

Assessment and **prognostic value** of regression after neoadjuvant therapy in rectal cancer : the role of **tumour shrinkage and fragmentation**

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Introduction

- Standard treatment for stage II & III rectal cancers : pre-operative chemoradiotherapy followed by TME¹
- Treatment response usually measured by:

Regression grading
(Dworak, Wheeler etc.)



Inconsistent correlation with prognosis²

T-downstaging



Prognostic value in most studies³

¹ Willett CF et al. Clin Cancer Res. 2007 Nov 15;13(22 Pt 2):6903s-8s

² Nagtegaal et al. Clin Cancer Res 2007;13(22); 6617-23

³ Kaminsky et al. Int J Radiat Oncol Biol Phys.1998;42(5):935-41

**How to assess response to
neoadjuvant treatment
reliably for
prognostication?**



Materials & Methods

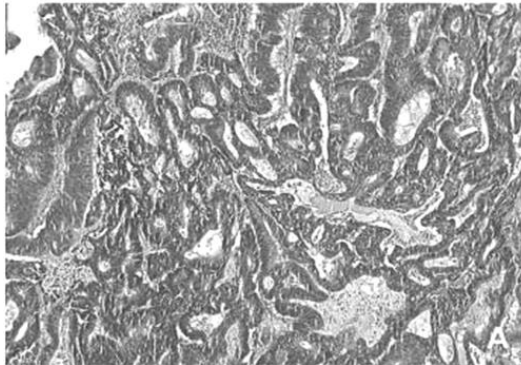
- 76 patients with stage II & III rectal cancer
- neoadjuvant CRT → TME @ UZGhent (PROCARE : Jan 06 – Jun 09)
- Histopathological variables : ypT, ypN, tumour differentiation, LVI, EMVI, PNI, ETDs, CRM (Quirke¹), T-downstaging, regression grading (Dworak²) → correlation with DFS & among inter-pathology variables
- Median F-U time : 17.5 months

¹ Quirke et al. Lancet 1986;2:996-999

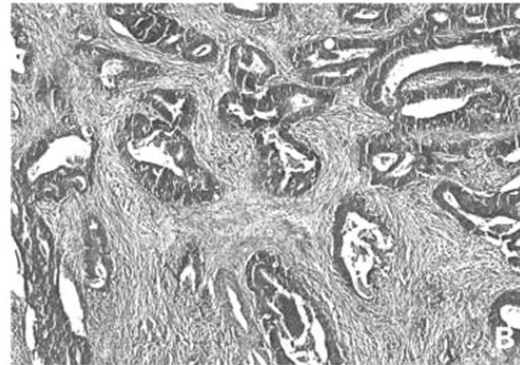
² Dworak et al. Int J Colorect Dis (1997) 12: 19–23

Regression grading : tumour/fibrosis

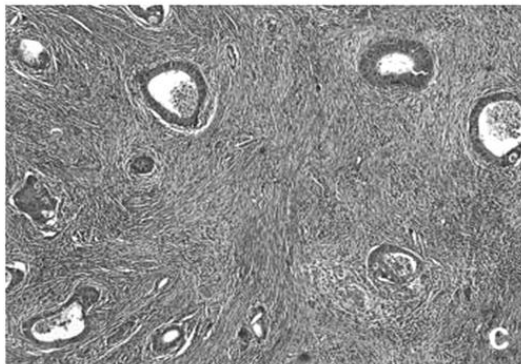
- Dworak grade 0
- Wheeler RCRG 3



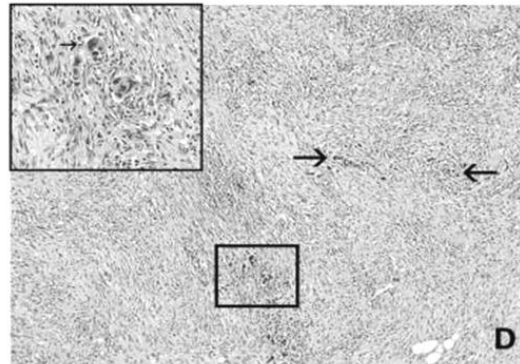
- Dworak grade 1
- Wheeler RCRG 2



- Dworak grade 2
- Wheeler RCRG 2



- Dworak grade 3
- Wheeler RCRG 1



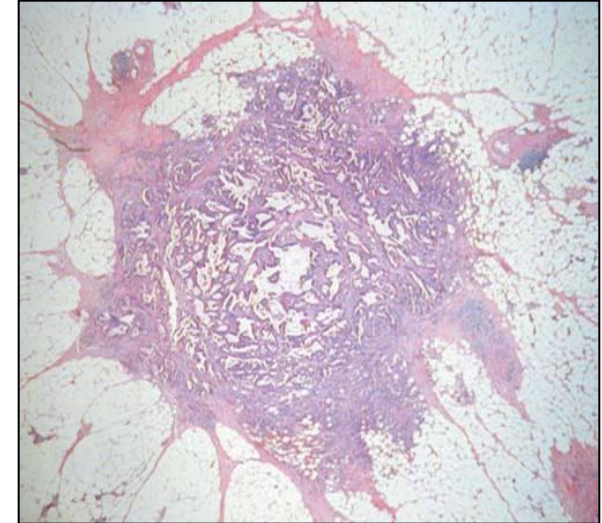
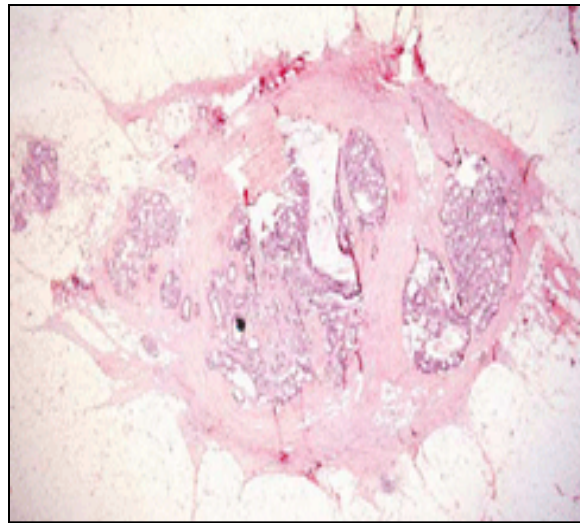
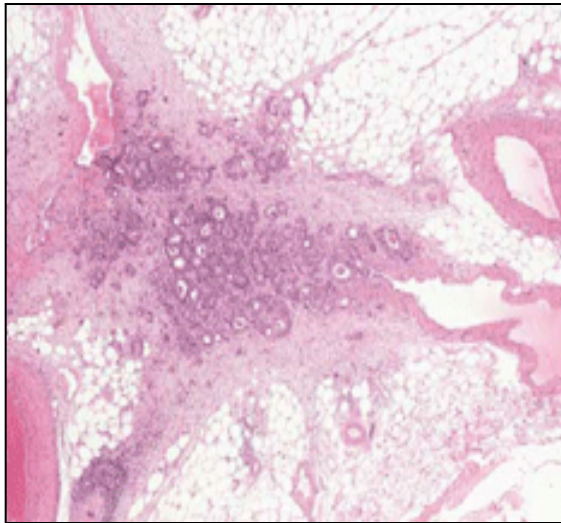
Dworak et al. Int J Colorect Dis (1997) 12: 19–23

Wheeler JM et al. Dis Colon Rectum. 2004 Dec;47(12):2025-31

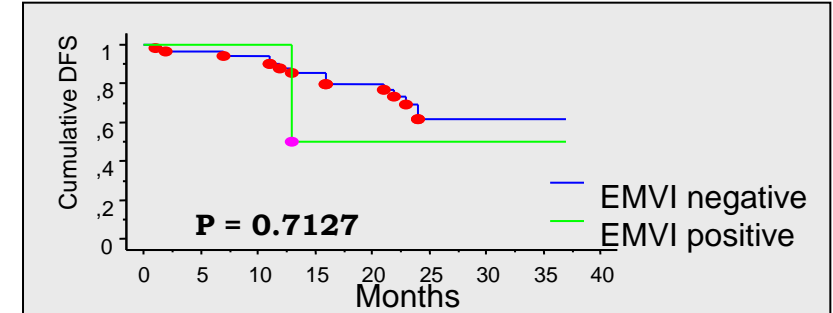
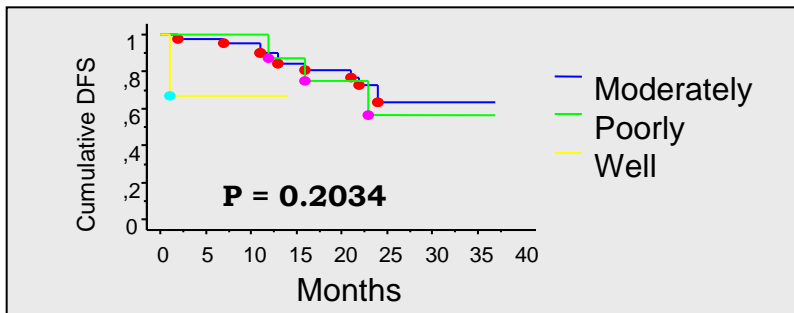
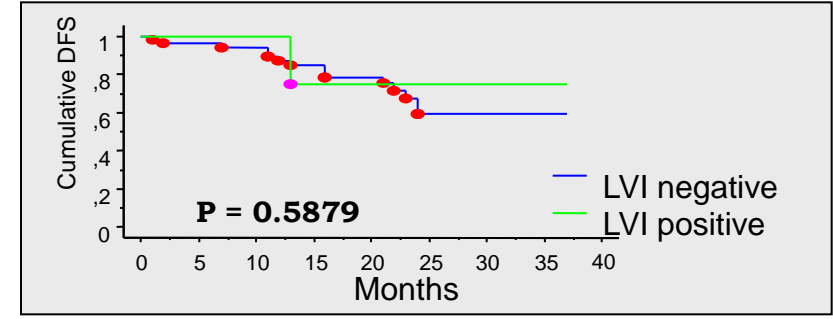
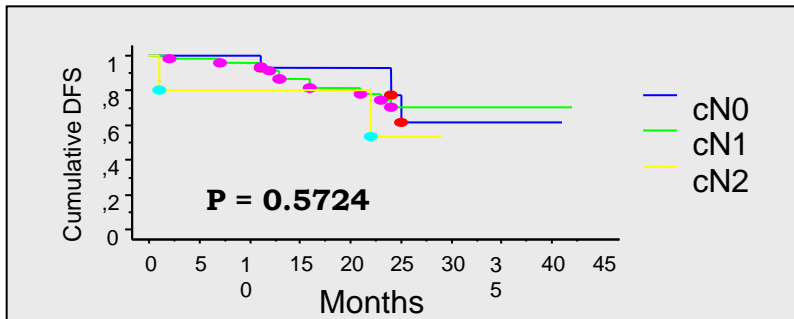
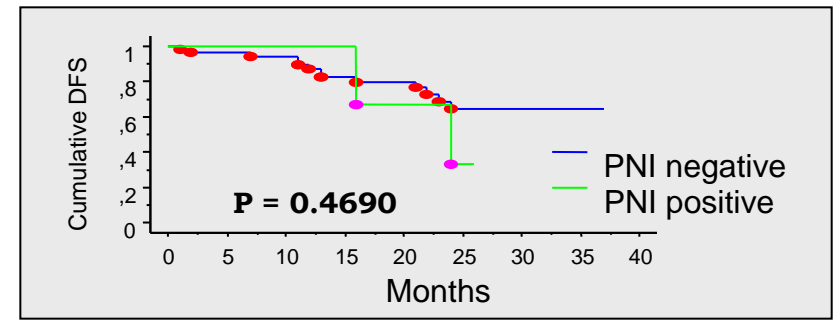
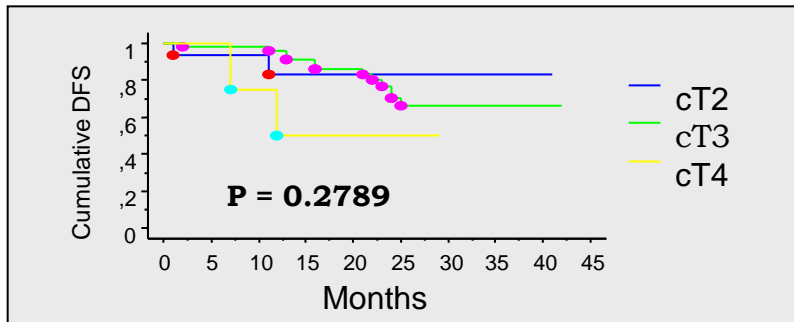
Gosens et al. Clin Cancer Res 2007;6617 13(22)

Our definition of Extramural Tumour Deposits (ETDs)

« **Groups of extramural tumour cells discontinuous from the main tumour mass and not found in recognized lymph node or vascular structure.** »



Results (1): cT, cN, Differentiation, PNI, LVI, EMVI & DFS



Results (2): T-downstaging, ypT<3, CRM & DFS

→ T-downstaging and ypT<3 correlated with longer DFS

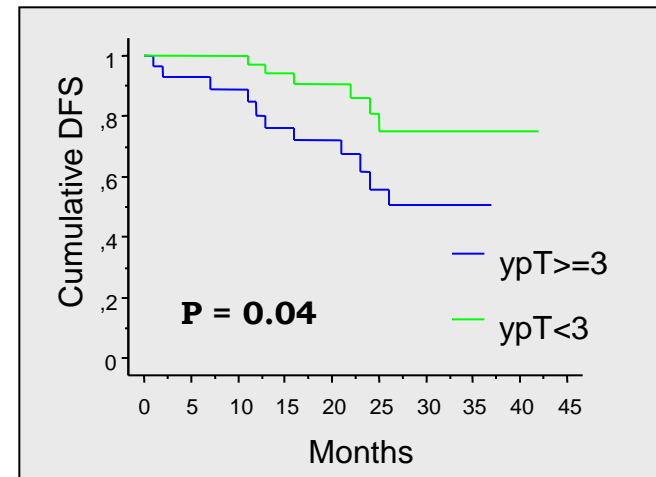
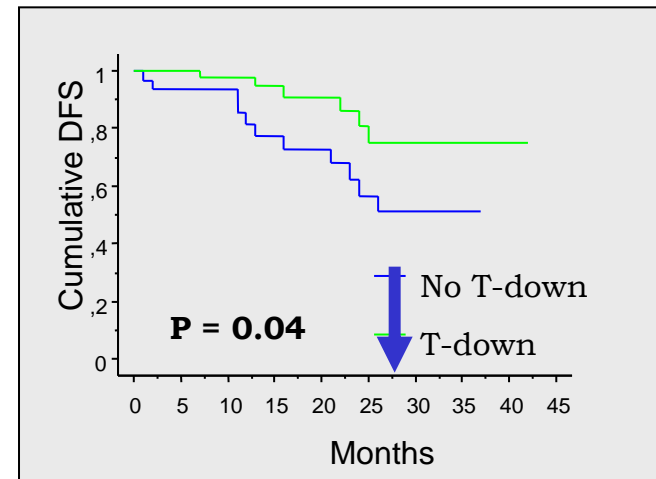


more favorable prognosis when regression is
accompanied by a decrease in depth of invasion
(tumor shrinkage)

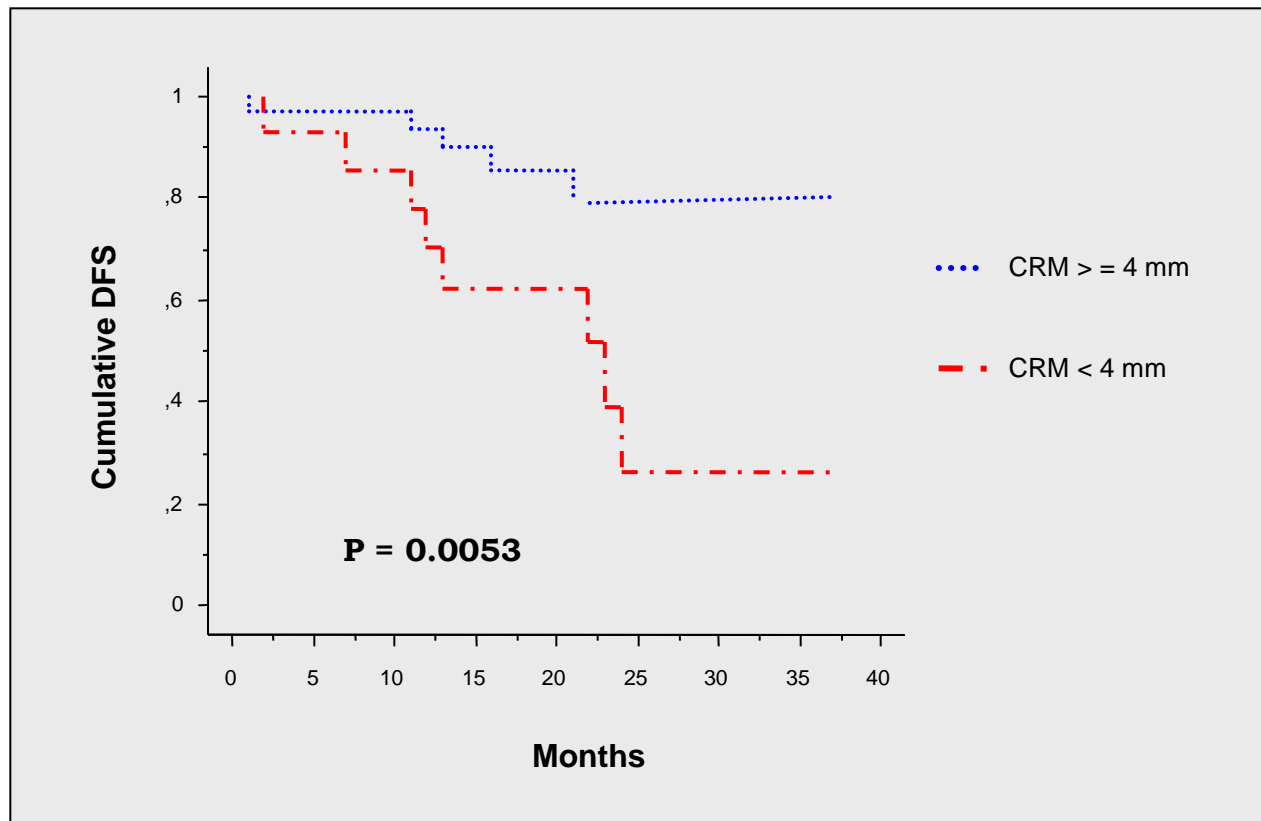
→ Increased CRM correlated with longer DFS (p=0.0183)



Tumour shrinkage reflects good response to neoadjv CRT



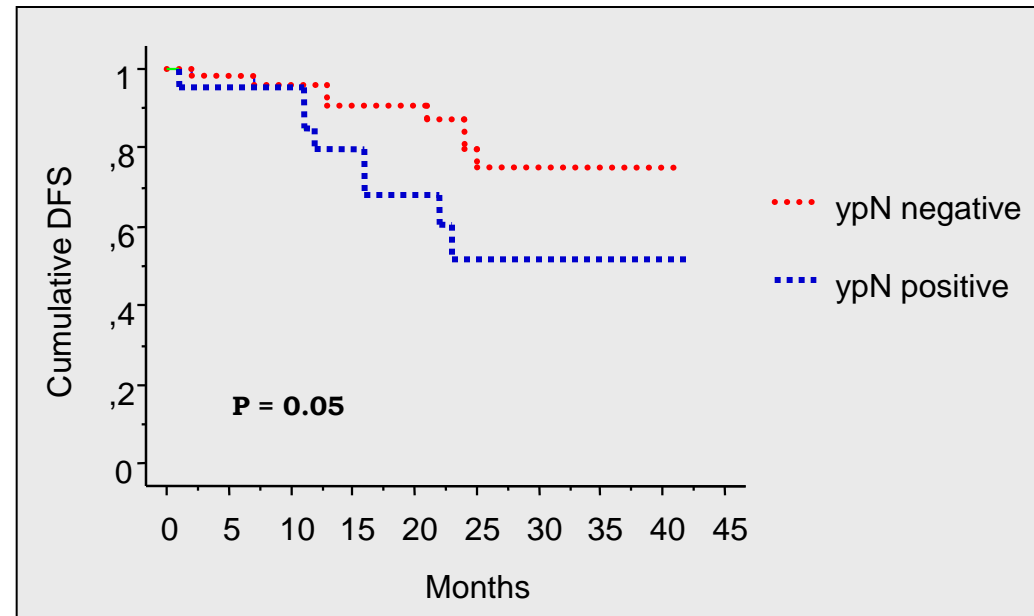
Results (3): CRM < 4mm, best cut-off



Results (4): ypN, LNR & DFS

→ ypN+ correlated with shorter DFS

→ LNR correlated better ($p = 0.0025$)

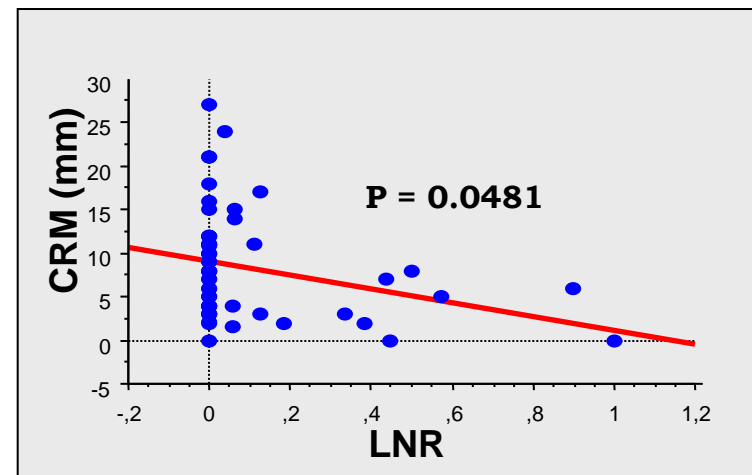
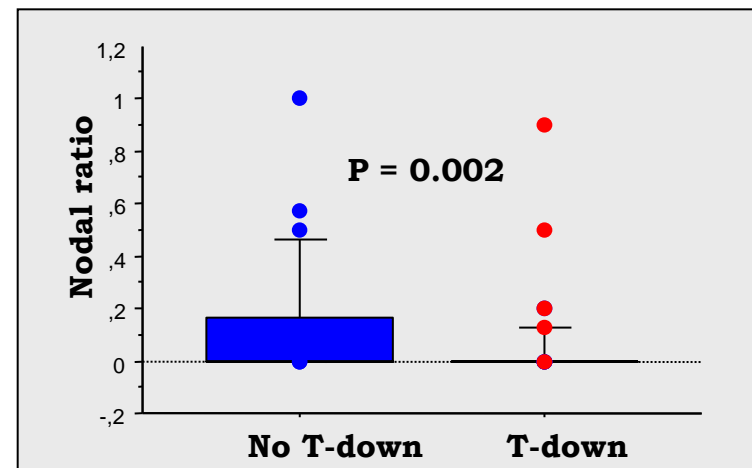


Results (5): LNR, T-downstaging, & CRM

- T-downstaging correlated with lower LNR
- Higher CRM correlated with lower LNR



Shrinkage of the primary tumour is associated with a decrease of tumour load in lymph nodes



Results (6): Dworak, T-downstaging, CRM

→ No correlation between Dworak & T-downstaging ($p=0.36$)
(Dworak 4 excluded = 24%)

→ Higher Dworak grade not associated with increased CRM

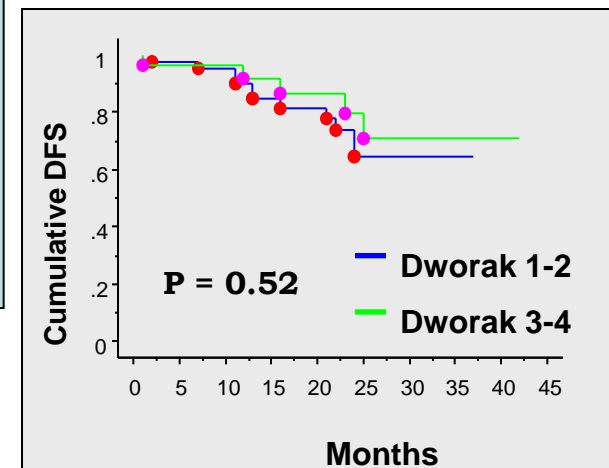
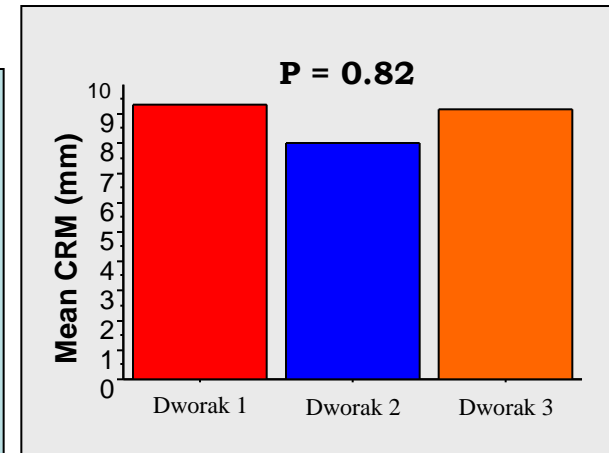


Tumour mass decrease is sometimes associated with tumour **fragmentation** rather than **shrinkage**

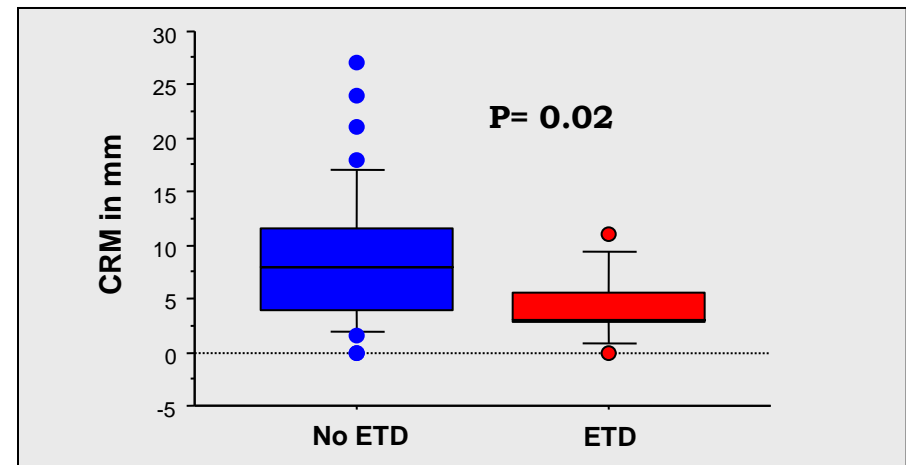
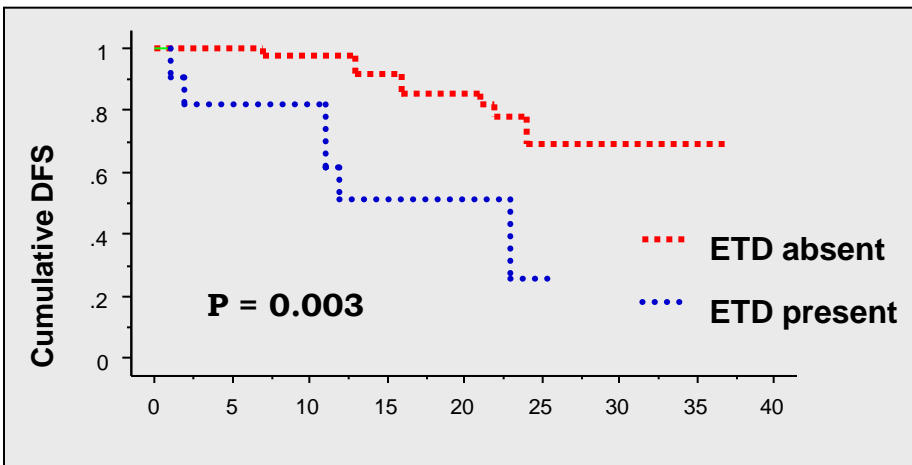
→ Dworak grade showed no prognostic value



Tumour fragmentation does not reflect a good response to neoadjuvant therapy



Results (7): ETDs & DFS



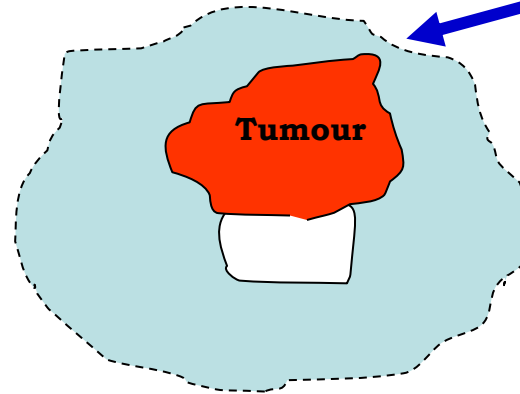
→ Presence of Extramural tumour deposit (ETD) correlated with poorer prognosis

→ Presence of ETD was associated with decreased CRM



Presence of ETDs might reflect absence of tumor shrinkage

Before neoadjuvant



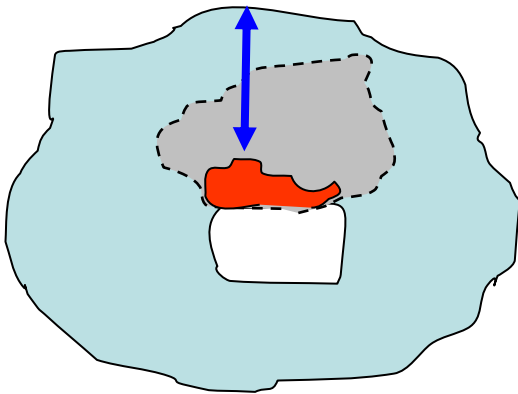
CRM at risk

Tumour

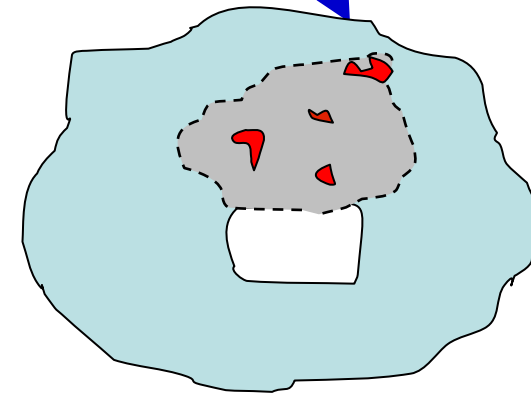
- Dworak 2
- T-downstaging

- Dworak 2
- No T-downstaging

After neoadjuvant



Tumour shrinkage



Tumour fragmentation

Conclusions

- 1. In rectal cancer, assessment of tumour shrinkage after neoadjuvant therapy via T-downstaging and CRM has prognostic relevance**
- 2. Shrinkage of the primary tumour is associated with a decreased nodal tumour load**
- 3. Assessing treatment response based on the amount of tumour in relation to stromal fibrosis does not accurately discern tumour fragmentation from shrinkage, which is most likely the reason why Dworak regression grading did not have a prognostic value.**
- 4. ETD was clearly associated with poor prognosis and might reflect absence of tumor shrinkage**

On-going work

**Assessment of prognostic value of treatment response variables
(T-downstaging, tumour regression grading, & CRM)
in multi-center study
(~600 cases from 5 centers: UZGhent, KUL, ULB, UCL, & Charleroi)**

References and suggested readings

1. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. *Int J Colorectal Dis.* 1997;12(1):19-23.
2. Wheeler JM et al. Preoperative chemoradiotherapy and total mesorectal excision surgery for locally advanced rectal cancer: correlation with rectal cancer regression grade. *Dis Colon Rectum.* 2004 Dec;47(12):2025-31.
3. Willett CF, Czito BG, Bendell JC. Radiation therapy in stage II and III rectal cancer. *Clin Cancer Res.* 2007 Nov 15;13(22 Pt 2):6903s-8s.
4. Lorena Losi et al. Prognostic value of Dworak grade of regression (GR) in patients with rectal carcinoma treated with preoperative radiochemotherapy. *Int J Colorectal Dis.* 2006 Oct;21(7):645-51.
5. Nagtegaal et al. Circumferential Margin Involvement Is the Crucial Prognostic Factor after Multimodality Treatment in Patients with Locally Advanced Rectal Carcinoma. *Clin Cancer Res* 2007;13(22); 6617-23.
6. Jean-Pascal Machiels, Selda Aydin, Marie-Alix Bonny, Fatima Hammouch, and Christine Sempoux. What Is the Best Way to Predict Disease-Free Survival After Preoperative Radiochemotherapy for Rectal Cancer Patients: Tumor Regression Grading, Nodal Status, or Circumferential Resection Margin Invasion? *J Clin Oncol* 2006, 24(8):1319-1321
7. Claus Rödel et al. Prognostic Significance of Tumor Regression After Preoperative Chemoradiotherapy for Rectal Cancer. *J Clin Oncol.* 2005 Dec 1;23(34):8688 – 96.
8. Annelies Debucquoy, Louis Libbrecht, Valerie Roobrouck, Laurence Goethals, William McBride, Karin Haustermans. Morphological features and molecular markers in rectal cancer from 95 patients included in the European Organisation for Research and Treatment of Cancer 22921 trial: Prognostic value and effects of preoperative radio (chemo) therapy. *Eur J Cancer* 2008; 44:791–797.
9. Iris D. Nagtegaal and Phil Quirke. What Is the Role for the Circumferential Margin in the Modern Treatment of Rectal Cancer? *J Clin Oncol* 2008, 26(2):303-312.