Stereotactic MR-guided adaptive radiation therapy (SMART) for locally advanced pancreatic tumors

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Locally-advanced Pancreatic cancer:

- Poor prognosis group
- No internationally accepted gold standard treatment
- Chemoradiation, chemo alone, chemo + local therapy

*Not efficient enough and/or too toxic*
Conflicting results about the addition of RTH

Recently published randomized LAP07 study:
- Benefit of CRT was increased local control
- No survival benefit of addition of fractionated RT\(^1\)

In contrast:
Systematic review including more than 8500 LAPC pt:
- CRT associated with an improved median survival (13.5 vs 10.6 mo)\(^2\)

@VUmc: conventional EBRT
- 28 x 1.8 Gy + gemcitabine
- Large mobility margins needed
- OAR tolerance dictates fractionation

\(^1\) Hammel et al, JAMA, 2016, \(^2\) Torgeson et al, Cancer, 2017
Limited outcome benefit

Costs in terms of toxicity
Costs in terms of trt duration

@Vumc: rarely RTH for LAPC because of the limited gain
Therefore hypofractionation might be more attractive?
Ample (non-randomised) literature on outcome of SBRT for treatment of PC:

- Efficacy higher with biological doses above 70 Gy (control, survival)\(^1\)
- Duodenal toxicity (bleeding, strictures, perforation) remains problem
- Reported rates of acute and late grade ≥3 GI toxicity up to 12.5% and 22.3%, resp. \(^2\)

**Most recent innovation in SBRT: MR-based set-up, adaptation and guidance during RT**

\(^1\) Krishnan S, et al, IJROBP, 2016
\(^2\) De Bari Berardino, et al; Crit Reviews in Oncol and Hematol, 2016
MRgRT using the MRIdian @VUmc

MR-guided RT (MRIdian, ViewRay, USA)
- Split core MRI 0.35 Tesla
- IMRT delivery (three cobalt sources)

Since May 2016:

Pie chart showing distribution of treatments:
- Prostate: 39%
- Abdomen: 13%
- Kidney: 6%
- Breast: 4%
- Bladder: 1%
- Adrenal: 6%
- Liver: 10%
- Lung: 11%
- Lymphoma: 1%
- Pelvic LN: 3%
- Pancreas: 16%

Bar chart showing treatment numbers:
- Bladder: N=205 (SEP 2017)
- Adrenal: N=1093 (SEP 2017)
- Liver: N=300
- Lung: N=200
- Lymphoma: N=100
- Prostate: N=100
- Kidney: N=50
- Breast: N=50
- Abdomen: N=50
SMART

Stereotactic
MR-guided
Adaptive
Radiation Therapy

Hypofractionation: SBRT/SABR suited for MRgRT

33 patients with PC treated using SMART

• all fx were delivered after daily adaptation
• precise set-up and MR-guidance (3mm margin)
• all with video-assisted breath-hold
SMART workflow @VUmc

Gated during BH

17s shallow inspiration

Within the first 3 cm of the PTV

Daily re-optimization of baseline plan
Patient-controlled breath-hold gated RT

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Amsterdam, The Netherlands
Online MR-guidance

Real-time projection of the GTV within the PTV on a sagittal tracking image derived from the MRIdian console
A single fraction of 7-8 Gy can be delivered within 20-30 min
Experiences with the video feedback system

- Video-feedback assisted treatment delivery was well tolerated (N=80)
- Ten pts reported considerable difficulty controlling the target
- The active role was appreciated by the vast majority
- Surprisingly, almost no pt considered it confronting seeing their tumor
An analysis was performed in the first 25 pts (125 fx) treated with SMART

- 12 female; 13 male
- Mean 66 years; (range 36-87)
- 23 pts with LAPC, 2 pts with local recurrence
- All patients treated with upfront chemotherapy (usually FOLFIRINOX)
- All treated with 5 x 8 Gy/2 weeks
- Two pts with local ingrowth (stomach) treated with 5 x 7 Gy/2 weeks
Delineation of the target volume

**GTV:**
- Gross tumor volume is contoured on the planning MR scan *(in collaboration with a dedicated GI intervention radiologist)*
- Elective lymph node regions are not part of the target volume

Planning target volume (PTV) = GTV + isotropic margin of 3 mm

A $PTV_{opt}$ is created: PTV minus the OAR – *sparing the OAR has priority*

$PTV_{opt}$ will be treated in 5 fractions of 8 Gy in 2.5 weeks OTT
Advanced set-up using HR MR scans

- Target and OAR contouring on a planning MR scan
- 17 sec MR scan in shallow inspiration BH
- Repeat MR scan and set-up performed by GTV alignment
Why daily adaptation?

The position of the OAR can change substantially in between fractions.
Why daily adaptation?

With daily setup on the GTV, there is a large interfraction variation in both the **volume** and **position** of the OAR adjacent to the PTV.
What is the goal of daily adaptation?
For SBRT, the high dose region around the PTV is most important for toxicity and therefore **optimal normal organ sparing prevails** over target coverage (driving force planning).

A planning procedure was developed using rings up to 3 cm around the PTV. Only parts of organs within these rings need to be adjusted to the anatomy of that day.

This allows fast and robust re-optimizing of the original plan to create a plan of the day.
Baseline scan of PC pt, after completion contouring GTV and OAR
Automated partitioning of the OAR’s within the first 3 cm is performed into a part of OAR within the 1st, 2nd, 3rd cm.
Dose distribution of the baseline plan

Generation of a baseline treatment plan using a.o. constraints for the partitioned OAR
Steepest dose gradients at borders of OAR
Repeat MR scan for the first fraction
Set-up is performed on the GTV
OAR contoured in the first 3 cm
Again, automated partitioning of OAR’s within the first 3 cm
Remember – baseline MR

Evident: position of the OAR around the PTV has changed between SIM – Fx 1
‘predicted plan’

First step: recalculation of the baseline plan on the new anatomy
Re-optimization of the baseline plan

Adaptation based on the partitioned OAR within 3 cm re-optimizes the baseline plan rapidly using the same number and direction of IMRT beams.
SMART 3cm strategy

Adapted dose distribution
The OAR$_{3\text{cm}}$ partition used to direct the steep dose gradients to there where needed.
The effect of SMART 3cm strategy in DVH’s

- Improved coverage GTV/PTV
- Improved sparing duodenum/stomach
**Vertical axis:**
GTV coverage

**Horizontal axis:**
High dose volume to the OAR ($V_{33\, Gy}$)

**Blue dots:**
Indicate plans fulfilling the institutional constraints

$V_{33\, Gy}$ duodenum $\leq$ 1cc
$V_{33\, Gy}$ stomach $\leq$ 1cc
$V_{33\, Gy}$ bowel $\leq$ 1cc
The baseline plan recalculated on the current anatomy

Red dots: Represent plans with insufficient GTV coverage and/or plans exceeding V33 Gy OAR constraints
Vast majority of plans comply with high-dose volume constraints, while improving target coverage.
More in detail:

**Baseline:** in four pts the GTV coverage (V95%) was <90% due to the OAR

**Predicted plans** *(Baseline plans recalculated on the anatomy of that moment):*

<table>
<thead>
<tr>
<th>Red boxes = plans</th>
<th>V95% of the GTV ≤ 90% and /or V33Gy &gt;1 cc and /or V25 Gy &gt; 20 cc</th>
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<tbody>
<tr>
<td>Green boxes = plans</td>
<td>Meeting the institutional constraints</td>
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Almost half of fx: a violation of constraints
A qualitative analysis was performed to assess the potential benefit of online adaptive re-optimization.

The potential benefit was defined as:

| Not needed: | Both the Predicted and Re-optimized plan meet our constraints |
| Benefit:    | Constraints were violated in Predicted plan |
|            | After re-optimization: Meeting constraints |
|            | Or a GTV coverage improvement of $\geq 10\%$ |
|            | And/or an OAR dose reduction of at least 0.5 cc |
| Failed:    | Constraints were violated in Predicted plan |
|            | After re-optimization: Constraints remained violated |
|            | Failed to improve GTV coverage |
|            | Failed to reduce OAR dose |
Finally, the effect of re-optimization

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**abbreviation**

VUmc
Finally, the effect of re-optimization

In summary:
Adaptive re-planning decreased the percentage of fx with suboptimal plans from 50% to less than 2%

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![Table Image](image-url)
Acute and subacute toxicity

Pain: Grade 2 (N=1); Grade 3 (N=1)
Fatigue: Grade 2 (N=9); Grade 3 (N=1)

Clinical use of daily adaption translated into only minimal observed toxicity

Exact role of adaptation uncertain
• SBRT with MRgRT & patient-controlled BH delivery is a novel approach

• With a dedicated approach, daily adaptation is feasible (within 15 min)

• Daily adaptation improves GTV coverage

• Daily adaptation diminishes high doses ($V_{33\text{Gy}}$) to relevant OAR
  • This may decrease the incidence of future serious toxicity?
• SBRT in 40 Gy/5 fx is feasible with minimal acute toxicity
  • Next step is going towards a higher dose of 50 Gy/5 fx

Clinical note:
This has now performed in LAPC, however this could/should be applied in earlier stages of pancreatic cancer