experimental indications for radiosurgery to treat functional disorders like obsessive compulsive disorder (OCD), depression, Parkinson, **atrial fibrillation**, etc. are underway.
How I convinced my administration to buy a CyberKnife® System?

- Patients today are more informed: I reported to my administration how many patients asked for the reduction of the radiation treatment duration

  Loss of patients (prostate, lung…….)

- Economic advantage

  In Italy the treatment is not paid per fraction, but as a package (7,000 €)

  Even though a CyberKnife® System treats less patients per day, more patients/year would be treated