MRO. ART
INNOVATIVE TREATMENTS AND PATIENTS COMPLIANCE
31° RESIDENTIAL COURSE

ANAL CANAL CANCER

Constraints and toxicity in interventional radiotherapy treatments

György Kovács

CONSTRAINTS AND TOXICITY IN ANAL CANAL CANCER INTERVENTIONAL RADIOTHERAPY TREATMENTS

At the time being,

there are no relevant publications nor study data regarding

interventional radiotherapy as monotherapy related dose constraints.

CONSTRAINTS AND TOXICITY IN ANAL CANAL CANCER INTERVENTIONAL RADIOTHERAPY TREATMENTS

WHAT IS THE DEFINITION OF THE ANAL CANAL ?

15 of 16 studies had positive findings relating dose-volume parameters and Normal Tissue Complication Probability (NTCP) models of the anal canal/ sphincter to late toxicity.

#

Most defined the anal canal as the distal *3 cm* of rectum.

WHAT IS THE DEFINITION OF THE ANAL CANAL ?

15 of 16 studies had positive findings relating dose-volume parameters and Normal Tissue Complication Probability (NTCP) models of the anal canal/ sphincter to late toxicity.

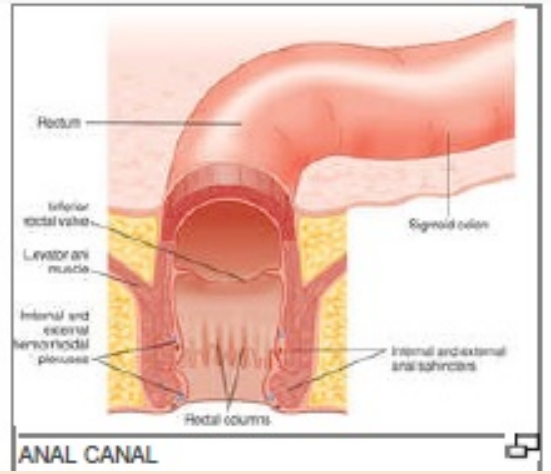
#

Most defined the anal canal as the distal *3 cm* of rectum.

anal canal

The *4 cm* long terminal section of the large intestine, beginning where the rectum passes downward and forward through the pelvic diaphragm and ending in the anus. The entire length of the anal canal is surrounded by sphincter muscles, and the canal remains closed except during defecation and passage of flatus.
See: illustration
See also: canal

"CITE" Medical Dictionary, © 2009 Farlex and Partners



anal canal The *5 cm*-long terminal portion of the intestine that lies immediately below the RECTUM. The anal canal contains two muscular rings (SPHINCTERS) that can close it tightly and seven or more longitudinal pads of MUCOUS MEMBRANE that contain veins and press together to act as an additional sealing mechanism.

"CITE" Collins Dictionary of Medicine © Robert M. Youngson 2004, 2005

WHAT IS THE DEFINITION OF THE ANAL CANAL ?

The anatomic anal canal is defined as beginning at the dentate line and ending at the anal verge.

#

On the other hand, the surgical anal canal is defined as the area

between the anorectal ring and the anal verge.

#

Having *adequate knowledge of ano-rectal anatomy* is the *most important factor* for

improving the oncologic and the *functional outcomes* in patients.

Lee JM and Kim NK, Ann Coloproctol 2018;34(2):59-71

ACTUAL KNOWLEDGE ON ANAL CANAL RADIOTOXICITY

Patients treated with (chemo)radiotherapy for anal cancer show high frequency of patient reported anorectal dysfunction.

#

Specific doses to the sphincters could become a useful predictor of anal incontinence and major LARS (lower anterior resection syndrome) should be incorporated into future radiotherapy planning studies.

Kronborg C.J.S. et al, Radiotherapy and Oncology 157 (2021) 141–146

COMMON ANAL CANAL RADIOTHERAPY ADVERSE EFFECTS

Acute effects on the anus include *epithelial discomfort* which may be aggravated by *radiation-induced diarrhea*.

Epithelial effects follow a sequential progression from *erythema* to desquamation. Shallow *erosions* and *ulcerations* can develop which can lead to *tenesmus*.

#

Direct radiation to the anus can result in *severe acute reactions* that are exacerbated with the use of chemotherapy.

#

There is limited information available on *sphincter continence* following radiation with or without chemotherapy for anal carcinoma. The reported rates of *colostomy* following EBRT for complications range from 0% to7%.

#

Strictures of the anus or *ulceration* are the most commonly reported.

Macconnell Greven and Paulescu, In: Radiation Toxicity: A Practical Guide, Ed. Small & Woloschak, Springer 2006, pp 131-132

COMMON ANAL CANAL RADIOTHERAPY ADVERSE EFFECTS

There are *inconsistent outcomes of anorectal studies* after pelvic radiotherapy not directed to the anus.

#

The *reported effects are conflicting* because of the mixture of retrospective and prospective investigations, different radiotherapeutic regimens, as well as the *variance in pretreatment sphincter function*, rectal capacity, and bowel activity.

#

A study involving a group of patients with cervical cancer demonstrated that *33%* of patients had late symptoms related to *anorectal dysfunction*.

Macconnell Greven and Paulescu, In: Radiation Toxicity: A Practical Guide, Ed. Small & Woloschak, Springer 2006, pp 131-132

THE CHALLENGE OF ANAL CANCER RADIOTHERAPY

In early stage tumours, a dose *reduction from 50 Gy to 45 Gy reduces* 2 year local control from *98% to 95%;* in late stage tumours, a *dose escalation from 50 Gy to 55 Gy improves* the 2 year local control rate from approximately *50% to 80%.*

#

A systematic analysis showed *higher outcomes* regarding every endpoint hence supporting the *addition of interventional radiotherapy* boost complementary to radiochemotherapy.

Muirhead R et al, Radiotherapy and Oncology 116 (2015) 192–196
Frakulli R et al, J Contemp Brachytherapy 2018; 10, 3: 246–253

EVIDENCES

Usually, we recommend restricting the use of brachytherapy to patients with tumors that extend *< 50% of the anal canal circumference*, are *< 5–10 mm in thickness*, and are *<5 cm in craniocaudal length*; however, these measures are *at time of the IRT boost* - and not prior to RCT.

#

3D EAUS and MRI are a valuable diagnostic tools in detection of anal cancer, although *3D EAUS is more accurate* than MRI for T1 stage.

#

3D EAUS-guided brachytherapy permits *local tumor control up to 93%* and results in minimal and low-grade treatment-related *morbidity (<10%).*

Niehoff P, Kovács G, J Gastrointest Oncol 2014;5(3):218-222
Reginelli A et al, Oncotarget, 2017, 8: 22980-22990
Doniec J et al, Surg Endosc , 2006, 20: 673–678

EVIDENCES

Potential radiation-induced *adverse effects* on anorectal function in patients with low rectal carcinoma are *dose-dependent*.

#

The *internal sphincter* (smooth muscle innervated through the myenteric plexus) seems to be more susceptible to injury than does the *external sphincter* (striated muscle innervated by the pudendal nerve).

Gervaz PA et al, J Am Coll Surg, 2002, 195(3):387–394

EVIDENCES

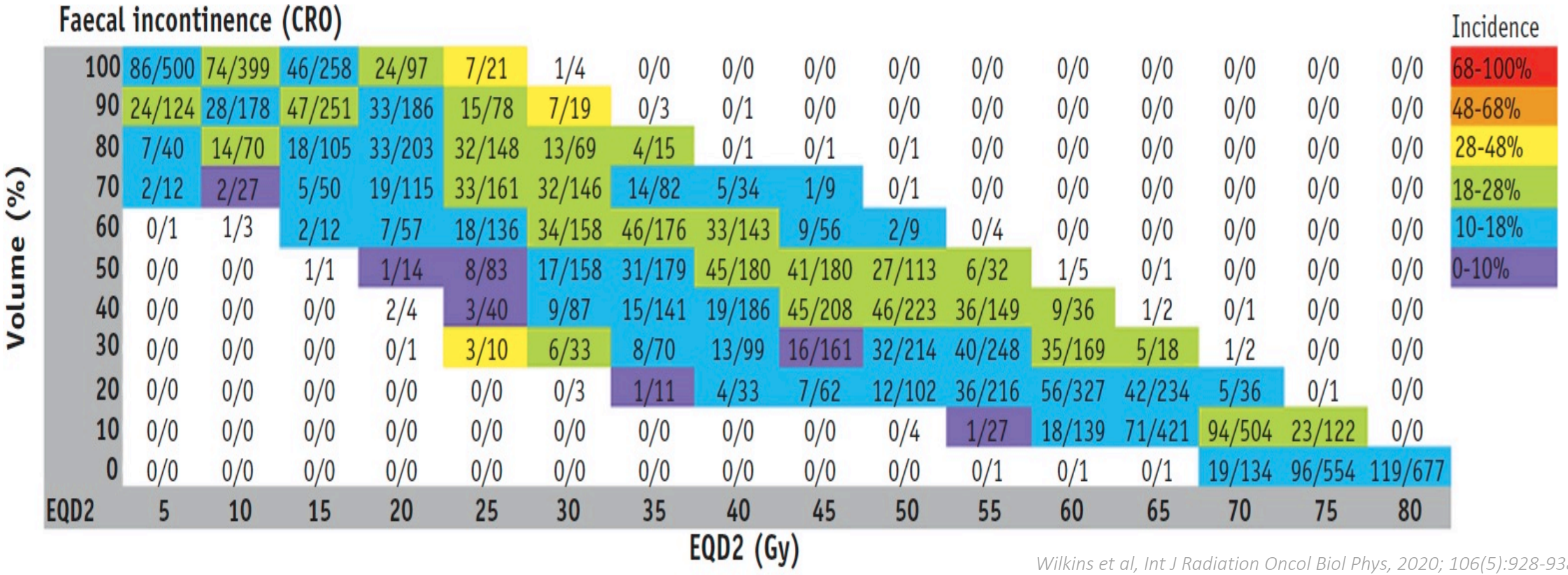
The anal canal is an important OAR for the development of late toxicity, and a large review study recommend an anal canal D_{mean} <40Gy as a constraint to reduce late incontinence.

Jadon et al. Radiation Oncology (2019) 14:57; https://doi.org/10.1186/s13014-019-1262-8

SHOULD WE FORGET LOCAL TARGET DOSE ESCALATION ?

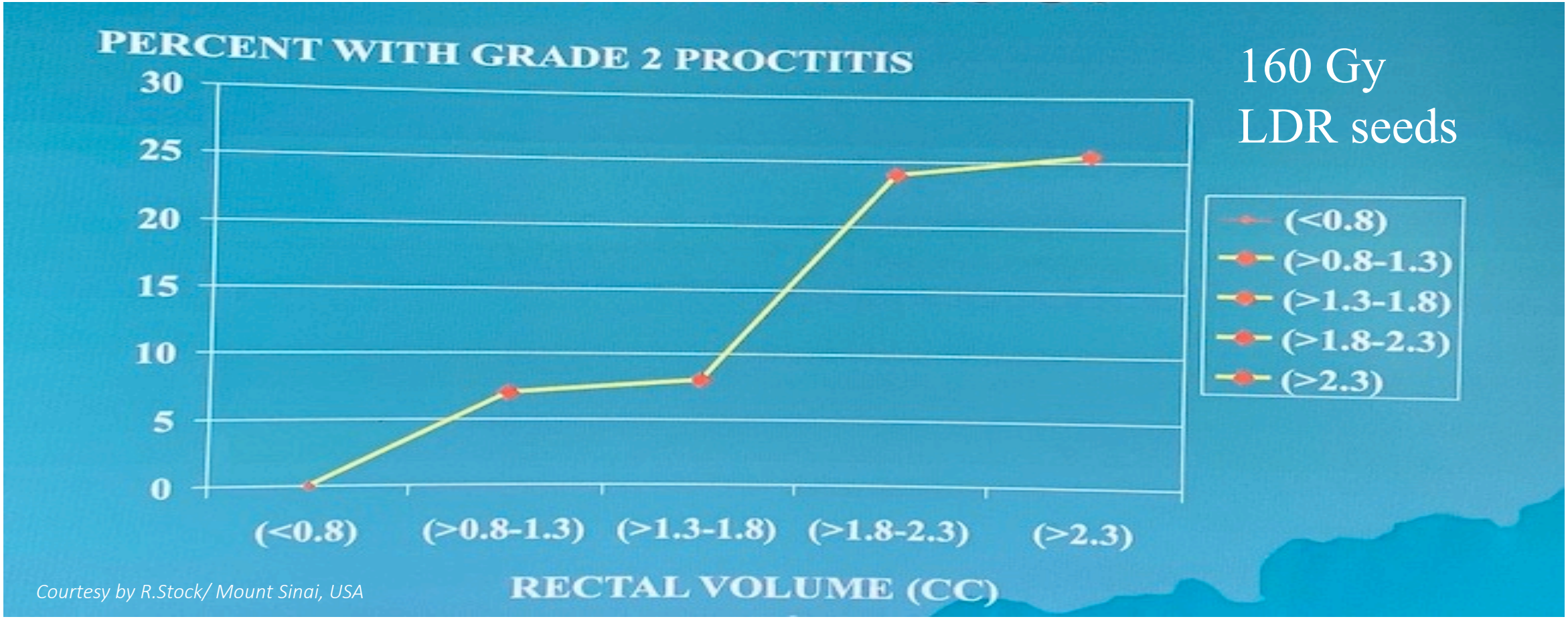
ANAL CANAL EBRT ADVERSE EFFECTS

The CHHiP trial randomized 3216 men with localized prostate cancer (1:1:1) to 3 radiation therapy fractionation schedules: 74 Gy in 37 fractions over 7.4 weeks; 60 Gy in 20 fractions over 4 weeks; and 57 Gy in 19 fractions over 3.8 weeks



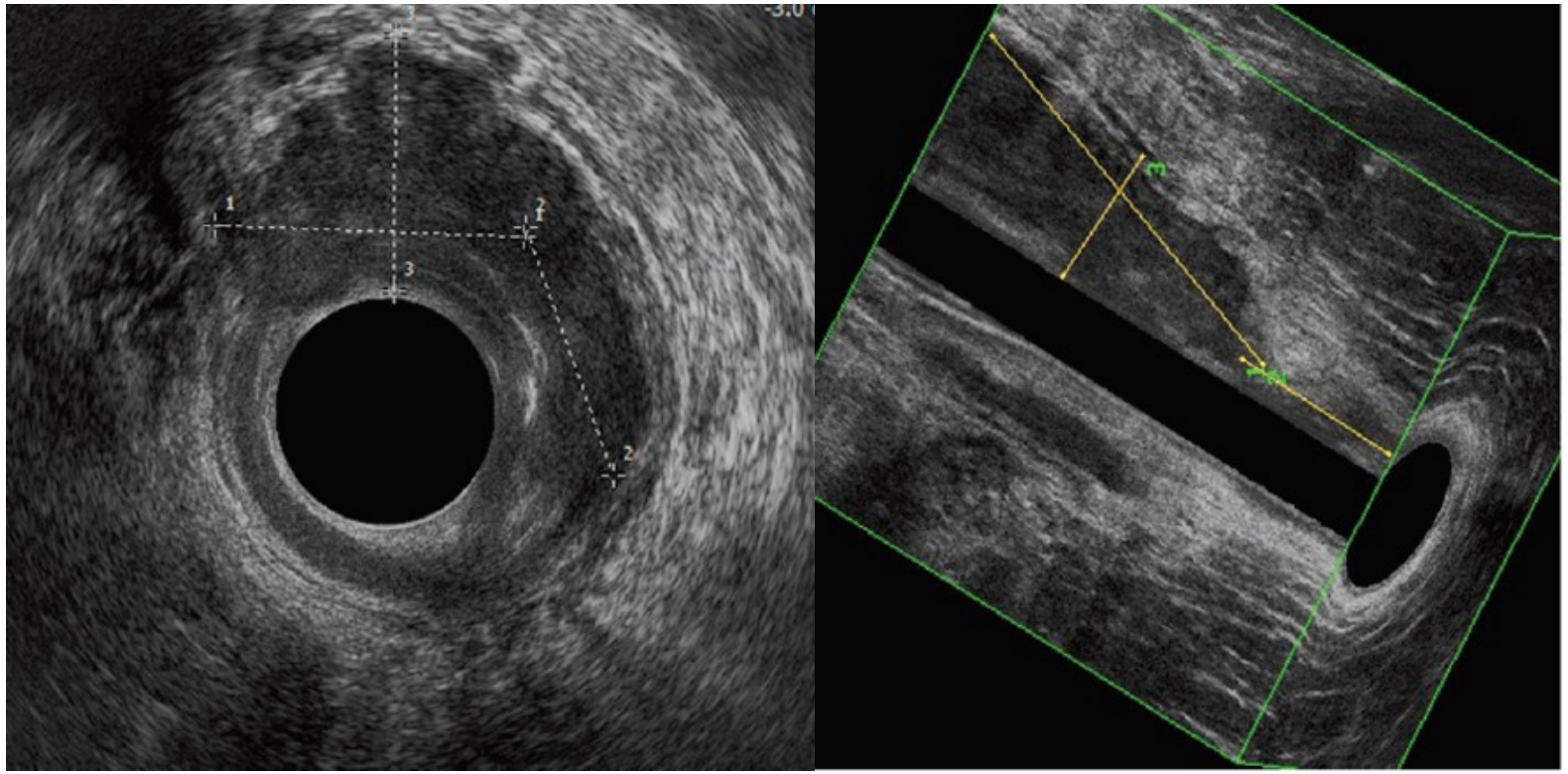
Wilkins et al, Int J Radiation Oncol Biol Phys, 2020; 106(5):928-938

RECTAL TOXICITY CAUSED BY IRT IS DOSE/VOLUME DEPENDENT



Courtesy by R.Stock/ Mount Sinai, USA

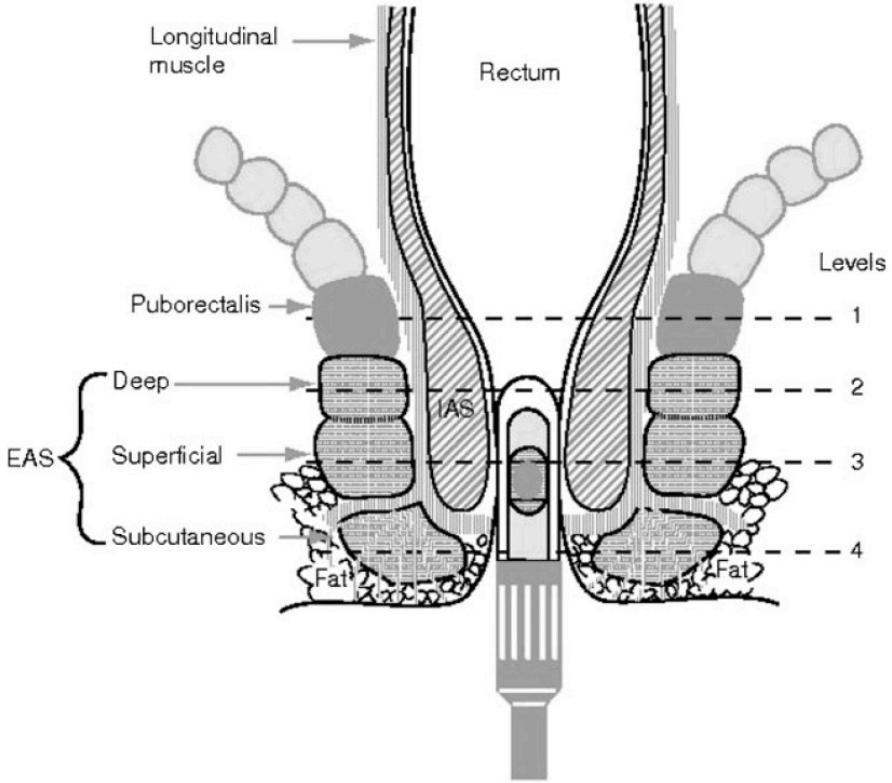
ANAL CANAL IMAGING FOR TARGET DEFINITION



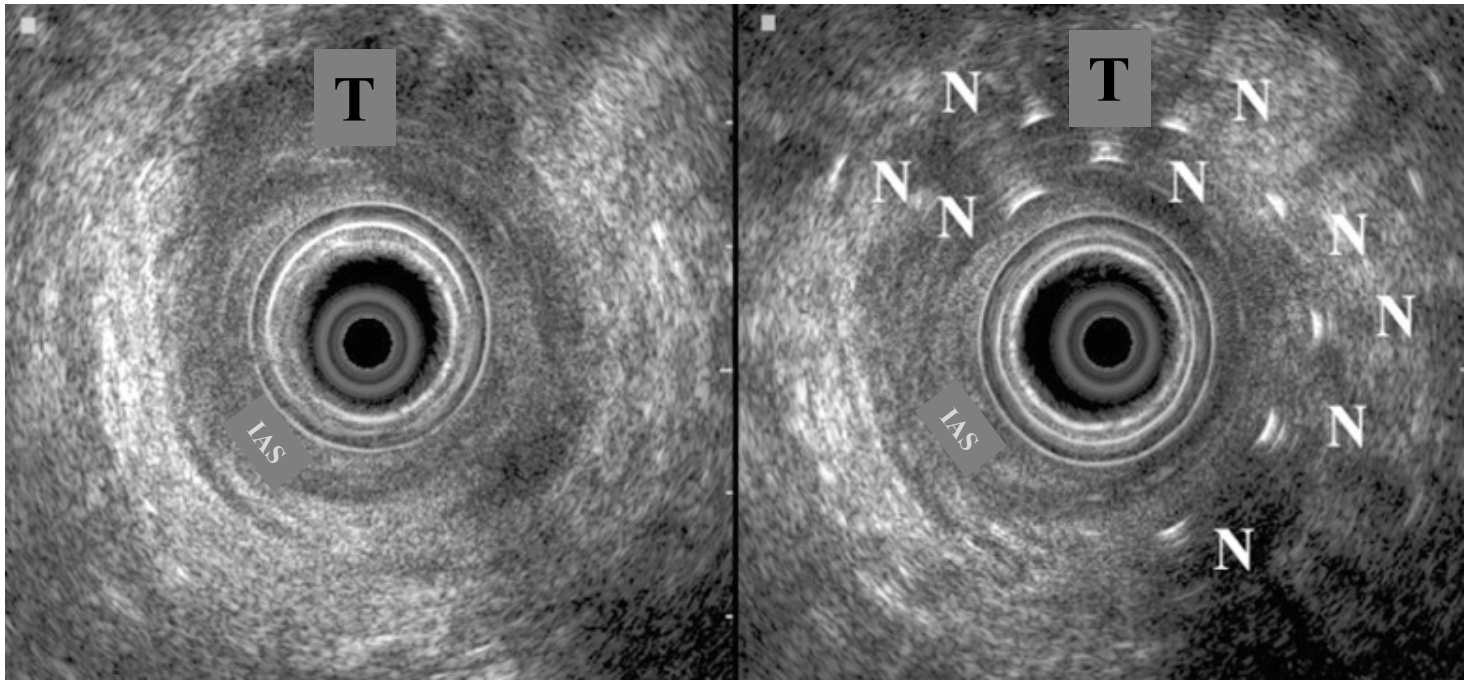
3D endo-anal sonography (EAUS) and MRI are accurate techniques in anal cancer staging, although *EAUS is more accurate* than MRI for T1 stage. MRI allows correct detection of neoplastic nodes and can properly stratify patients into responders or non responders.

Reginelli A et al, Diagnostic performance of magnetic resonance imaging and 3D endoanal ultrasound in detection, staging and assessment post treatment, in anal cancer Oncotarget, 2017, 8: 22980-22990

ANAL CANAL ANATOMY



Abdool et al, British Journal of Radiology, 85 (2012), 865–875



T = tumor

N = IRT needles

Doniec et al, Surg Endosc (2006) 20: 673–678

SUMMING UP

The ACCORD-03 study demonstrated improved 5-year local control for the group treated with dose-escalated boost (83.1%) vs. standard 15 Gy boost (78.2%)

#

In a cohort treated with 56 Gy, one-third of patients experienced fecal incontinence.

#

Very high doses delivered to the lamina propria and anal sphincter may also result in stricture and stenosis.

#

Therefore, efforts are needed to balance these risks with potential improvements in local control.

#

The primary tumour itself may contribute to later dysfunction if the cancer invades the anal sphincter and pelvic floor and the tumour is replaced by fibrotic tissue.

Dee et al, Cancers 2021; 13, 1208. https://doi.org/10.3390/cancers13061208

DOSE *versus* FUNCTION

Pathological similarities between anal canal patients treated with radiochemotherapy and the impaired anorectal sensory functions found in patients with idiopathic fecal incontinence were observed.

#

However, we are *not able to make recommendations* on dose constraints, specific doses *to the sphincter complex* (Dmean, V50Gy and D90%).

#

There is evidence of decreased peripheral nerve conduction velocity from the rectum in combination with altered cortical processing in response to distension of both the rectum and the anal canal in anal cancer patients treated with RT/CRT. Findings indicate that *RT/CRT causes impaired peripheral and cortical processing* that may cause dysintegration of consciously perceived anorectal sensory stimuli.

Haas et al, Radiotherapy and Oncology, 2018; 128(2):369-372

DOSE *versus* FUNCTION

The *internal anal sphincter* (IAS) is the main contributor to *the anal resting pressure*. Somatic innervation submit the external anal sphincter (EAS) and *puborectalis muscle* to voluntary control making them the main contributors to the *anal squeeze pressure.*

#

Damage to any of the structures carries a risk of fecal incontinence or defecatory disturbances.

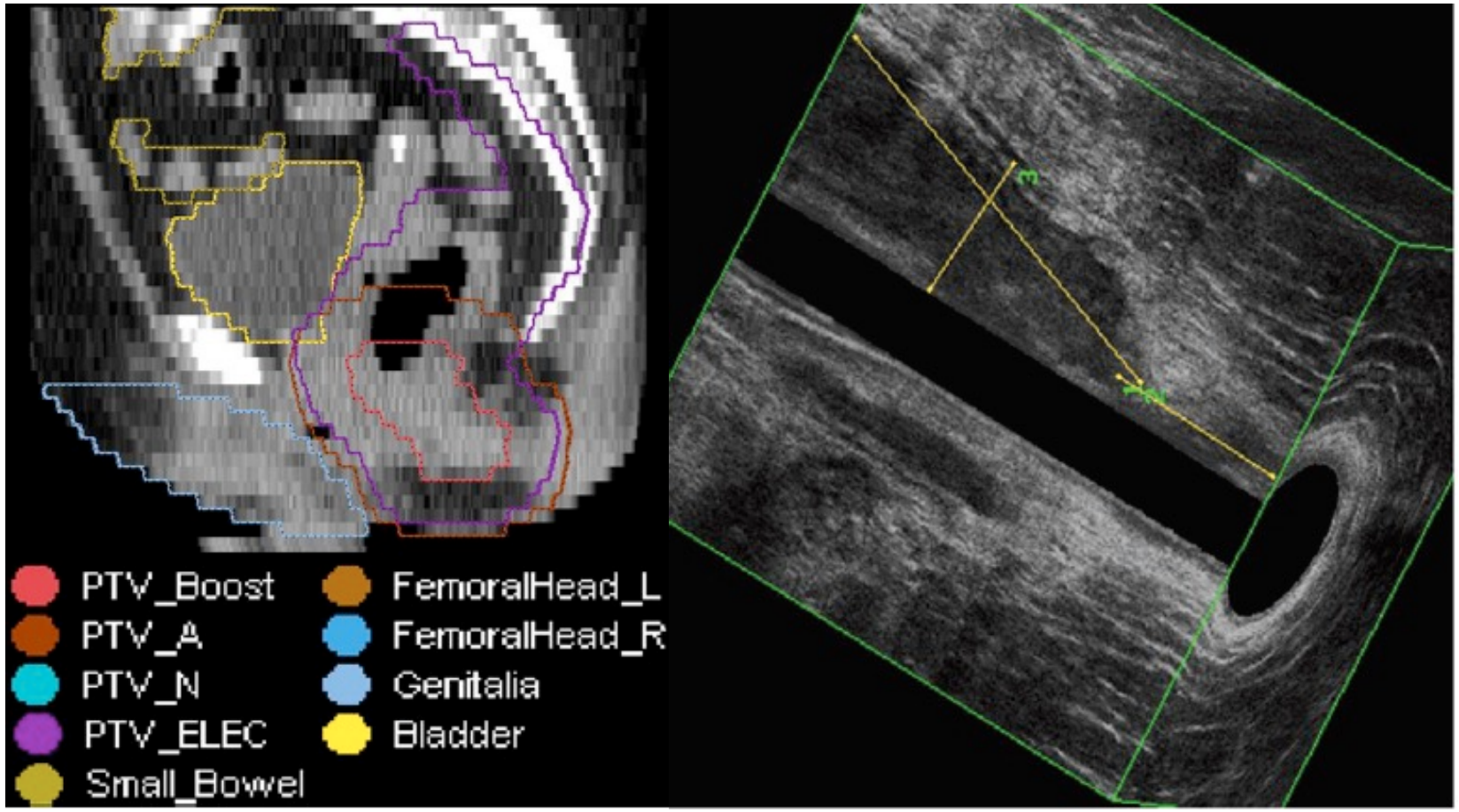
#

Increased distensibility suggest a degenerative transformation of tissue, theoretically both muscle and nerve, as opposed to severe fibrosis. Examining the geometrical configuration of the anal canal during rest, a weakening of the hourglass-like shape in the anal canal of anal cancer patients is observable. This reflects reduced resistance in the middle part of the anal canal where the IAS is thickest and covered by the EAS. This may indicate *damage of both the IAS and the EAS*.

Haas et al, Acta Oncologica, 2018; 57(4): 465-472

CAN WE AVOID LOCAL DOSE ESCALATION RELATED TOXICITY WITH MORE PRECISE TARGET VOLUME DEFINITION AND DOSE DELIVERY?

	Standard	Dose Escalation Arm 1	Dose Escalation Arm 2
PTV_Boost:	n/a	58.8Gy	61.6Gy



N. ABBOTT et al,
PLATO trial – Treatment Planning

EP-1732

Reginelli A et al

Diagnostic performance of magnetic resonance imaging and 3D endoanal ultrasound in detection, staging and assessment post treatment, in anal cancer

Oncotarget
2017, 8: 22980-22990

A PERSONAL EXPERIENCE

In 1992, we intended to introduce the technique of endosonographic three-dimensional tumor delineation and TRUS-guided high-dose rate (HDR) afterloading therapy for anal canal cancers.

#

In order to translate Papillion´s classic IRT technique (20 Gy LDR boost) to HDR technology, Jack Fowler calculated the equivalent HDR dose, which was 2x 6 Gy, with a minimal interfraction time of 6 hours.

#

Since at the first 3 patients we observed an unusually rapid residual tumor volume decrease, I changed the dose for 2x4 Gy.

#

Our rate of therapy-related sphincter injury and resulting incontinence was 6% (three patients) at 93% CSS at 5 yrs in N_0 cases. Two of these patients required colostomy. One patient who was treated with a brachytherapy dose of 6 Gy developed severe sphincter necrosis and resulting incontinence and required colostomy as a radiation side effect.

Doniec et al, Surg Endosc (2006) 20: 673–678

CONCLUSION

The current standard of care, CRT with 5-FU/MMC, remains a toxic regimen despite providing high cure rates. Future directions are focusing on mitigating toxicities as well as optimizing survival and individualizing treatment approaches in anal cancer patients.

#

The next generation of clinical trials largely seeks to focus on personalizing the treatment based on tumor properties.

Ludmir et al, Surg Oncol Clin N Am 26 (2017) 91–113

ADDITIONALLY, NO PLANNED FUTURE TRIALS INVESTIGATE THE ROLE OF PERSONALIZED HIGH-QUALITY TARGET VOLUME DEFINITION AND ADEQUATE IMAGE GUIDED RADIATION APPLICATION BASED TUMOR DOSE ESCALATION EFFECTS ON THE OUTCOME.