Cancer du canal anal

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www.eaux-vives.com

GENOLIER
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Introduction

- Uncommon cancer (≈ 2.0 / 100’000)
- 2.4 percent of all digestive system malignancies
- Incidence is increasing over the last 30 years
- *<u>Associated with</u>*:
  - Female
  - HPV infection
  - Genital warts
  - Smoking
  - Receptive anal intercourse
  - HIV

➔*Etiology similar to genital malignancies*

CAVE: In HIV-positive patients rates ~37/100,000

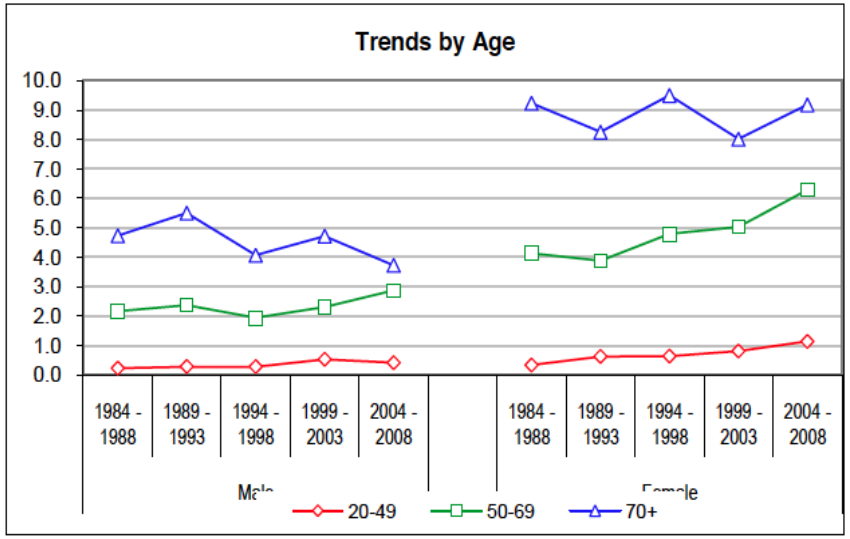
AU Siegel R, Naishadham D, Jemal ASO. Cancer statistics, 2013. CA Cancer J Clin. 2013 Jan;63(1):11-30
Johnson LG, Madeleine MM, Newcomer LM, et al: Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973-2000. Cancer 101:281-8, 2004

Incidence

Crude rates by age-group & mean annual trends

*, **: Significant variations cf. Mantel-Haenszel test (95%, 99%)
Signification of mean annual trends not computed

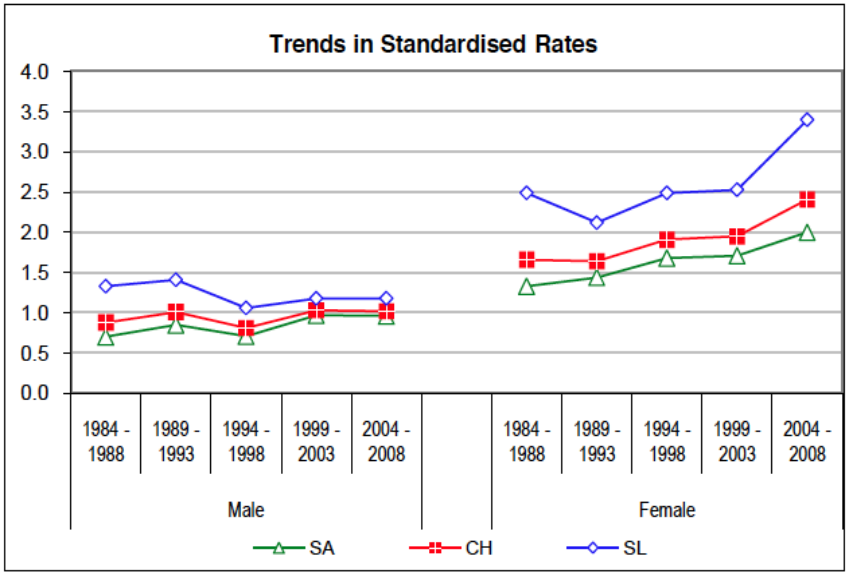
Gender	*Period*	*0-19*	*20-49*	*50-69*	*70+*
Male	1984 - 1988	0.00	0.22	2.16	4.73
	1989 - 1993	0.00	0.28	2.37	5.50
	1994 - 1998	0.00	0.27	1.93	4.06
	1999 - 2003	0.00	0.53 *	2.31	4.72
	2004 - 2008	0.00	0.41	2.87	3.72
Female	1984 - 1988	0.00	0.33	4.14	9.24
	1989 - 1993	0.00	0.62 *	3.88	8.25
	1994 - 1998	0.00	0.64	4.79 *	9.50
	1999 - 2003	0.03	0.81	5.04	8.02
	2004 - 2008	0.00	1.14	6.29 *	9.19
Male	Annual trend		1.041	1.040	0.991
Female	Annual trend		1.060	1.028	0.997
	(3 last periods)				



European standardized rate by period

Gender	*Period*	*SA*	*CH*	*SL*	*C.I. 95% of CH*	
Male	1984 - 1988	0.70	0.88	1.33	0.20	1.70
	1989 - 1993	0.85	1.01	1.41	0.40	1.73
	1994 - 1998	0.71	0.81	1.06	0.32	1.39
	1999 - 2003	0.97	1.03	1.18	0.53	1.61
	2004 - 2008	0.96	1.02	1.18	0.55	1.55
Female	1984 - 1988	1.33	1.66	2.49	0.83	2.62
	1989 - 1993	1.44	1.64	2.12	0.95	2.41
	1994 - 1998	1.68	1.91	2.49	1.21	2.67
	1999 - 2003	1.71	1.95	2.53	1.28	2.67
	2004 - 2008	2.00	2.41	3.40	1.72	3.18
Male	Annual trend	1.031	1.023	1.011		
Female	Annual trend	1.018	1.024	1.032		
	(3 last periods)					

SA Alemannic Switzerland
CH Switzerland
SL Latin Switzerland

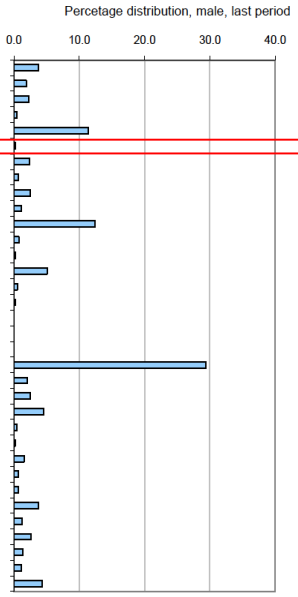


Incidence: Switzerland (II)

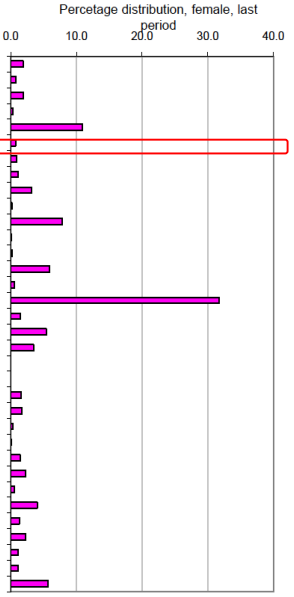
Incidence **Switzerland** Summary

Percentage distribution by site, in %

ICD10	Site	Male 1984 - 1988	1989 - 1993	1994 - 1998	1999 - 2003	2004 - 2008
C00-14	Oral Cavity & Pharynx	4.3	4.3	4.1	3.6	3.7
C15	Oesophagus	1.7	1.7	1.8	1.9	1.9
C16	Stomach	4.9	4.1	3.6	2.9	2.3
C17	Small Intestine	0.4	0.5	0.4	0.5	0.4
C18-20	Colon, Rectum	12.1	11.7	11.5	11.6	11.4
C21	Anus & Anal Canal	0.2	0.2	0.2	0.2	0.2
C22	Liver & Intrahepatic Bile Ducts	2.2	2.2	2.3	2.4	2.4
C23-24	Gallbladder & Extrahepatic Bile Tract	0.8	0.7	0.7	0.6	0.7
C25	Pancreas	2.8	2.7	2.6	2.5	2.5
C32	Larynx	1.7	1.5	1.4	1.3	1.2
C33-34	Lung, Bronchus, Trachea	18.0	16.5	14.5	13.2	12.4
C38.4, C45.0	Pleura	0.4	0.5	0.6	0.6	0.7
C40-41	Bones, Joints, Cartilage	0.3	0.3	0.2	0.2	0.2
C43	Skin Melanoma	3.0	3.3	3.9	4.5	5.1
C47, C49	Soft Tissues	0.6	0.6	0.7	0.6	0.5
C50	Breast	0.2	0.2	0.2	0.2	0.2
C53	Cervix Uteri	-	-	-	-	-
C54-55	Corpus Uteri & NOS	-	-	-	-	-
C56	Ovary	-	-	-	-	-
C61	Prostate	19.6	22.3	25.5	28.8	29.4
C62	Testis	2.2	2.3	2.2	2.0	2.0
C64	Kidney	2.8	2.9	2.6	2.6	2.5
C67	Bladder	5.2	4.8	4.8	4.4	4.6
C65-66, C68	Other Urinary Organs	0.6	0.5	0.5	0.5	0.5
C69	Eye	0.2	0.3	0.2	0.2	0.2
C70-72	Brain & Central Nerves	1.8	1.6	1.6	1.6	1.6
C73	Thyroid	0.6	0.6	0.6	0.6	0.7
C81	Hodgkin's Disease	0.8	0.7	0.7	0.6	0.7
C82-85, C96	Non Hodgkin Lymphoma	3.4	3.8	4.0	3.7	3.7
C90	Multiple Myeloma	1.1	1.3	1.4	1.2	1.3
C91-95	Leukaemia	3.2	2.9	2.7	2.8	2.6
C91	Lymphoid Leukaemia	1.7	1.6	1.4	1.5	1.4
C92-94	Myeloid Leukaemia	1.3	1.2	1.2	1.1	1.1
Others	Other sites	4.9	5.1	4.7	4.1	4.3
C00-43, C45-97	All Cancers except non-melanotic Skin	100.0	100.0	100.0	100.0	100.0



ICD10	Site	Female 1984 - 1988	1989 - 1993	1994 - 1998	1999 - 2003	2004 - 2008
C00-14	Oral Cavity & Pharynx	1.4	1.7	1.7	1.8	1.9
C15	Oesophagus	0.6	0.7	0.7	0.7	0.8
C16	Stomach	3.7	3.2	2.7	2.0	2.0
C17	Small Intestine	0.4	0.4	0.4	0.4	0.3
C18-20	Colon, Rectum	12.4	12.0	11.5	11.3	10.9
C21	Anus & Anal Canal	0.6	0.6	0.6	0.6	0.7
C22	Liver & Intrahepatic Bile Ducts	0.8	0.8	0.9	0.9	0.9
C23-24	Gallbladder & Extrahepatic Bile Tract	1.7	1.6	1.4	1.2	1.1
C25	Pancreas	3.5	3.3	3.0	2.9	3.2
C32	Larynx	0.2	0.2	0.3	0.3	0.2
C33-34	Lung, Bronchus, Trachea	4.8	5.5	5.9	6.8	7.8
C38.4, C45.0	Pleura	0.1	0.1	0.1	0.1	0.1
C40-41	Bones, Joints, Cartilage	0.2	0.3	0.2	0.2	0.2
C43	Skin Melanoma	4.1	4.4	4.7	5.5	5.9
C47, C49	Soft Tissues	0.6	0.7	0.6	0.6	0.6
C50	Breast	29.0	29.6	31.2	32.5	31.7
C53	Cervix Uteri	3.2	2.7	2.5	1.9	1.4
C54-55	Corpus Uteri & NOS	6.6	6.0	5.9	5.6	5.4
C56	Ovary	4.7	4.6	4.2	3.6	3.5
C61	Prostate	-	-	-	-	-
C62	Testis	-	-	-	-	-
C64	Kidney	1.9	1.8	1.7	1.6	1.6
C67	Bladder	2.0	1.9	1.9	1.8	1.7
C65-66, C68	Other Urinary Organs	0.5	0.5	0.4	0.4	0.3
C69	Eye	0.3	0.3	0.2	0.2	0.1
C70-72	Brain & Central Nerves	1.5	1.5	1.4	1.4	1.4
C73	Thyroid	1.6	1.7	1.9	1.9	2.3
C81	Hodgkin's Disease	0.6	0.6	0.6	0.6	0.6
C82-85, C96	Non Hodgkin Lymphoma	3.3	3.9	4.1	3.8	4.0
C90	Multiple Myeloma	1.2	1.4	1.3	1.4	1.3
C91-95	Leukaemia	2.7	2.4	2.3	2.5	2.3
C91	Lymphoid Leukaemia	1.3	1.1	1.1	1.3	1.1
C92-94	Myeloid Leukaemia	1.3	1.2	1.1	1.1	1.1
Others	Other sites	5.6	5.8	5.8	5.5	5.7
C00-43, C45-97	All Cancers except non-melanotic Skin	100.0	100.0	100.0	100.0	100.0



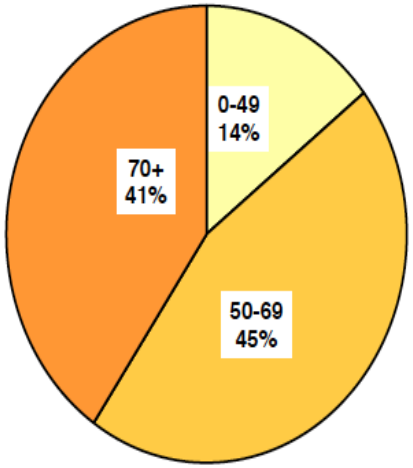
	1984 - 1988	1989 - 1993	1994 - 1998	1999 - 2003	2004 - 2008
Anus & Anal Canal	0.2	0.2	0.2	0.2	0.2
Anus & Anal Canal	0.6	0.6	0.6	0.6	0.7

Incidence: Switzerland (III)

Incidence **Anus & Anal Canal** Switzerland

Number of new cases - three last periods

Gender	*Period*	*0-49*	*Age group 50-69*	*70+*	*Total*	*Yearly average*
Male	1984 - 1988	16	68	59	143	29
	1989 - 1993	22	79	72	173	35
	1994 - 1998	22	70	57	149	30
	1999 - 2003	42	91	73	206	41
	2004 - 2008	33	124	64	221	44
Female	1984 - 1988	24	144	189	357	71
	1989 - 1993	48	141	178	368	74
	1994 - 1998	50	184	220	455	91
	1999 - 2003	65	207	198	471	94
	2004 - 2008	92	278	242	612	122
Total	Total (3 last periods)	304	954	855	2'113	141

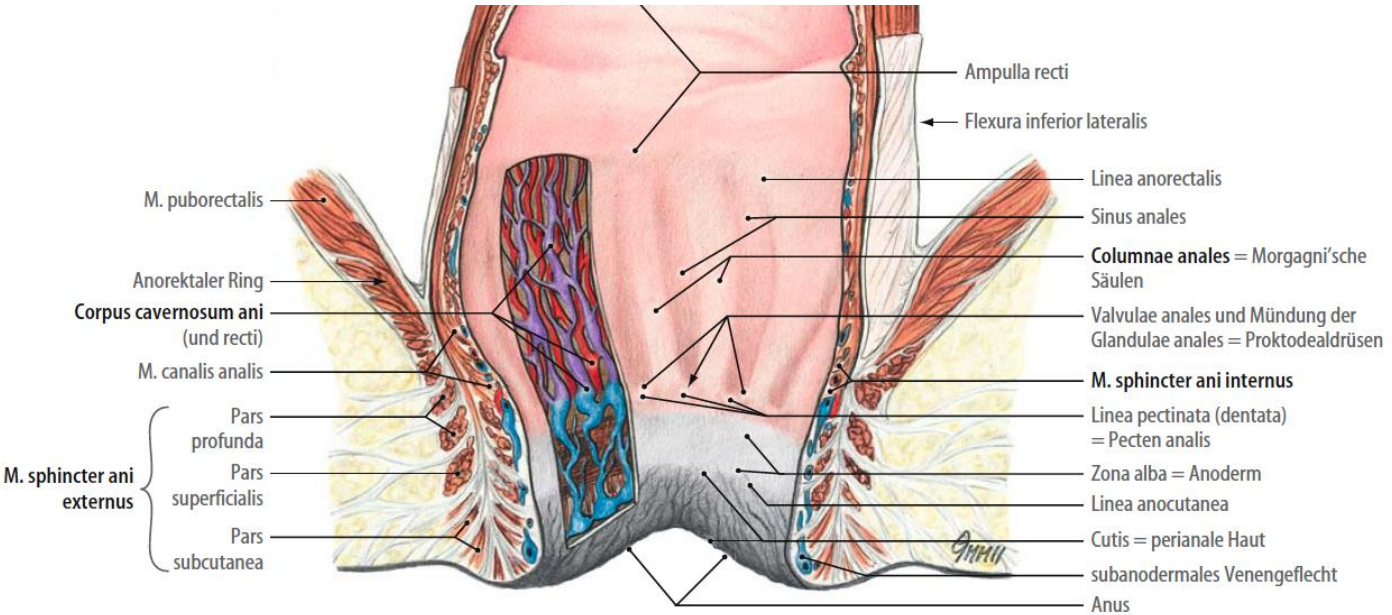


Anatomy

Junction of levator ani muscle and the external anal sphincter
Extends distally to the anal verge

Dentate line: transition from glandular to squamous mucosa

Approximately 4 cm.



Anatomy (II)

Cancers that arise in the perianal skin are termed ‘perianal cancers’

The anal margin is the pigmented skin immediately surrounding the anal orifice, extending laterally to a radius of 5 cm (ESMO guidelines 2010)

Primary tumours of the anal margin: 15– 20% of anal SCC

Distinction between anal canal and anal margin is important as anal canal lesions are more aggressive

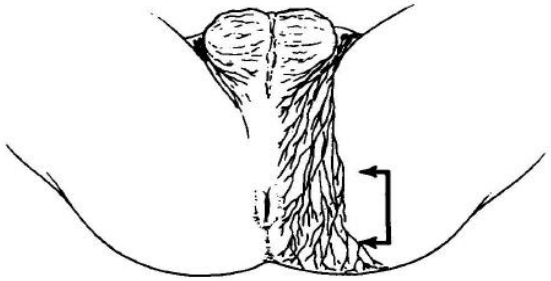
Anal margin cancer are biologically similar to other skin tumours
➔high cure rates with wide local excision alone if they are < 3 cm in diameter, well differentiated and superficial. *(Level of evidence: III)*

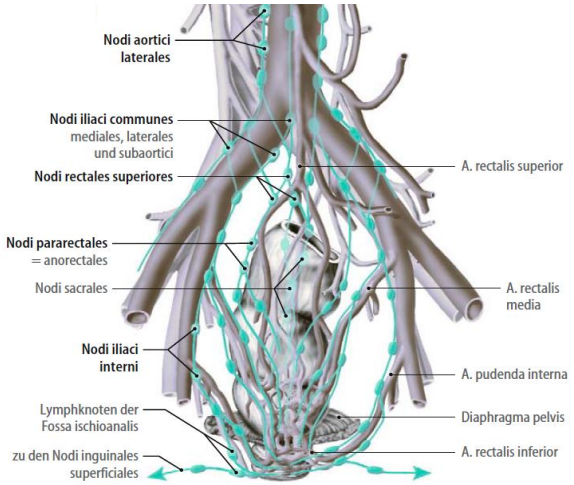
Lymphatics

The lymphatic drainage varies in different parts of the canal.

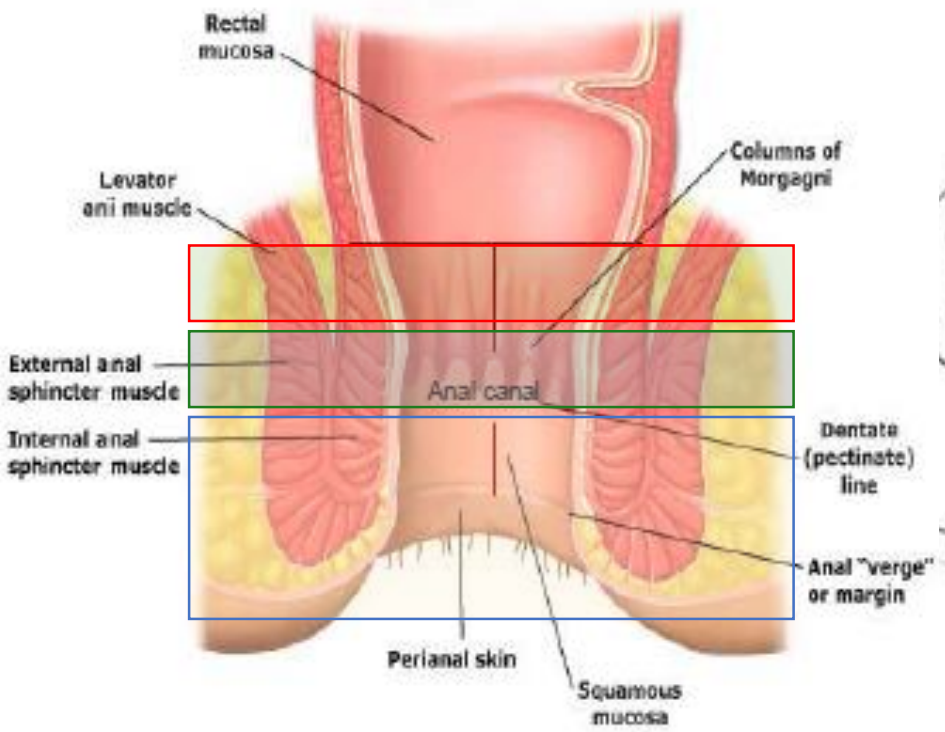
Above the dentate line:
perirectal nodes &
inferior mesenteric artery

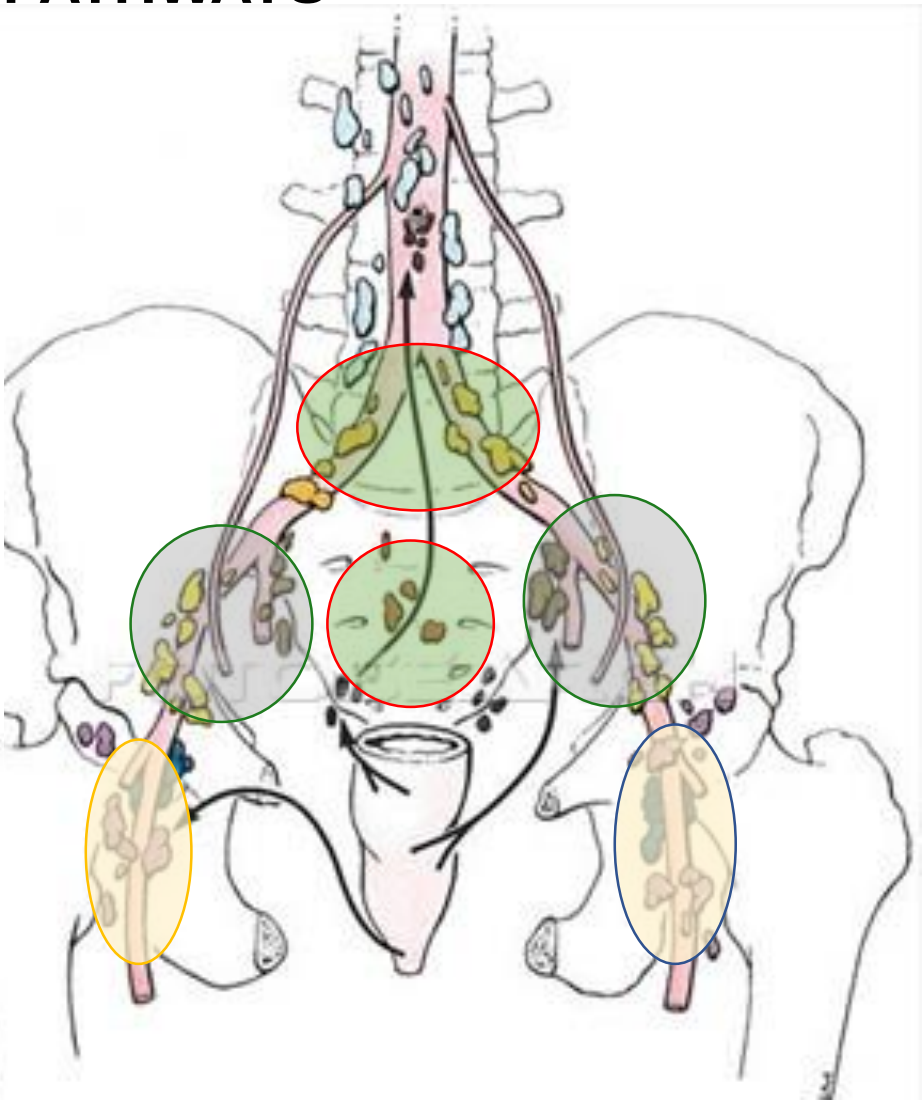
Below the dentate line:
inguinal, femoral &
external iliac nodes





LYMPHATIC PATHWAYS





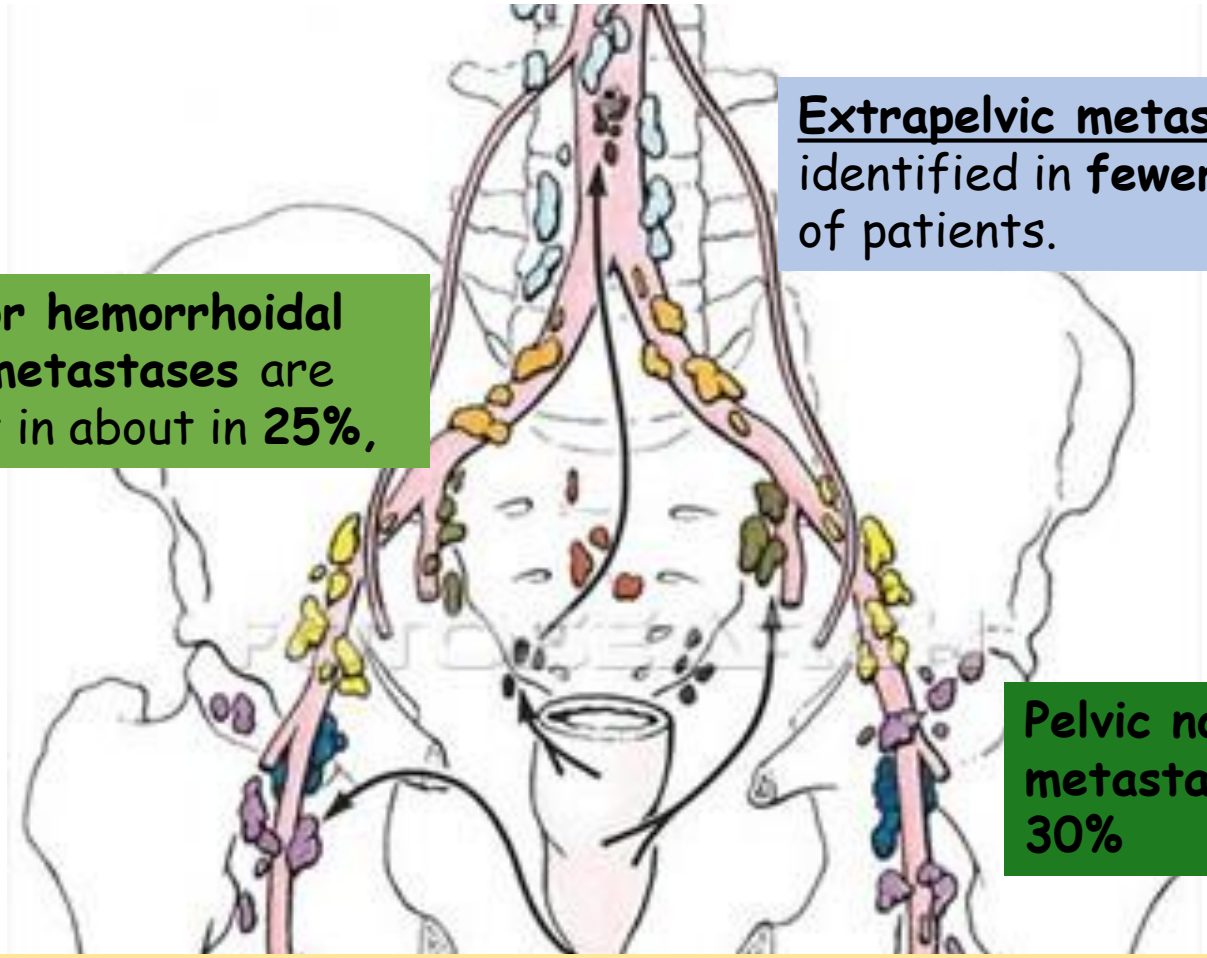
Perirectal, superior hemorroidal and inferior mesenteric nodes

Internal pudendal, hypogastric and obturator nodes

Inguinal, femoral and external iliac nodes

RISK OF NODAL INVOLVEMENT

The overall risk of **regional nodal involvement** at diagnosis is about **25%**.



Extrapelvic metastases are identified in **fewer than 10%** of patients.

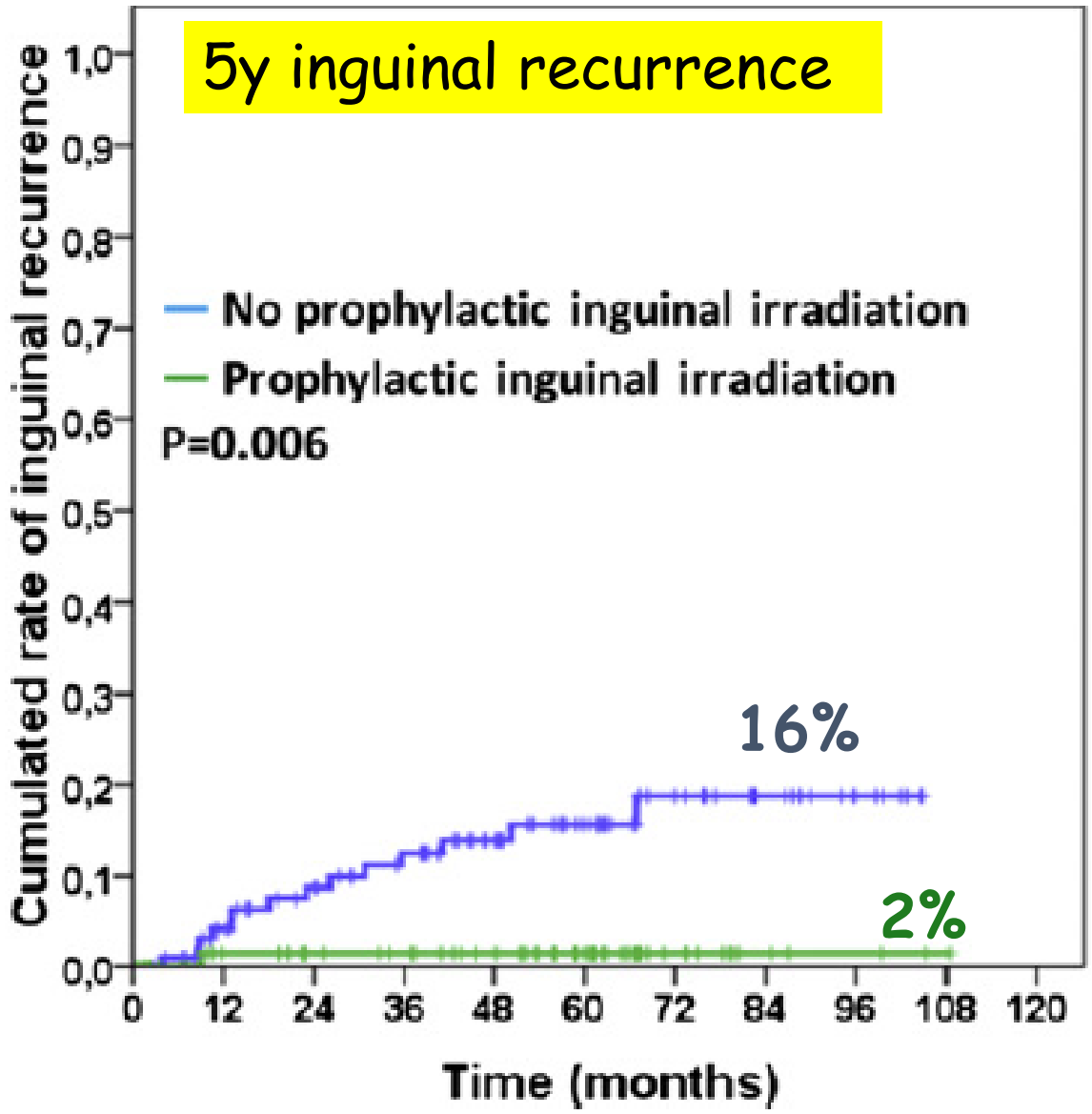
Superior hemorrhoidal nodes metastases are present in about in **25%,**

Pelvic nodes metastases in **30%**

Inguinal metastases are clinically detectable in up to 20% of patients at initial diagnosis and are present subclinically in a further 10% to 20%.

Stearns MW, et al. Cancer of the anal canal. Curr Probl Cancer 1980

PROPHYLACTIC INGUINAL IRRADIATION



In the PII group 5-year CRIR was significantly lower (p= 0.006)

In the PII group, no Grade >2 toxicity of the lower extremity was observed

In the **no PII group**, the 5-year CRIR was **12%** for **T1-T2** and **30%** for **T3-T4** (p = 0.02).

In the **PII group**, the 5-year CRIR was not different in **T1-2 vs T3-4 (0% vs 3%)**

PII didn't affect OS and DFS

C. ORTHOLAN et al. Int. J. Radiation Oncology Biol. Phys., 2012

Pathologic classification

- Epidermoid carcinoma (SCC):

  80–85% anal canal carcinoma

- No significant prognostic differences between the subtypes of SCC

➔

- SCC can be used to cover all histological variants of SCC of the anal canal

Table I WHO histological classification of tumours of the anal canal: [14].

Epithelial tumours
Intraepithelial neoplasia1 (dysplasia)
Squamous or transitional epithelium
Glandular
Paget disease 8542/32
Carcinoma
Squamous cell carcinoma 8070/3
Adenocarcinoma 8140/3
Mucinous adenocarcinoma 8480/3
Small cell carcinoma 8041/3
Undifferentiated carcinoma 8020/3
Others
Carcinoid tumour 8240/3
Malignant melanoma
Nonepithelial tumours

Aetiology

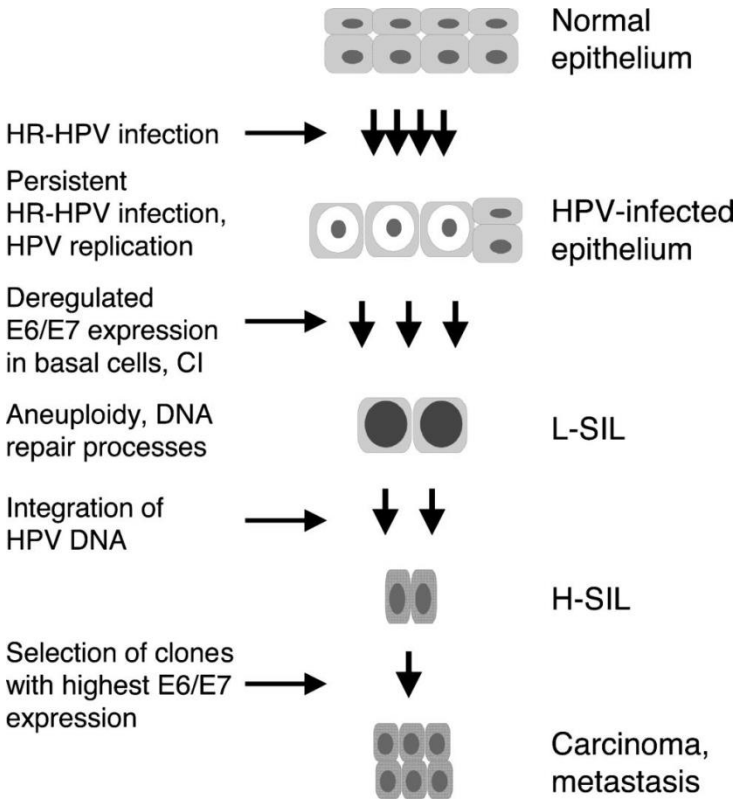
Anal cancer is strongly associated with human papilloma virus

PCR: HPV genome in 80%–85% of cases

Other important risk factors include HIV

Progression from AIN 1 and 2 to AIN 3 and from AIN 3 to invasive malignancy in immunocompetent patients is uncommon…

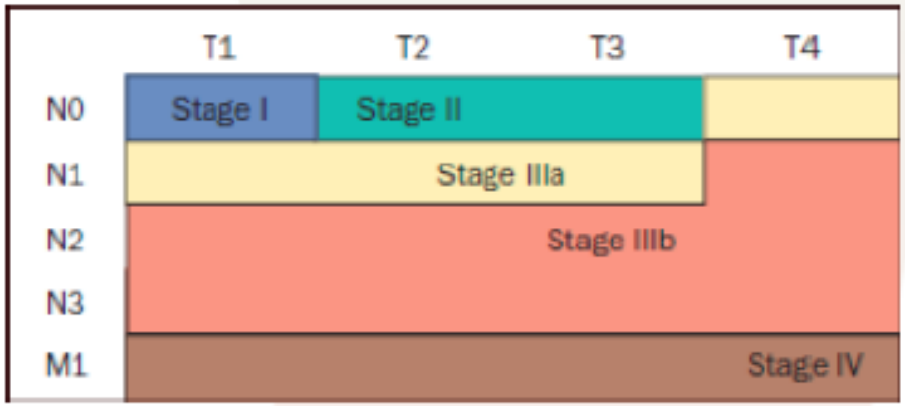
…while it is more likely in systemically immunosuppressed



Staging

Table 1. TNM staging

Tx	Primary tumour cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumour ≤2 cm
T2	Tumour >2–5 cm
T3	Tumour >5 cm
T4	Tumour invades other organ (vagina, urethra, bladder, sacrum): anal canal
	Tumour invades deeper structures (skeletal muscle or cartilage): anal margin
N	Regional nodes are perirectal, internal iliac and inguinal
Nx	Regional nodes cannot be assessed
N0	No regional node metastases
N1	Metastasis in perirectal nodes
N2	Metastasis in unilateral internal iliac and/or inguinal nodes
N3	Metastasis in perirectal and/or bilateral internal iliac or inguinal nodes
M0	No metastasis
M1	Metastasis present



Staging (II): Evaluation

Physical examination including:

- digital rectal examination
- vaginal examination
- assessment of the inguinal nodes

Loco-regional staging:

- MRI of the pelvis
- Endorectal US (usefull for small tumors)
- Pet –CT

Distant metastases:

- CT, thorax and abdomen
- Pet-CT

ESMO guidelines 2010

Staging (III): Role of Pet-CT

The effect of positron-emission tomography (PET) on staging anal cancer in the few studies published to date.

Authors	Country	Date	No. of patients	Upstaged by PET or PET/CT (%)	Downstaged by PET or PET/CT (%)	Change in management (%)
The present study	UK	2008–2011	44	17	19	29
Nguyen et al.[3]	Australia	1996–2006	50—compared to CT only	17	–	19
Winton et al.[2]	Australia	1997–2005	61—not all with conventional imaging and PET	15	8	16
Trautmann et al.[4]	America	1999–2002	21—compared to CT only	24	–	–
Cotter et al.[5]	America	2003–2005	41—compared to CT only	25	–	–
Vercellino et al.[6]	France	2004–2008	44 comparison to conventional imaging not made	–	–	20
Iagaru et al.[7]	America	2009	8	–	–	38
Bannas et al.[8]	Germany	2010	22	9	18	–
Krengli et al.[13]	Italy	2005–2008	27—compared to CT only	18.5	–	4

Data are overall figures, including initial staging and follow-up examinations.

Staging: Role of Pet-CT

44 patients with anal cancer
(30 initial staging, 20 were post-treatment)

All patients received PET/CT imaging in addition to CT and MRI

Conventional imaging was retrospectively assessed.

The PET/CT findings altered patient management in 29% (14/48) of cases

CONCLUSION: PET/CT alters the initial staging sufficiently frequently that it should be used routinely in anal cancer, where it is available

Wells IT, Fox BM: PET/CT in anal cancer - is it worth doing? Clin Radiol 67:535-40, 2012

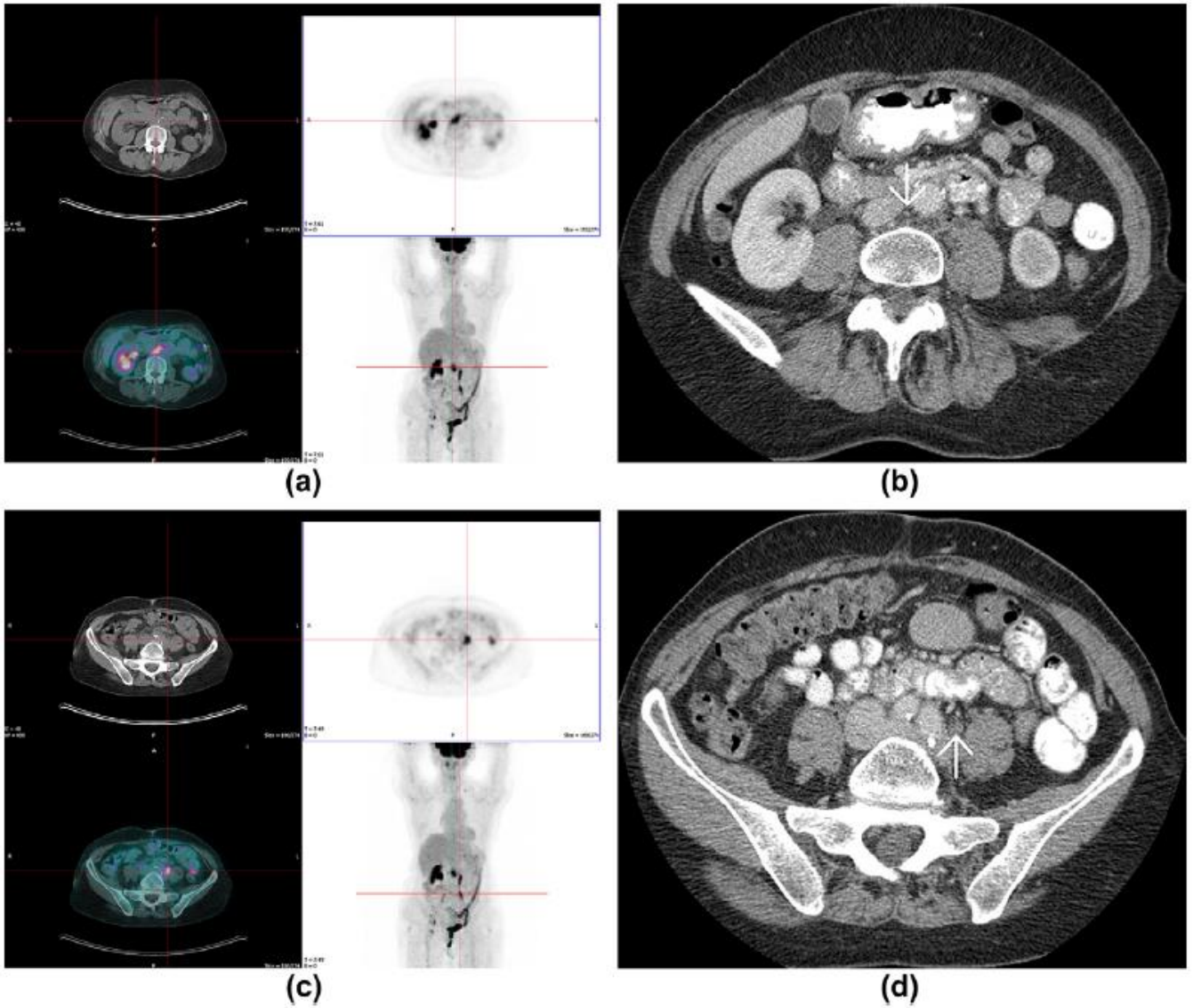


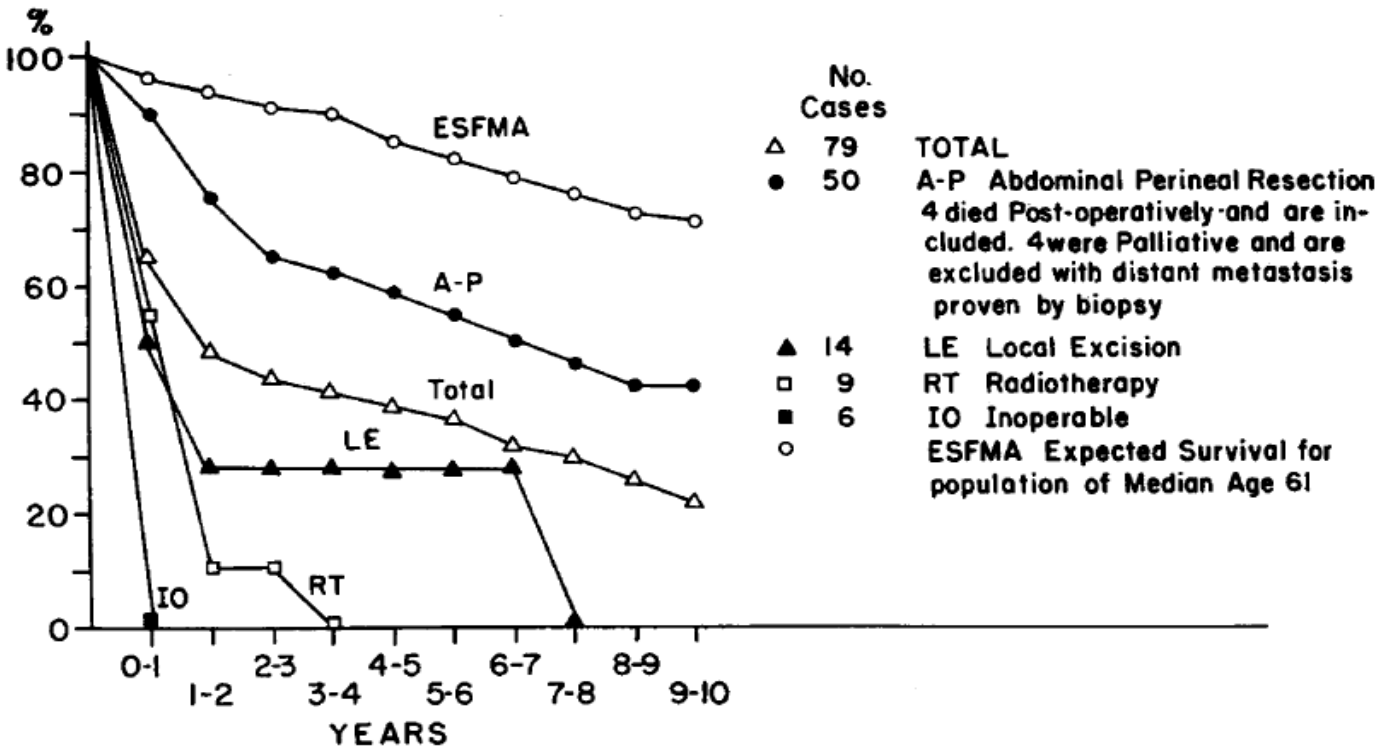
Figure 1 Example of a patient with unsuspected distant nodal metastasis found on PET/CT. PET/CT shows avid FDG uptake (SUV max 8.9) in a tiny aortocaval node (a), which was considered normal on CT performed 4 weeks previously (b) (arrow). There is also avid FDG uptake in a left para-aortic node on PET/CT (c). This node measured 7 mm on CT and was also considered normal (d) (arrow).

Wells IT, Fox BM: PET/CT in anal cancer - is it worth doing? Clin Radiol 67:535-40, 2012

Treatment: 1960th

Abdominoperineal resection:

review of 70 patients treated between 1940 & 1957



All cases of epidermoid cancer of anus and contrasting forms of therapy.

5-Year survival for abdomino-
Perineal resection: 58%

Dillard BM, Spratt JS, Jr., Ackerman LV, et al: Epidermoid cancer of anal margin and canal.
Review of 79 cases. Arch Surg 86:772-7, 1963

New paradigm: sphincter preservation

Wayne State: to decrease surgical failure

- Preoperative 5-fluorouracil (5-FU) and mitomycin with 30 Gy radiation therapy (small tumors)
- The surprising finding: complete pathologic responses in the first 3 patients
- New strategy: sphincter preservation
- ➔ equivalent local control and survival rates with preservation of sphincter function and thus avoidance of a colostomy

Nigro ND, Vaitkevicius VK, Considine B Jr. Combined therapy for cancer of the anal canal: a preliminary report. Dis Colon Rectum 1974;17:354– 6.

Standard treatment:

- 3 phase III trials confirmed the combination of radiotherapy with concurrent 5-FU and MMC
- 5FU and MMC CRT as the definitive treatment for squamous cell cancer of the anus, replacing surgical abdomino-perineal resection

- UKCCCR Anal Cancer Working Party. Epidermoid Anal Cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5- fluorouracil and Mitomycin. *Lancet 1996;348:1049–54*.
- Bartelink H, Roelofsen F, Eschwege F, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European organization for research and treatment of cancer radiotherapy and gastrointestinal cooperative groups. *J Clin Oncol 1997;15:2040–9*
- Flam M, John M, Pajak TF, et al. Role of mitomycin in combination with fluorouracil and radiotherapy and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. *J Clin Oncol 1996;14:2527–39*.

No Photo

ID: 598214
Plan date: Oct 19, 2007 9:45:33 AM
Oncologist: DR RADIO-ONCOLOGIE, .
Disease: CTINJ

Plan: Plan_02
Plan status: Approved
DQA plan:
Patient position: HFS

Adjust Fractionization Schedule

- Modify the fraction count or adjust details for each fraction as necessary.
- Run **Final Dose**.

When you are satisfied with the plan, click Final Accept.

ROIs | Optimization | Fractionation | Delivery QA Setup | Delivery QA Analysis

Fraction Count: 20

The plan has *20* fractions defined for a planned delivery of *36.0* Gy.
95.0% of the *PTV36* volume receives at least *36.0* Gy for the current plan.
Modulation factor for this tomotherapy IMRT plan is *1.359*

Unlock Future Fractions

Fraction	Locked	Fraction Date
1	☐	October 31, 2007
2	☐	November 01, 2007
3	☐	November 02, 2007
4	☐	November 05, 2007
5	☐	November 06, 2007
6	☐	November 07, 2007
7	☐	November 08, 2007
8	☐	November 09, 2007
9	☐	November 12, 2007
10	☐	November 13, 2007
11	☐	November 14, 2007
12	☐	November 15, 2007
13	☐	November 16, 2007
14	☐	November 19, 2007
15	☐	November 20, 2007

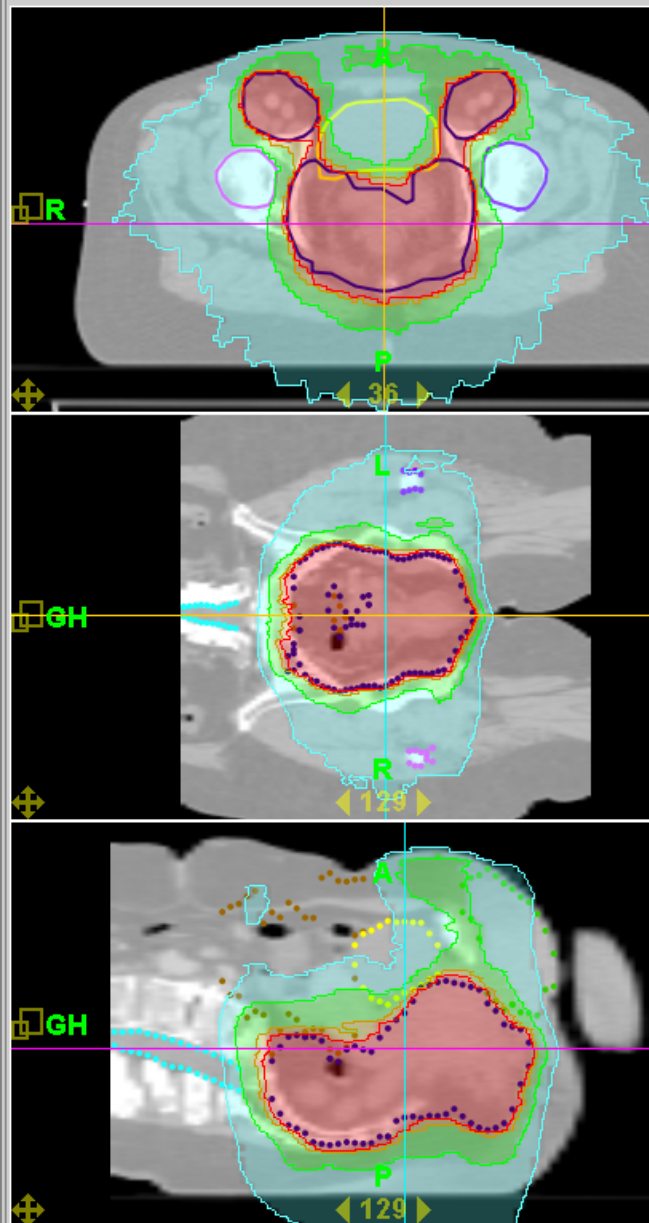
Fraction	Locked	Fraction Date
16	☐	November 21, 2007
17	☐	November 22, 2007
18	☐	November 23, 2007
19	☐	November 26, 2007
20	☐	November 27, 2007

Dose Display

☑ Isodose

39.6
34.2
32.4
25
15

Patient Images



Finalize

Final Dose
Final Accept
Plan Report

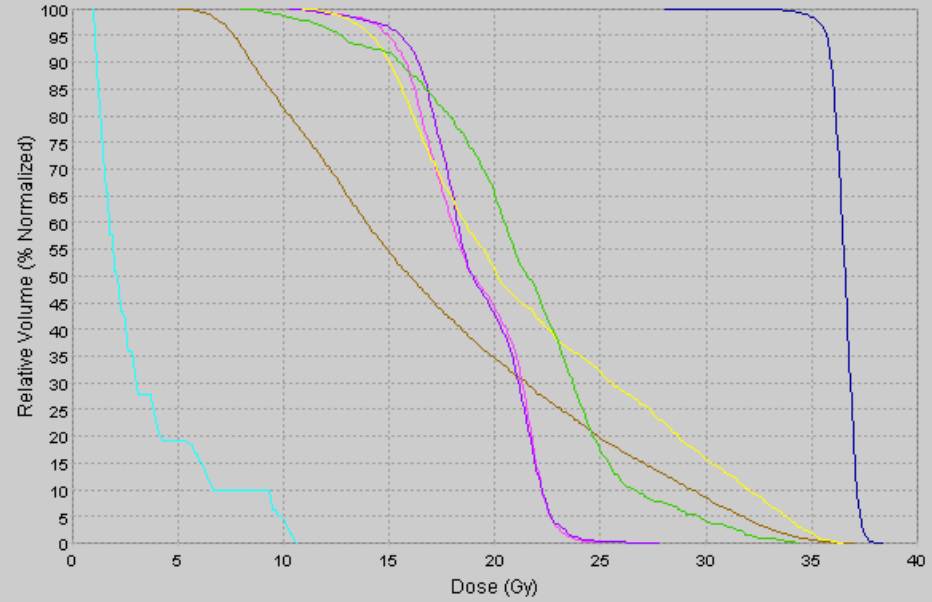
Tumor Settings

Name	Display	Color
PTV36	☑	

Sensitive Structure Settings

Name	Display	Color
GRELE	☑	
MOELLE	☑	
FEMUR D	☑	
FEMUR G	☑	
VESSIE	☑	
COUCH	☐	
GTV59.4	☐	
CTV59.4	☐	
CTV36	☐	

Dose-Volume Histogram - Cumulative Mode Relative



Vol Min < 0.0 > Gy Min < 0.0 > Gy Max < 40.0 >