Nuove Tecnologie in Radioterapia e prospettive future

Renzo Corvò

AIRO- Padova, 10 novembre 2014

Technology assessment and research

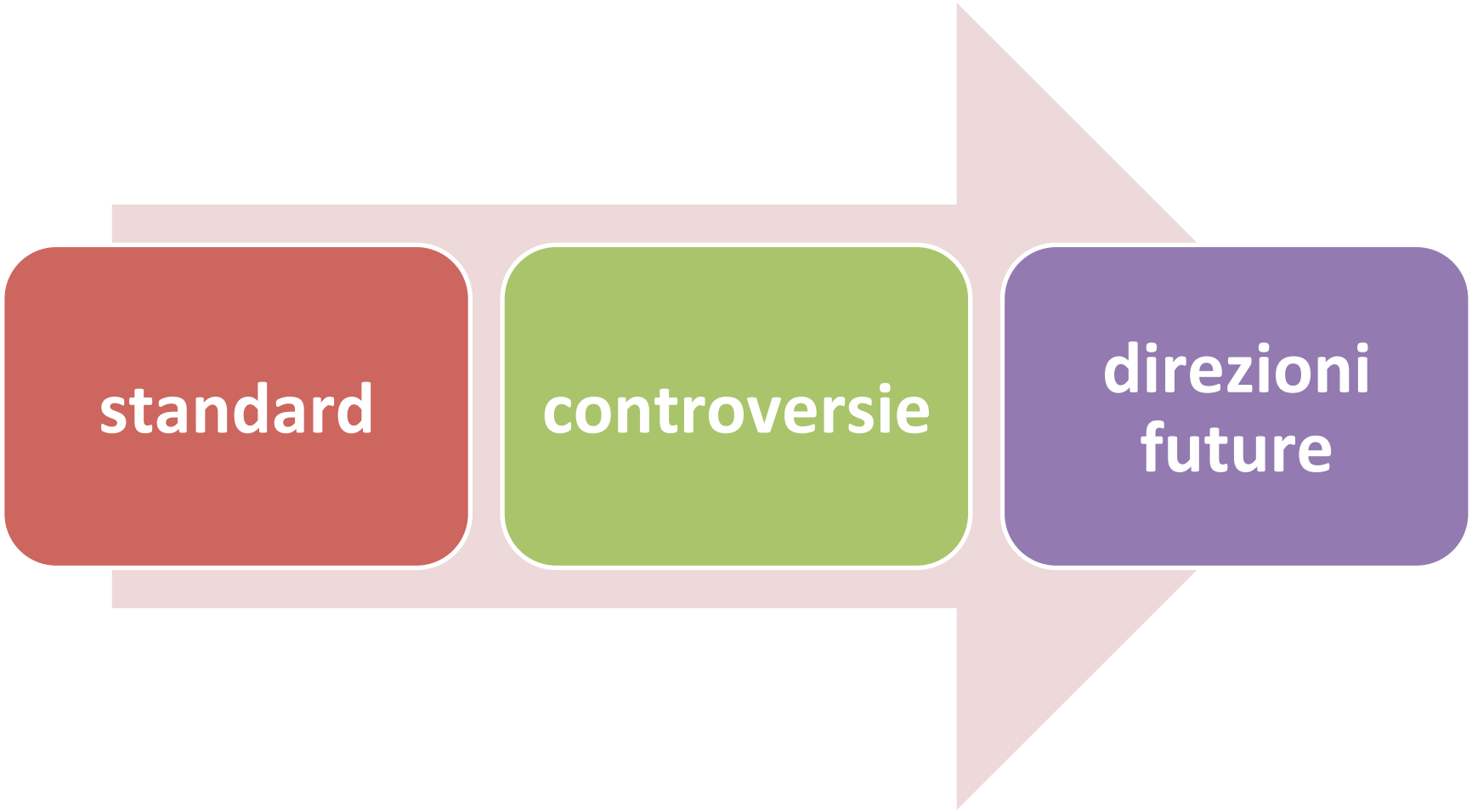
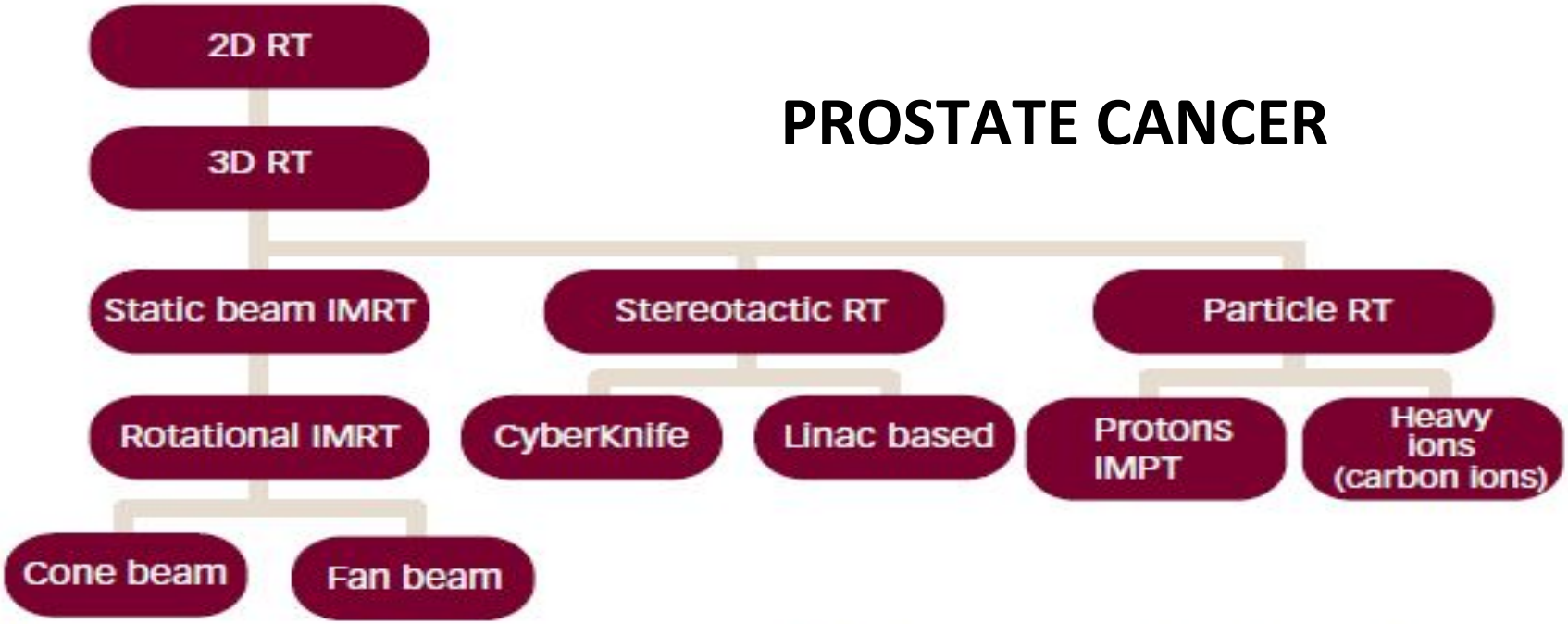


Figure 1: An Overview of the Recent Evolution in External Beam Radiotherapy

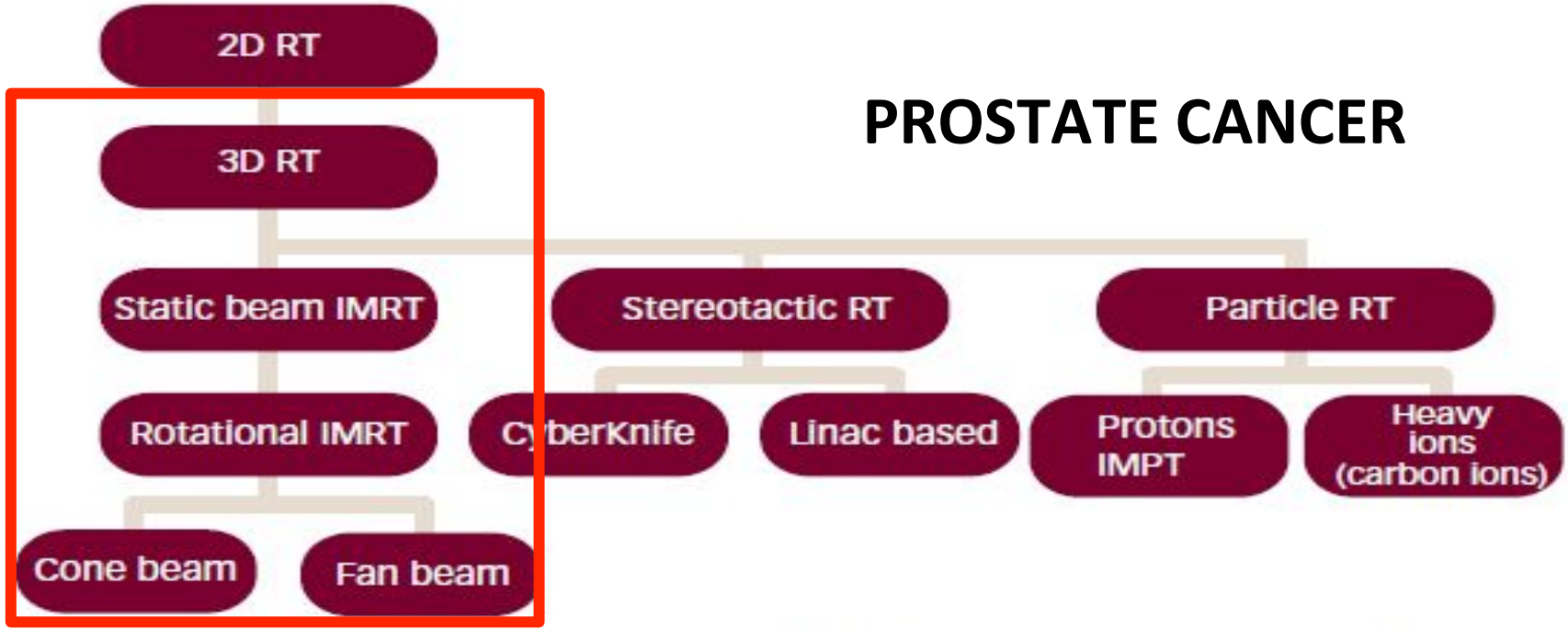


PROSTATE CANCER

IMPT = intensity-modulated particle therapy; IMRT = intensity-modulated radiotherapy; linac = linear accelerator; RT = radiotherapy.

Dirk van Gestel et al, Oncology & Hematology Media, 2013

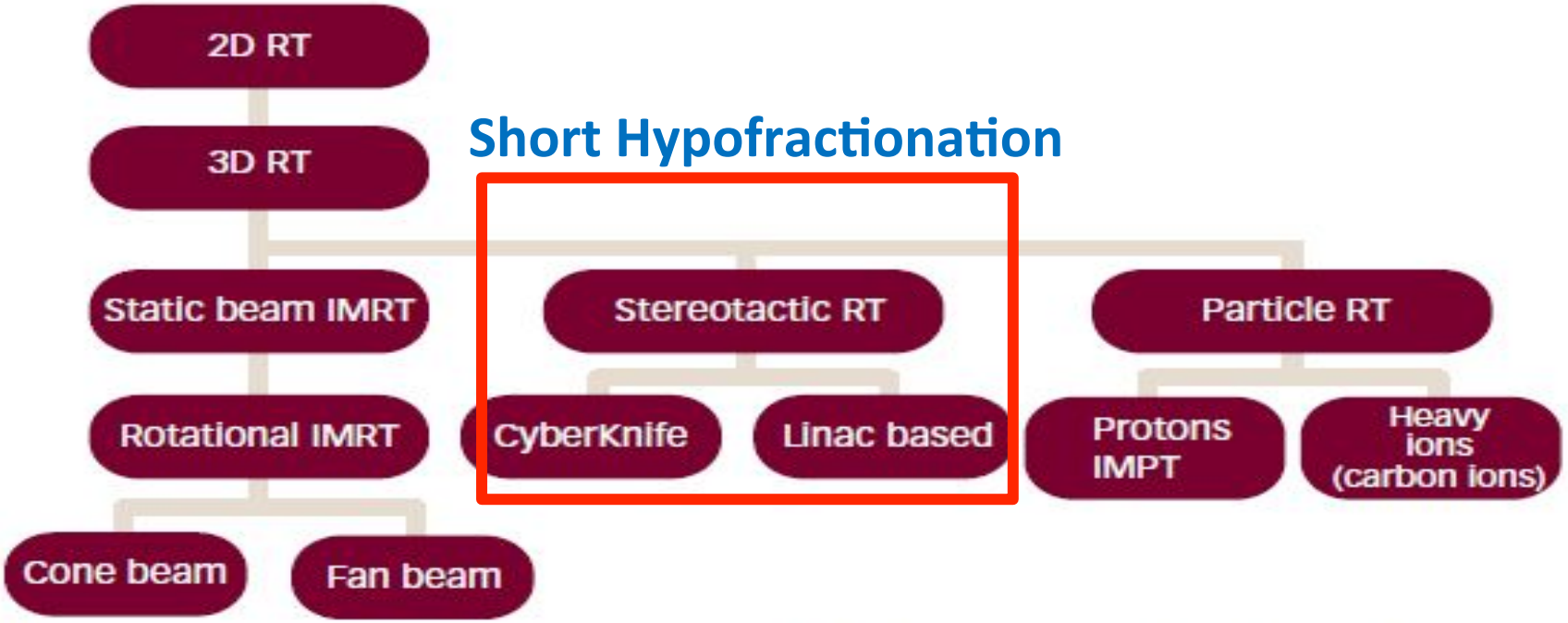
Figure 1: An Overview of the Recent Evolution in External Beam Radiotherapy



PROSTATE CANCER

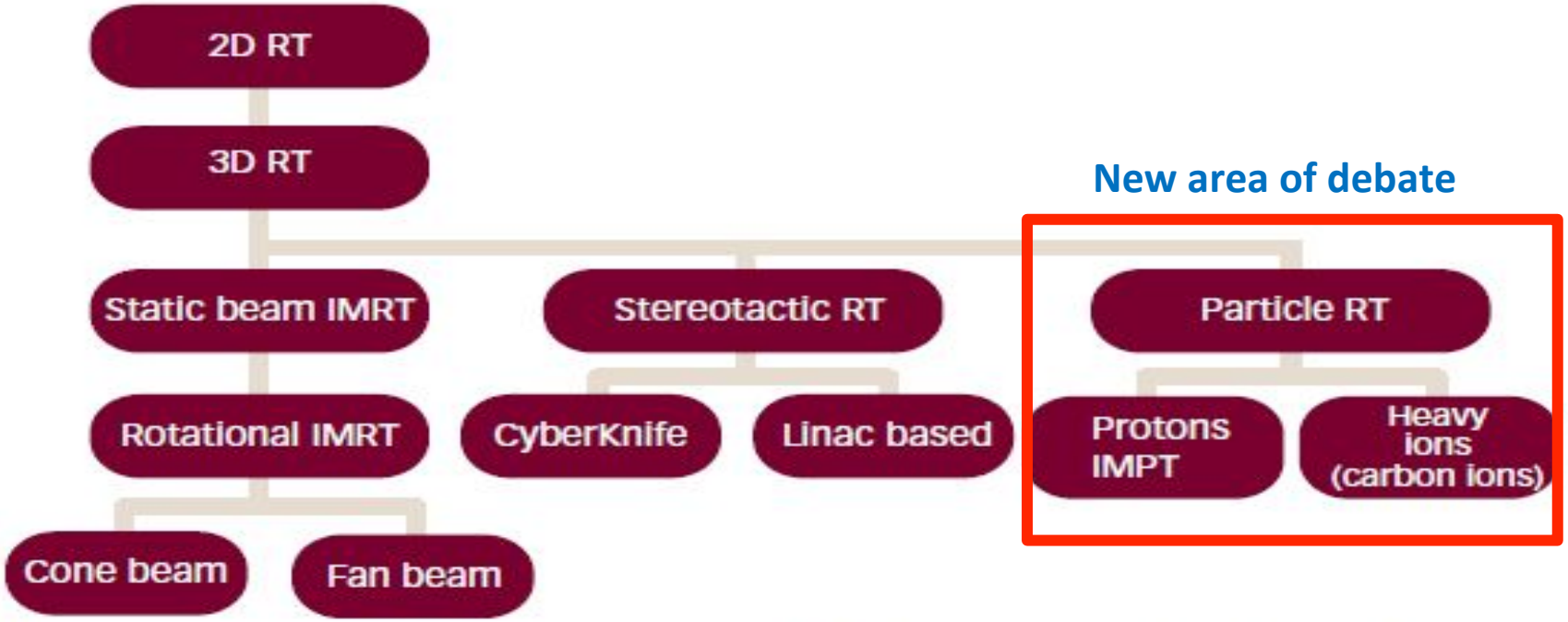
IMPT = intensity-modulated particle therapy; IMRT = intensity-modulated radiotherapy; linac = linear accelerator; RT = radiotherapy.

Figure 1: An Overview of the Recent Evolution in External Beam Radiotherapy



IMPT = intensity-modulated particle therapy; IMRT = intensity-modulated radiotherapy; linac = linear accelerator; RT = radiotherapy.

Figure 1: An Overview of the Recent Evolution in External Beam Radiotherapy



IMPT = intensity-modulated particle therapy; IMRT = intensity-modulated radiotherapy; linac = linear accelerator; RT = radiotherapy.

Dirk van Gestel et al, Oncology & Hematology Media, 2013

Figure 2: The Radiotherapeutic Balance between Tumor Control and Toxicity

Toxicity ↓

- Better ballistics
  - CT - MRI - (PET)
  - IGRT
- New RT techniques
  - IMRT
  - Stereotactic RT
  - IMPT

Loco-regional control ↑

- Simultaneous integrated boost
- Dose escalation
- Dose painting by numbers
- Heavy ions

CT = computed tomography; MRI = magnetic resonance imaging; IGRT = image-guided RT; IMPT = intensity-modulated particle therapy; IMRT = intensity-modulated RT; PET = positron emission tomography; RT = radiotherapy.

Figure 2: The Radiotherapeutic Balance between Tumor Control and Toxicity

Toxicity ↓

- Better ballistics
  - CT - MRI - (PET)
  - IGRT
- New RT techniques
  - IMRT
  - Stereotactic RT
  - IMPT

Loco-regional control ↑

- Simultaneous integrated boost
- Dose escalation
- Dose painting by numbers
- Heavy ions

CT = computed tomography; MRI = magnetic resonance imaging; IGRT = image-guided RT; IMPT = intensity-modulated particle therapy; IMRT = intensity-modulated RT; PET = positron emission tomography; RT = radiotherapy.

Current standards for prostate cancer radiation therapy

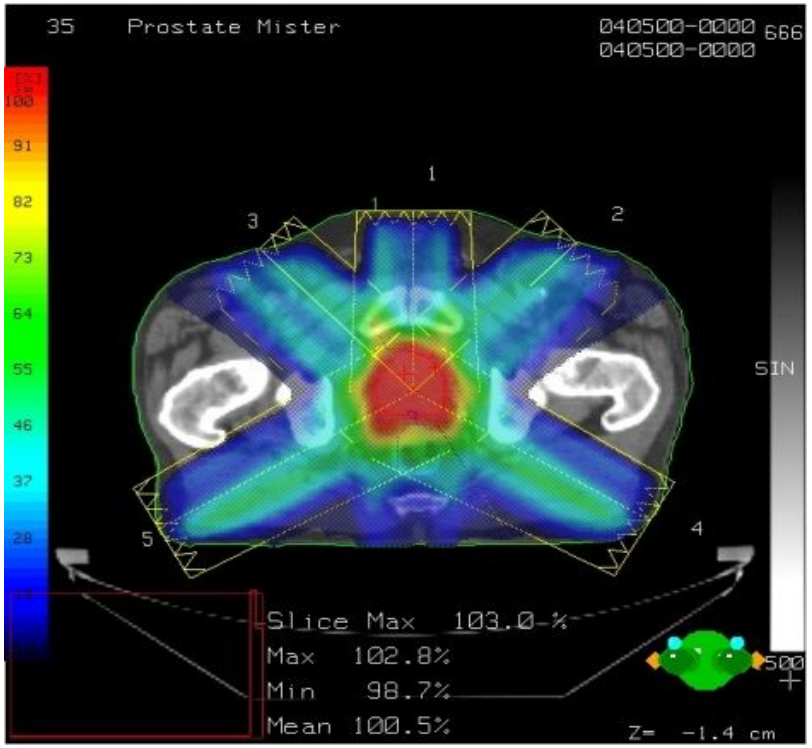
- Modern "standard" external beam radiotherapy includes:

- **Intensity modulated radiotherapy** (**IMRT**)

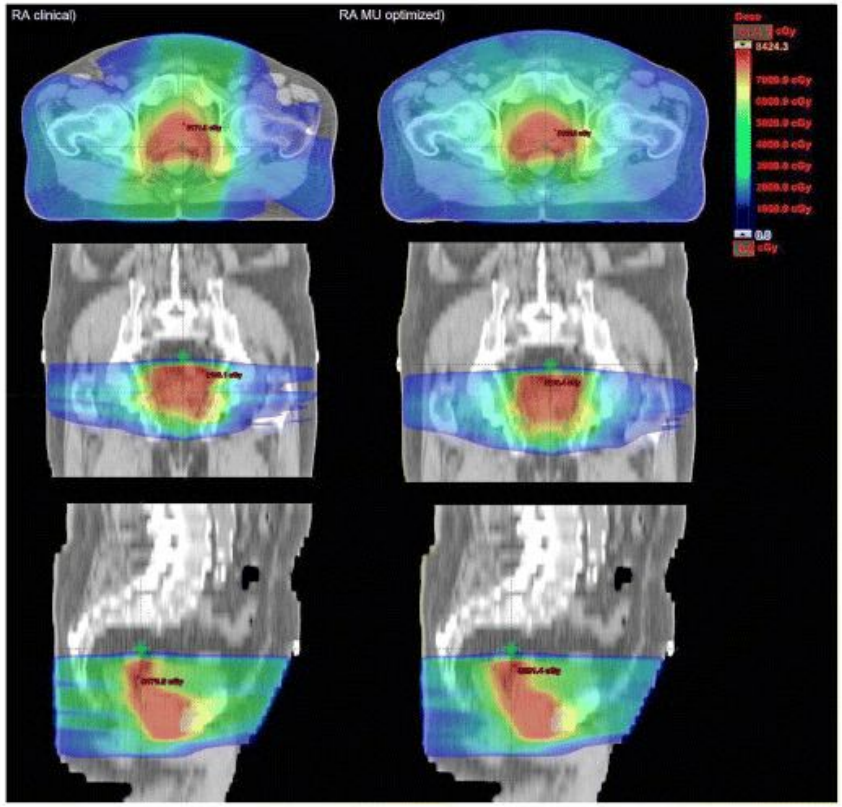
- **Image-guided radiotherapy** (**IGRT**)

IMRT

Step&shoot
Static IMRT



Rapidarc/VMAT/Tomotherapy
Dynamic IMRT



Current standards for prostate cancer external radiation therapy

- **Target volumes** should include:
- the whole prostate with:
- the base of seminal vesicles for intermediate and high risk patients
- and
- pelvic lympho nodes for patients with an invasion risk of > 15%

(Partin or Kartan nomograms):

Target Volume

- **Extraprostatic extension** in **30%-40%** primarily postero-laterally.
- A **seminal vesicle involvement** found in about **10%-20%** (in prostatectomy series)
- Recommendations for inclusion of the **base of seminal vesicles** in the CTV for the complete treatment (not limited to 50-60 Gy in intermediate and high-risk patients as only the 2 cm are involved in the 90% of patients)
- → **No studies on seminal vesicles irradiation**

Radiobiology of prostate cancer

- a/b ratio for BED = 1.5-1.8 Gy
- Long potential doubling time
- Low proportion of proliferating stem cells
- Probably, treatment timing and interruptions do not impair efficacy
- Standard Fx → moderately Hypo Fx
- HDR→ SBRT

Current standards for prostate cancer radiation therapy

- **Dose escalation** up to **> 76-78 Gy** in conventional fractionation is associated with a significant improved **bRFS** in **all** risk groups, as well as improved prostate cancer-specific mortality for **high – risk** patients
- Benefit from short-term and long-term androgen deprivation with Dose Escalation?

Current standards for prostate cancer radiation therapy

- **Prostate brachytherapy** can be alternatively applied as a **single modality** for low-risk and selected intermediate patients

  or

- as a **boost** to external beam radiotherapy for patients with adverse prognostic factors

Current standards for prostate cancer radiation therapy: ***hypofractionation***

- Currently available **phase III trials** indicate:
- similar biochemical outcomes for the hypofractionation in comparison to conventional (1.8 Gy- 2 Gy) treatments
- **Level 1 evidence ?** (iso-effective- iso-toxic)

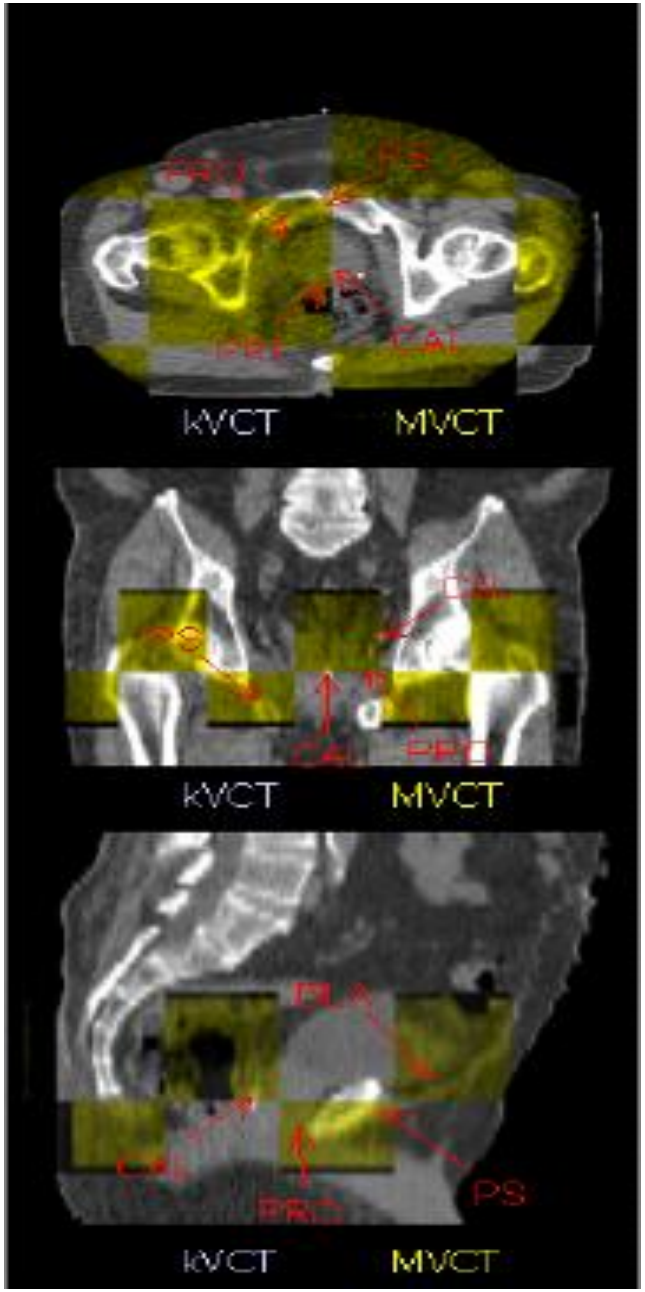
Hypofractionation for primary management

Koontz BF et al, Eur Urol 2014

- Six randomized trials of standard vs ***moderate hypofractionation*** (dose 2.5-4 Gy per fraction)
- Low and intermediate risk groups
- Follow-up ranging from 4 to 8 yrs
- Similar biochemical control > 80% at 5 yrs
- Similar safety
- **No data at 10 yrs follow-up**
- **Standard?**

IGRT

Essential for IMRT



IGRT may correct

“translational and rotational motion of prostate”

(inter and intra-fraction movement)

IGRT: controversies

- Several different options are available in order to **reduce safely margins** and treatment volumes:

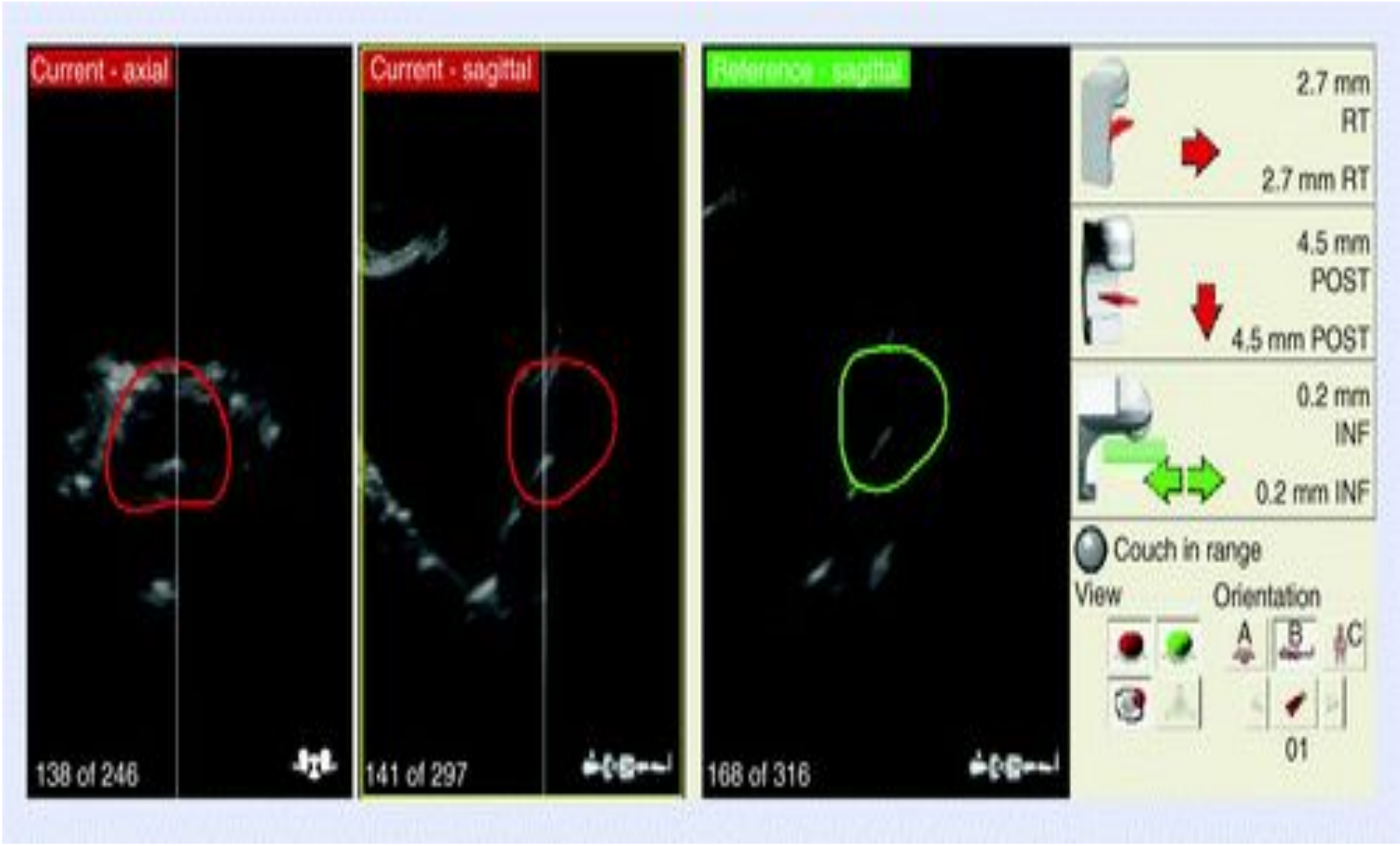
- - **radio-opaque or electromagnetic markers**
  (< 5 mm PTV margins)
- - **cone beam computed tomography**
  (> 5 mm PTV margins)

IGRT: controversies

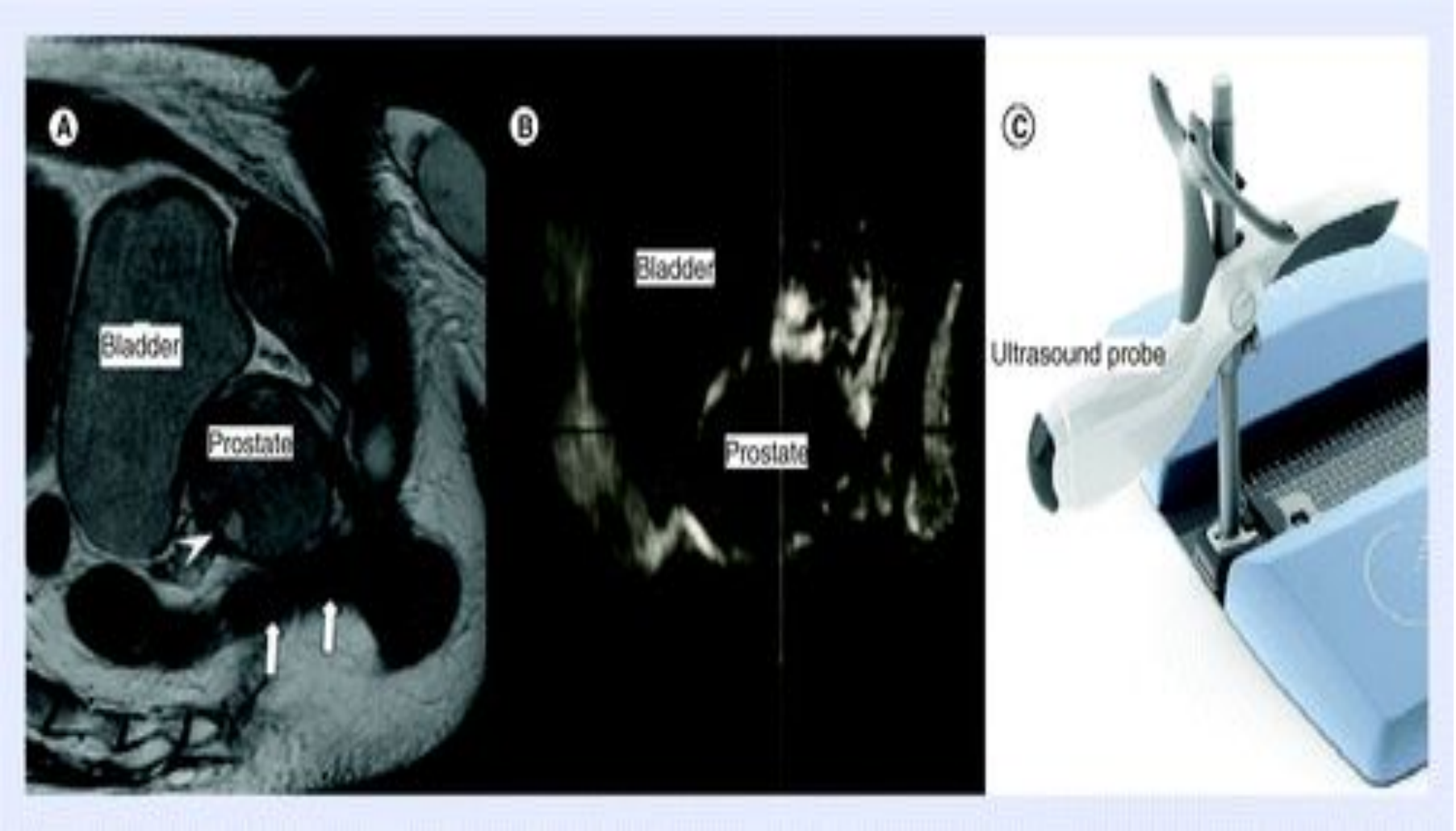
- Several different options are available in order to **reduce safely margins** and treatment volumes:

- - **radio-opaque or electromagnetic markers**
  (availability, costs and expertise)
- - **cone beam computed tomography**
  (3-6 cGy/fraction up to 120-240 cGy in 40 fx)

Ultrasound-based IGRT



Transperineal-ultrasound IGRT approach



Real-time IGRT according to different technologies

(R.Meier, Transl Cancer Res 2014)

Technology Platfome	Real-time correction	Rotational Correction
Cyberknife	Continuous, automated sub-mm correction	yes, continuous automatic
Varian (Trilogy,Truebeam) BrainLab (Vero)	Intermittent, treatment interuption and manual correction	6D couch available
Elekta (Synergy, Versa HD)	Intermittent	6D couch available
Calypso	Continuous, treatment interruption and manual correction	no
Tomotherapy	no	no

Future Directions

- **Short Stereotactic Radiotherapy** with even extreme single fractions of 6-10 Gy is increasingly used
- Treatment can be shortened substantially increasing patient convenience
- Short hypofractionated concepts have a great potential to gain more acceptance in the next 5-10 years

SBRT for prostate cancer according to Technology and Outcomes

- **7 Gy x 5 fx** **5 –yr bDFS** 94%
- **7.25 Gy x 5 fx** 94%-97%
- **8 Gy x 5 fx** 97%-99%
- **10 Gy x 5 fx** ??

- Low risk group: > 90-95%%
- Intermediate risk group: > 90%
- High risk group: 75%-81%

SBRT for prostate cancer: severe late effects

7 Gy x 5 fx	**late G3 GU**	1%	**late G3 GI**	0%
7.25 Gy x 5 fx		2-3%		0%
8 Gy x 5 fx		1%		0%
10 Gy x 5 fx		-		**5%**

SBRT for prostate cancer: severe late effects

• **7 Gy x 5 fx**	**late G3 GU**	1%	**late G3 GI**	0%
• **7.25 Gy x 5 fx**		2-3%		0%
• **8 Gy x 5 fx**		1%		0%
• **10 Gy x 5 fx**		-		5%

• ----------

→ **seemingly, no differences with Cyberknife, Tomotherapy, Rapidarc and VMAT**

Controversies

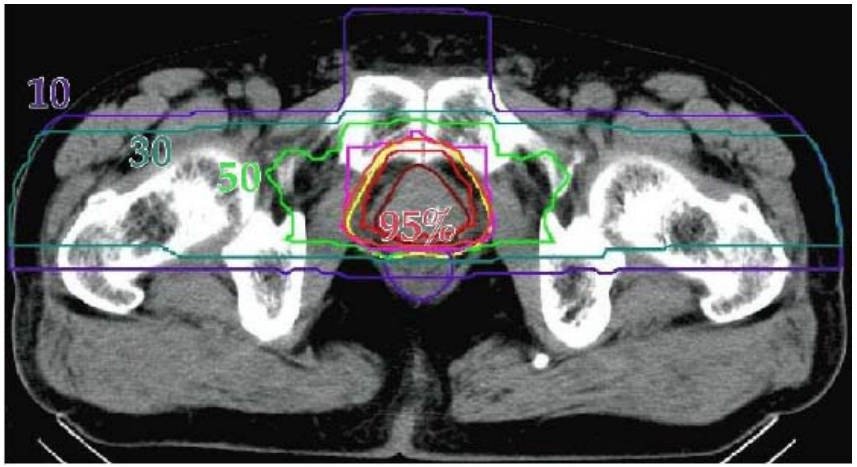
- *The application of a **hydrogen spacer** is a short and well tolerated procedure to effectively protect the rectal wall, resulting in a distance up to 1 cm between prostate and rectal wall.*

- **Expertise !**
- **Really needed with optimal IGRT?**

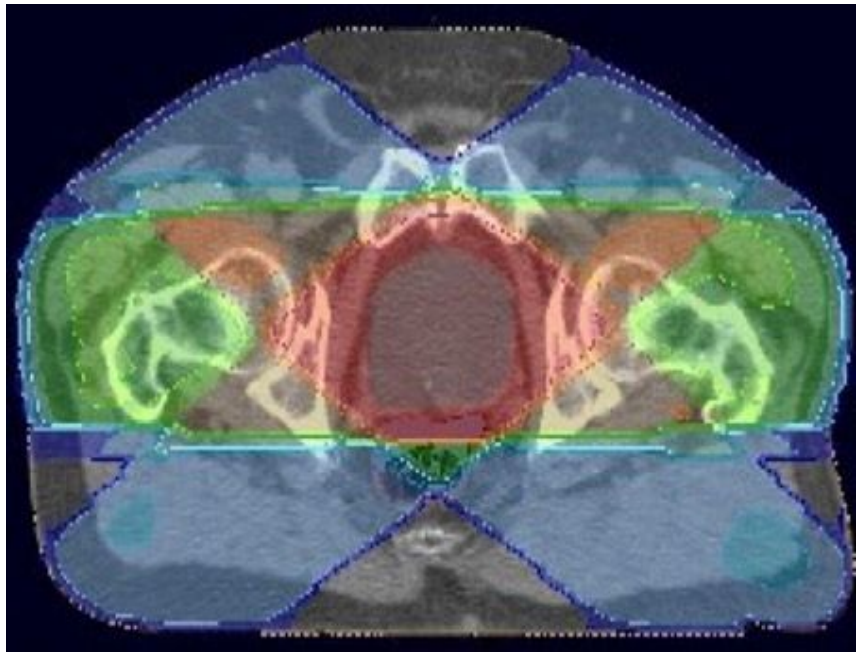
Axial transrectal ultrasound before (a) and after (b) hydrogel injection

Future Directions: Particles Therapy

Carbon Ions



Proton Therapy



Future Directions

- Considerable experience exists with **proton treatment** **without proven benefit** in comparison to photon IMRT but great potential for dose escalation or SBRT

- **Carbon Ions** are **experimentally used** only for a few patients

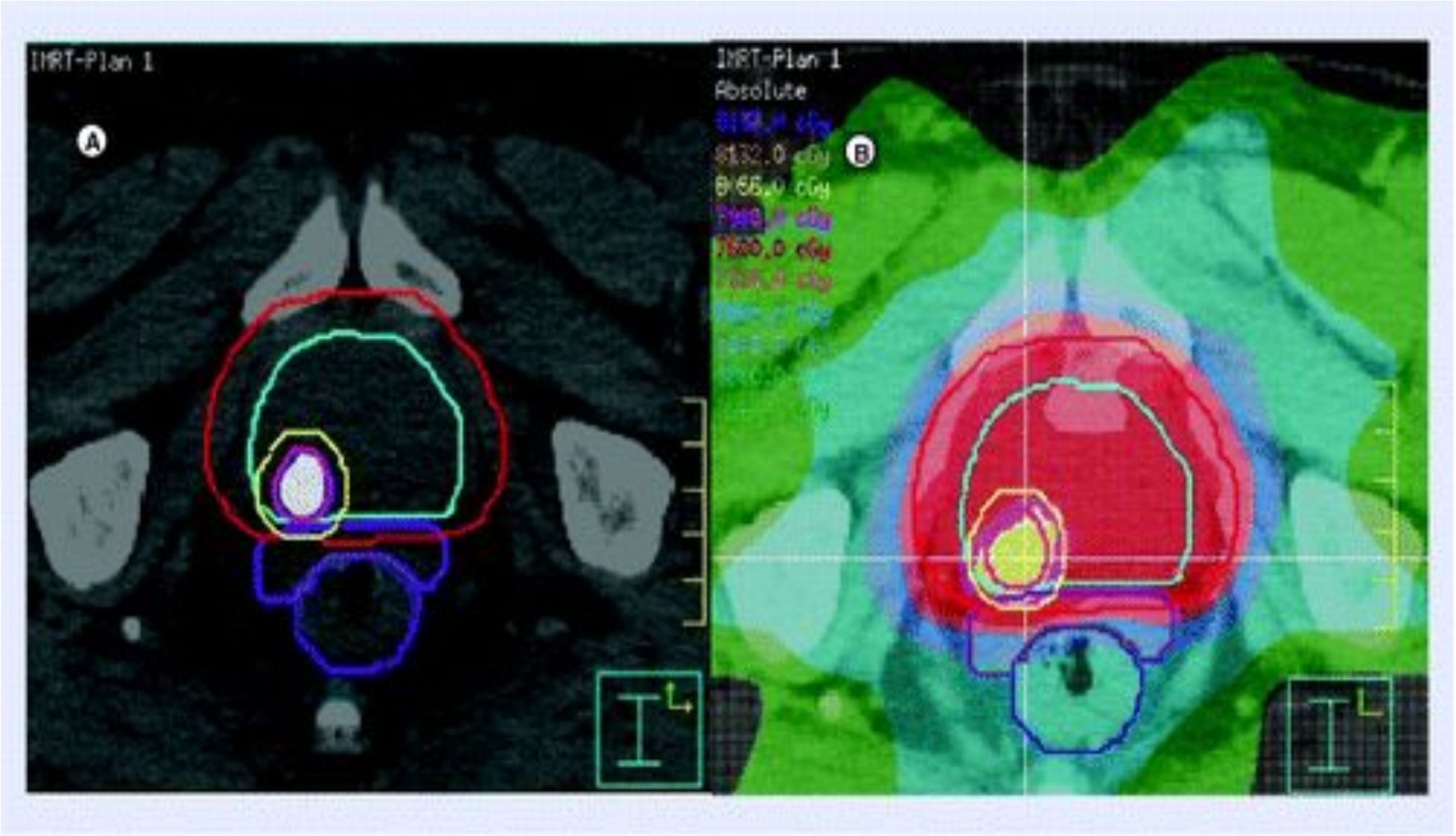
Future Directions

- The **Simultaneous integrated Boost** (SIB) concept can be used applying choline PET/ computed tomography or MRI/magnetic resonance spectroscopy allowing:

- a dose escalation to the macroscopic tumor
- a best possible normal tissue protection

Simultaneous Integrated Boost on macroscopic disease

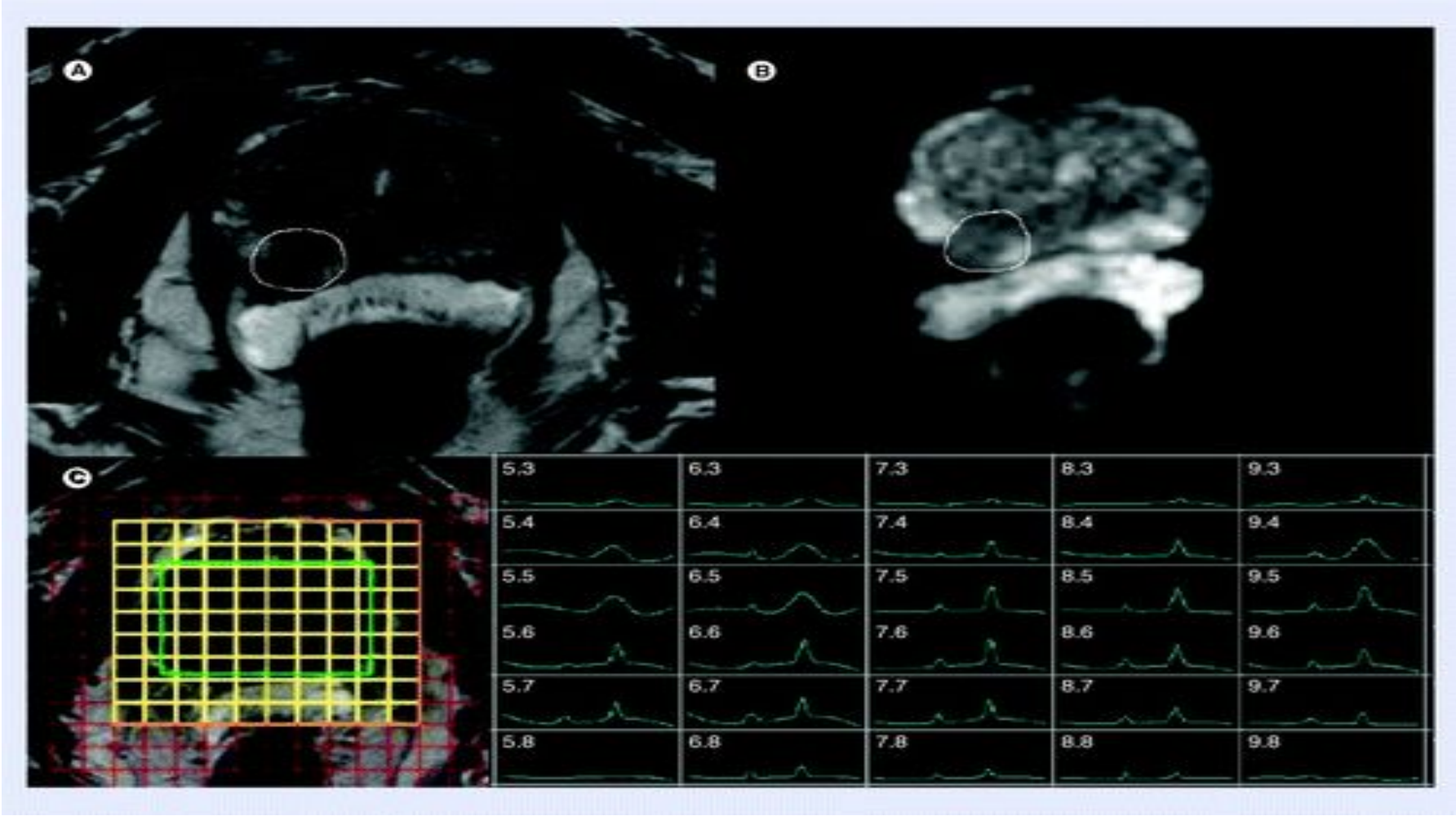
by using 18F-choline PET/CT



Pinkawa M. et al, Expert Rev Anticancer Ther 2013

Prostate cancer identified in MRI

a) T2-weighted image; b) Diffusion-weighted image, c) MR spectoscopy



Pinkawa M. et al, Expert Rev Anticancer Ther 2013

What is the level of evidence of new techniques in prostate cancer radiotherapy?

Technique	Advantages	Inconvenients	Level of evidence
IMRT hypofractionation	Less dose to OARS Improved dose to the target	Risk of secondary cancer	Moderate/high?

What is the level of evidence of new techniques in prostate cancer radiotherapy?

Technique	Advantages	Inconvenients	Level of evidence
IMRT hypofractionation	Less dose to OARS Improved dose to the target	Risk of secondary cancer	Moderate/high?
Stereotactic radiotherapy	**Short overall treatment time** **Cost-effective** **Radiobiology benefit**	**Risk of secondary cancer**	**Moderate/Low**

What is the level of evidence of new techniques in prostate cancer radiotherapy?

Technique	Advantages	Inconvenients	Level of evidence
IMRT hypofractionation	Less dose to OARS Improved dose to the target	Risk of secondary Cancer	Moderate/high?
Stereotactic radiotherapy	Short overall treatment time Cost-effective Radiobiology benefit	Risk of secondary cancer	Moderate/low
Brachytherapy HDR	**Minimum dose to OARs** **Low risk of secondary cancer**	**General anesthesia**	**High/moderate level if HDR boost**

What is the level of evidence of new techniques in prostate cancer radiotherapy?

Technique	Advantages	Inconvenients	Level of evidence
IMRT hypofractionation	Less dose to OARS Improved dose to the target	Risk of secondary Cancer	Moderate/high?
Stereotactic radiotherapy	Short overall treatment time Cost-effective Radiobiology benefit	Risk of secondary cancer	Moderate/low
Brachytherapy HDR	Minimum dose to OARs Low risk of secondary cancer	General Anesthesia	High/moderate level if HDR boost
Hadrontherapy	**High conformation to target** **Low dose to OARs** **Low risk of tumors**	**Cost-effectiveness?** **Geographical logistic problems**	**Low**

What will be the level of evidence of new techniques in prostate cancer radiotherapy?

Technique	Advantages	Inconvenients	Level of evidence
IMRT hypofractionation	Less dose to OARS Improved dose to the target	Risk of secondary Cancer	**High**
Stereotactic radiotherapy	Short overall treatment time Cost-effective Radiobiology benefit	Risk of secondary cancer	**High in intermediate-risk**
Brachytherapy HDR	Minimum dose to OARs Low risk of secondary cancer	General Anesthesia	**High/moderate level if HDR boost?**
Hadrontherapy	High conformation to target Low dose to OARs Low risk of tumors	Cost-effectiveness? Geographical logistic problems	**Low/moderate?**

“Value” framework in prostate cancer radiotherapy

- Porter MF et al, NEJM 2010 What is value in health care?

Value is the health outcome

for Euro/Dollar spent (three tiered system)

1.tier: health status achieved for patient (bDFS, OS)

2.tier: recovery process (lasting effects)

3.tier: sustainability of health (technology)