Waiting time to treatment: cervix cancer

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NHS Foundation Trust

Cervix cancers are fast proliferating.

- 81 patients, 2010 - 2011

- Median time from first consultation to simulation = 55 days (range 18-211)

- 43% of tumours increased in size or extent.

- 27% changed stage.

- Most of the upstaging occurred around 40 to 65 days.

University of the Witwatersrand

Question

- How much delay is acceptable before clinical outcome is affected?

- Limited studies - Ca cervix prioritised for treatment in most centres.

Canada 2005

CLINICAL INVESTIGATION　　　　　　　　　　　　　　　　　　　**Cervix**

RADICAL RADIOTHERAPY FOR CERVIX CANCER: THE EFFECT OF WAITING TIME ON OUTCOME

CHOAN E, M.D., F.R.C.P.C.,* SIMONE DAHROUGE, M.Sc.,[†] RAJIV SAMANT, M.D., F.R.C.P.C.,*
AMENEH MIRZAEI, M.D.,[‡] AND JULIE PRICE, B.Sc.[‡]

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Study population

- 195 patients, 1976 – 1981

- Median age   50 (range 22-91)

- Stage   IB-IVA
    - IB   25%
    - IIB   44%
    - III   20%

- Squamous   81%

Treatment

- EBRT 1.8-2Gy/#   95%

- BT   97%
  - Pt A dose ≥80 Gy   85%

- Chemo   24%

Waiting time definition

Start of radiotherapy from

1. Date of diagnostic biopsy
2. EUA
3. RT consultation

Waiting times in cohort

Weeks	From diagnosis	From EUA	From RT consult
<2	11%	32%	36%
3	10%	22%	28%
4	11%	15%	16%
5	13%	9%	11%
6	14%	10%	5%
7	13%	5%	1%
8	0%	9%	3%
9	0%	6%	1%
10	6%	2%	1%
>11	8%	3%	2%

Waiting times in cohort

Weeks	From diagnosis	From EUA	From RT consult
<2	11%	32%	36%
3	10%	22%	28%
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5	13%	9%	11%
6	14%	10%	5%
7	13%	5%	1%
8	0%	9%	3%
9	0%	6%	1%
10	6%	2%	1%
>11	8%	3%	2%
Within 5 weeks	45%	78%	91%

Disease progression

- 45% had progression at time of analysis.
  - Local progression = disease recurrence (or persistence) within RT field.
  - Distant progression = appearance of new disease outside RT field.

- 80% power to detect HR of 1.7 to 2.1 (2-sided).

Univariate analysis
No correlation between longer waiting times and outcomes

	Consult to XRT	Examination under anesthesia to XRT	Diagnosis to XRT
Local progression	0.63	0.89	0.38
Distant progression	0.79	0.44	0.15
First progression	0.81	0.54	0.30
Survival (overall)	0.80	0.11	0.45
Survival (disease specific)	0.25	0.14	0.96

Multivariate analysis
Longer waiting times had an adverse effect on survival (but not recurrence)

	Consult to RT		EUA to RT		Diagnosis to RT	
	p value	HR	p value	HR	p value	HR
Local progression	0.58		0.24		0.27	
Distant progression	0.77		0.39		0.94	
First progression	0.58		0.2		0.4	
Survival (overall)	0.019	1.161	0.012	1.145	0.087	1.079
Survival (disease specific)	0.004	1.199	0.014	1.148	0.038	1.1

Delays between initial biopsy and treatment start were greater for

- Older patients ($p = 0.025$)
  - 5.8 weeks for <40 years old
  - 6.6 weeks for >70 years old

- Those with smaller tumours ($p < 0.001$)
  - 5.0 weeks for >4 cm
  - 6.3 weeks for <4 cm

Their conclusion

- Delay to start of therapy decreases probability of survival for patients treated with radical radiotherapy for cervix cancer.

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Distant progression	0.79	0.44	0.15
First progression	0.81	0.54	0.30
Survival (overall)	0.80	0.11	0.45
Survival (disease specific)	0.25	0.14	0.96

Their conclusion

- Gradual increase in risk with each week of delay.
  - No cut-off mark beyond which risk was significantly higher.

Japan 2012

GYNECOLOGIC ONCOLOGY

Prognostic factors in stage IA–IIA cervical cancer patients treated surgically: does the waiting time to the operation affect survival?

Tomokazu Umezu · Kiyosumi Shibata ·
Hiroaki Kajiyama · Eiko Yamamoto ·
Mika Mizuno · Fumitaka Kikkawa

Study population

- 117 patients, 1999 – 2010

- Median age   45 (range 19-71)

- Stage   IA - IIA

- Squamous   61%

- Radical hysterectomy with pelvic LND

Initial visit to surgery

- Median = 48 days (range 20–92)

Recurrence-free/overall survival
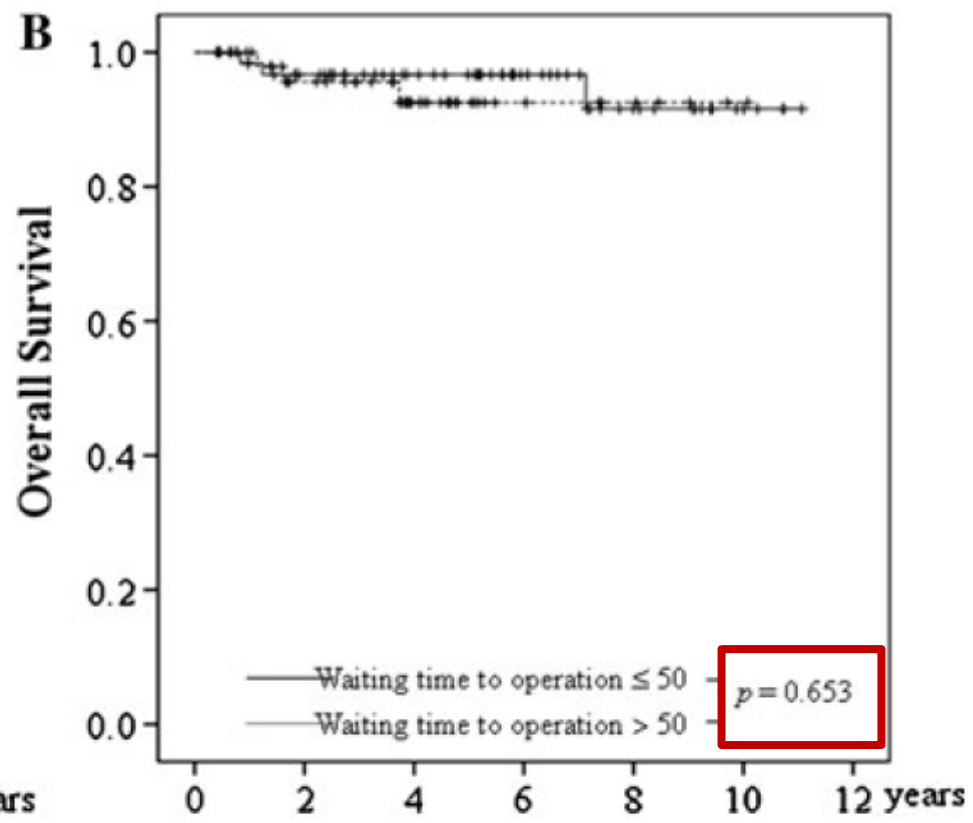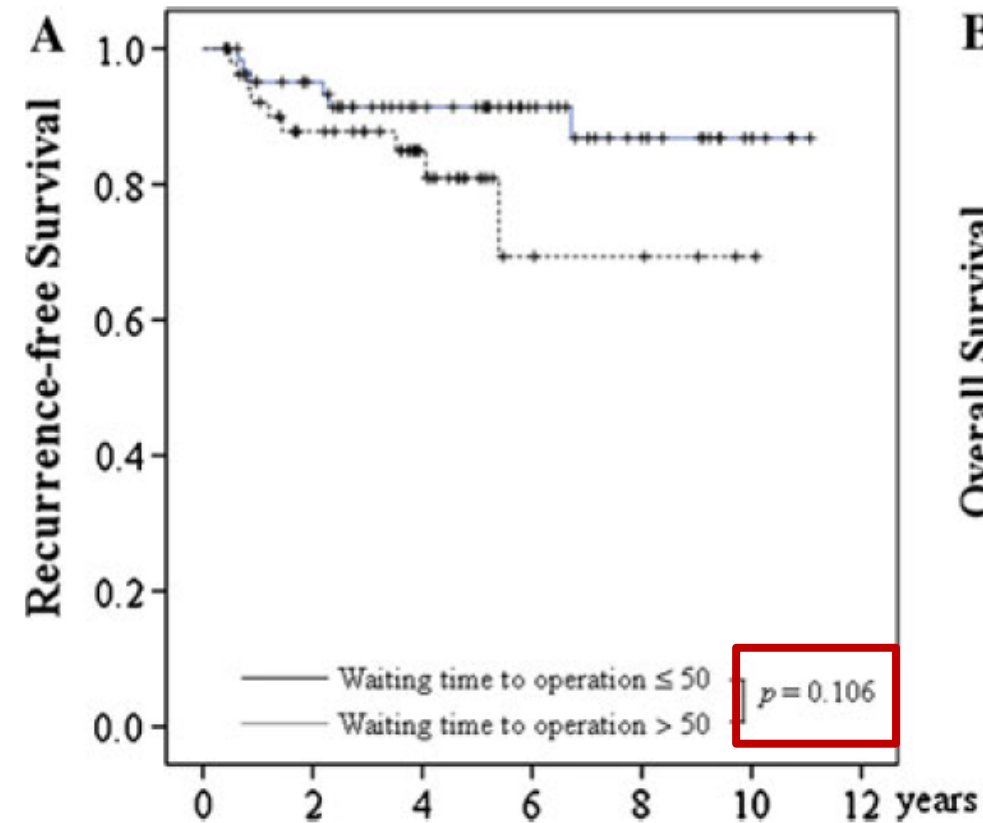
Their conclusion

- The waiting time from initial visit to surgical intervention <u>does not</u> adversely affect the outcome of cervical cancer.

A

Recurrence-free Survival

Waiting time to operation ≤ 50
Waiting time to operation > 50
] $p = 0.106$

0   2   4   6   8   10   12 years

B

Overall Survival

Waiting time to operation ≤ 50
Waiting time to operation > 50
] $p = 0.653$

0   2   4   6   8   10   12 years
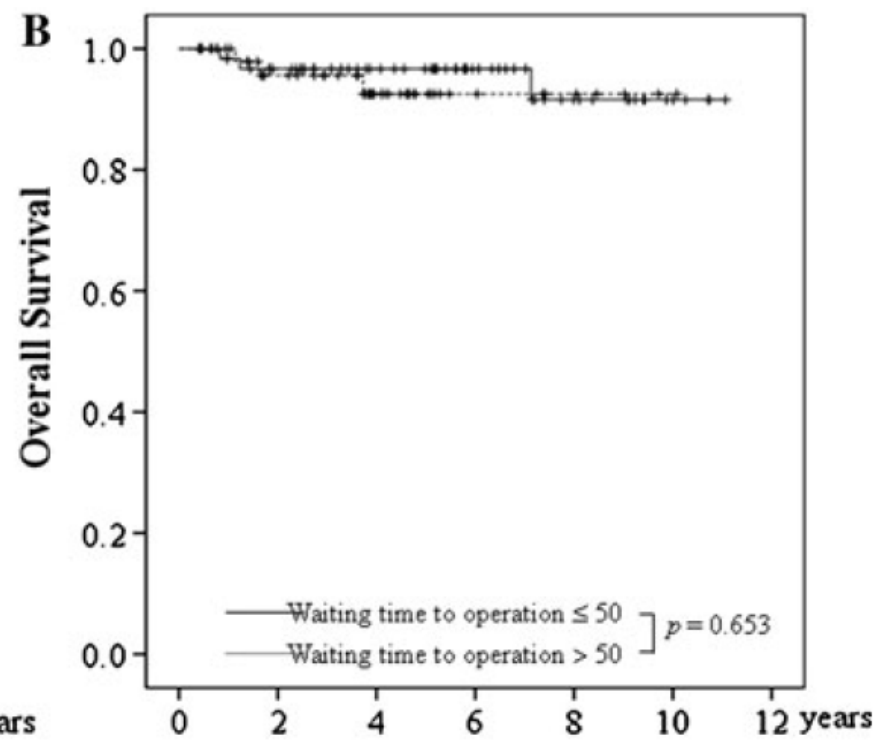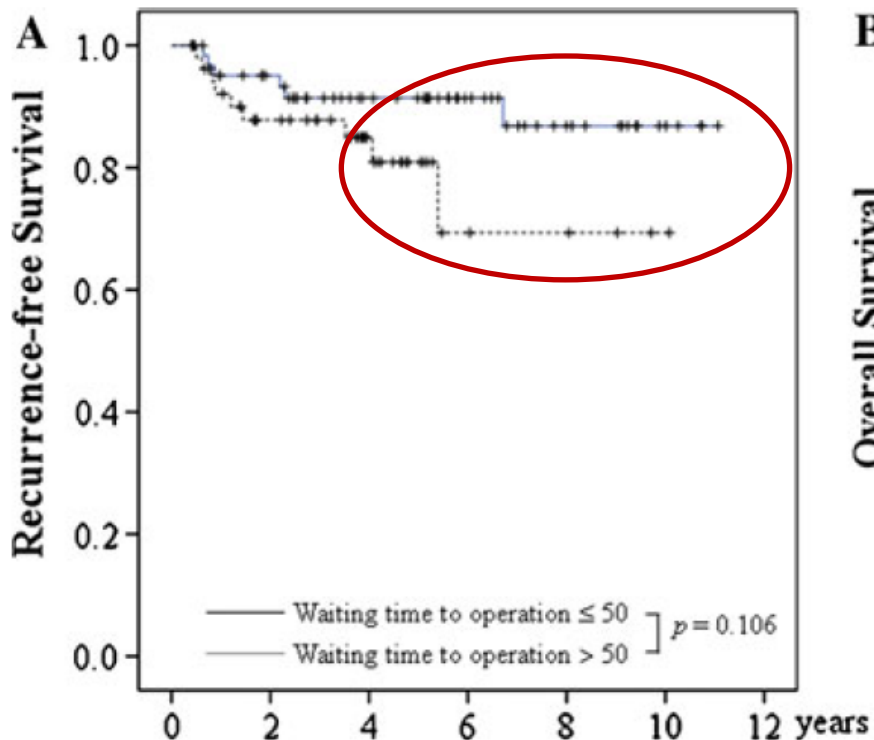
Israel 2014

Effect of Treatment Delay on Survival in Patients With Cervical Cancer

A Historical Cohort Study

Tamar Perri, MD,*† Gal Issakov, MD,*† Gilad Ben-Baruch, MD,*† Shira Felder, MD,†‡
Mario E. Beiner, MD,*† Limor Helpman, MD,*† Liat Hogen, MD,*† Ariella Jakobson-Setton, MD,*†
and Jacob Korach, MD*†

Study population

- 321 patients, 1999 – 2010

- Median age   46

- Stage   IA2 - IVB

- Squamous   78%

First treatment

- IA2, IB1, IIA   surgery or chemo-RT

- IB2, IIB, III, IVA   chemo-RT

- IVB   chemo

Surgery	43%
Chemo-RT	40%
Chemo	17%

Diagnosis to first treatment

- ≤30 days   43%

- 31-45 days   26%

- >45 days   31%

Overall survival
(adjusted for age, stage, LN status, histology)
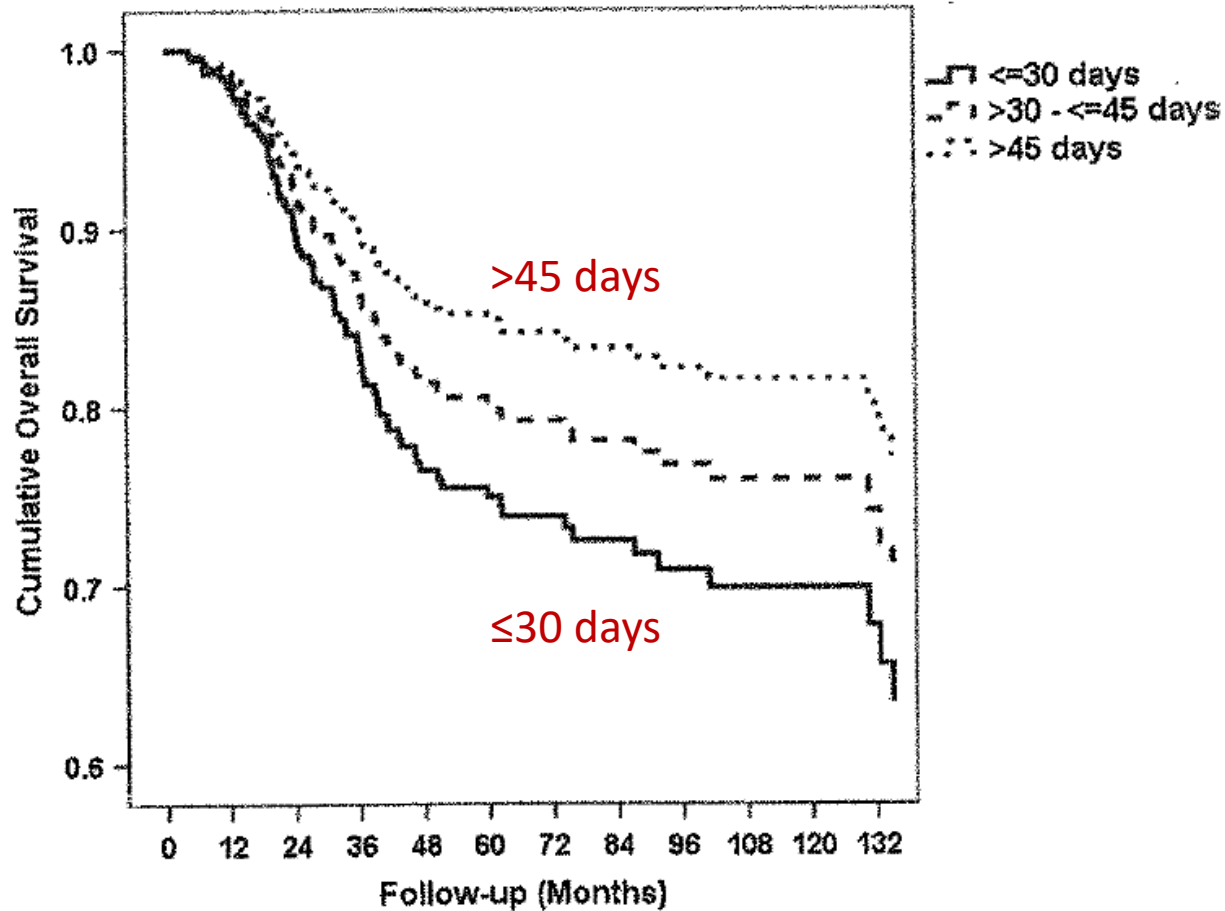
Their conclusion

- Longer waiting times from diagnosis to treatment <u>was not</u> associated with worse survival.
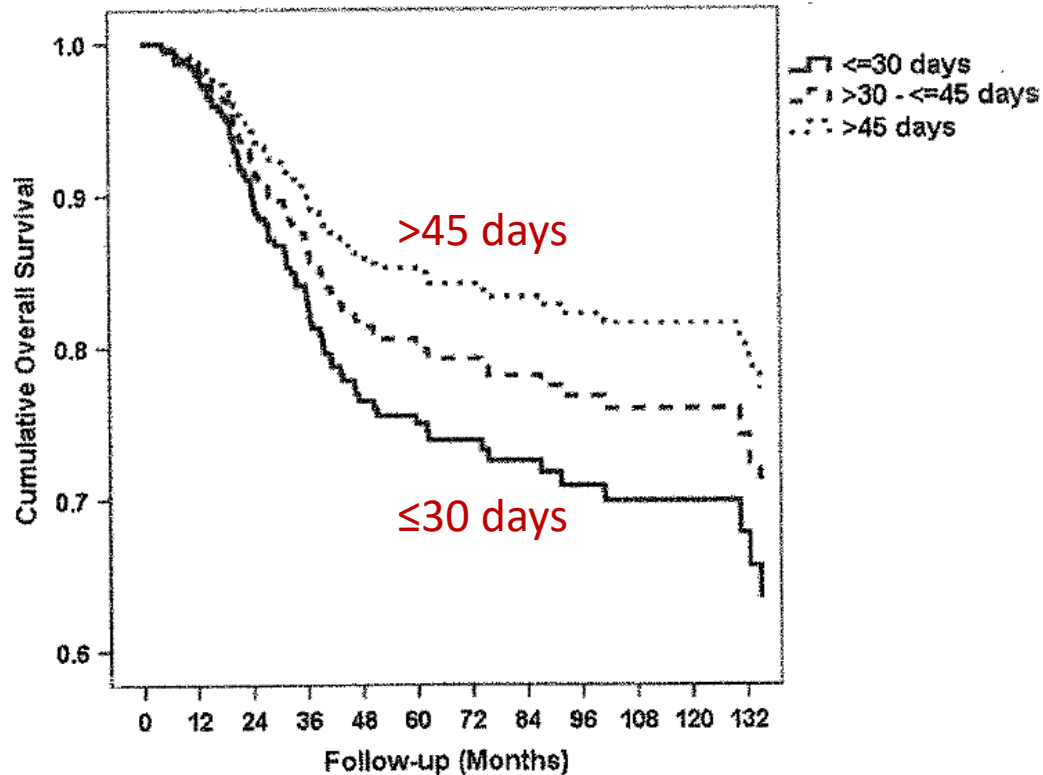
Thailand 2015

Longer waiting times for early stage cervical cancer patients undergoing radical hysterectomy are associated with diminished long-term overall survival

Kulisara Nanthamongkolkul*, Jitti Hanprasertpong*
Department of Obstetrics and Gynecology, Prince of Songkla University Faculty of Medicine, Songkhla, Thailand

Study population

- 441 patients, 1996 – 2012

- Median age   46 (range 26-78)
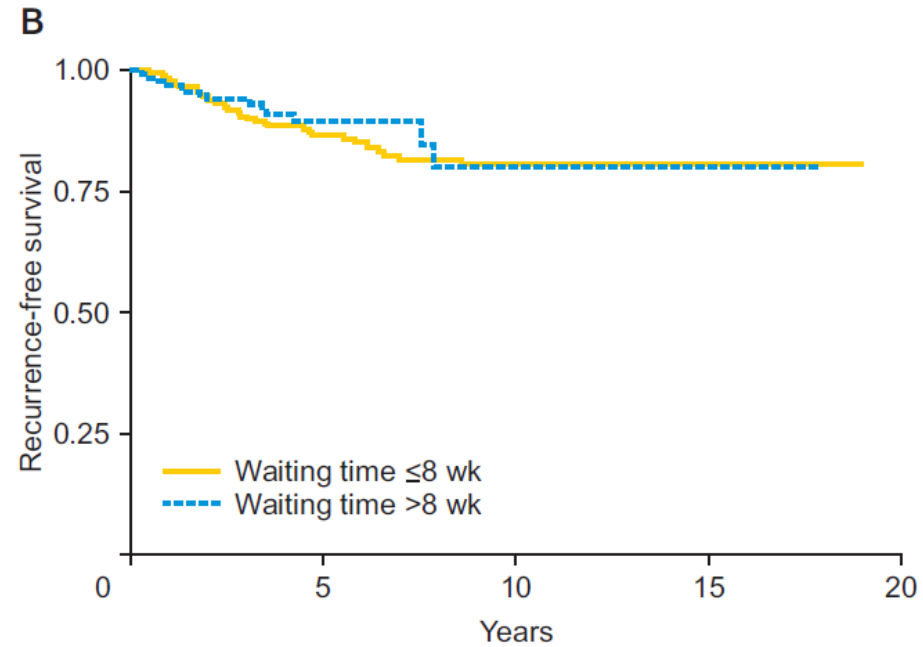
- Stage   IA2 or IB1

- Squamous   60%

- Radical hysterectomy with pelvic LND

Diagnosis to surgery

- Median = 43 days (interquartile 29 to 65 days)

- 64.4% underwent surgery within 8 weeks
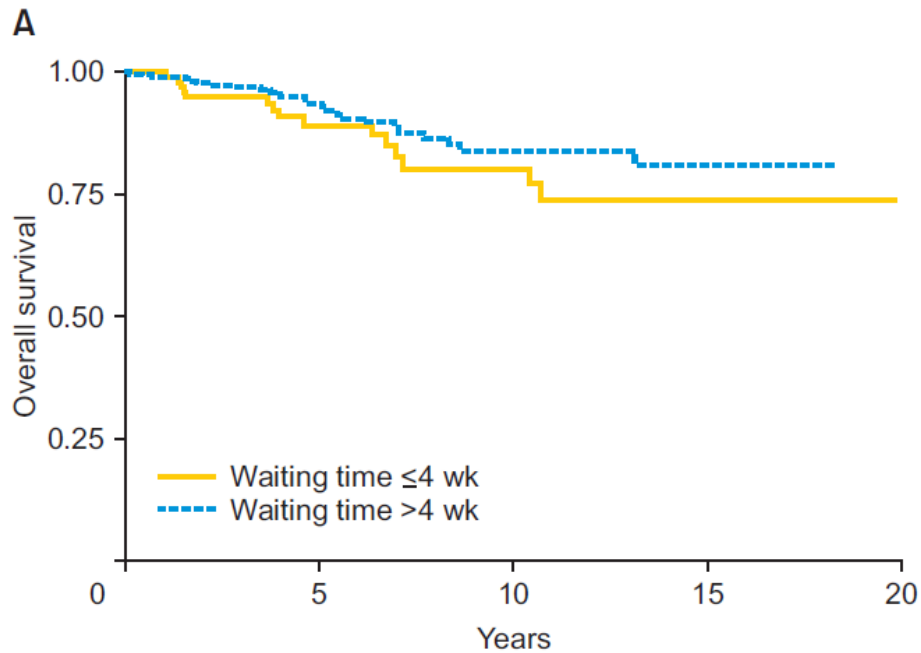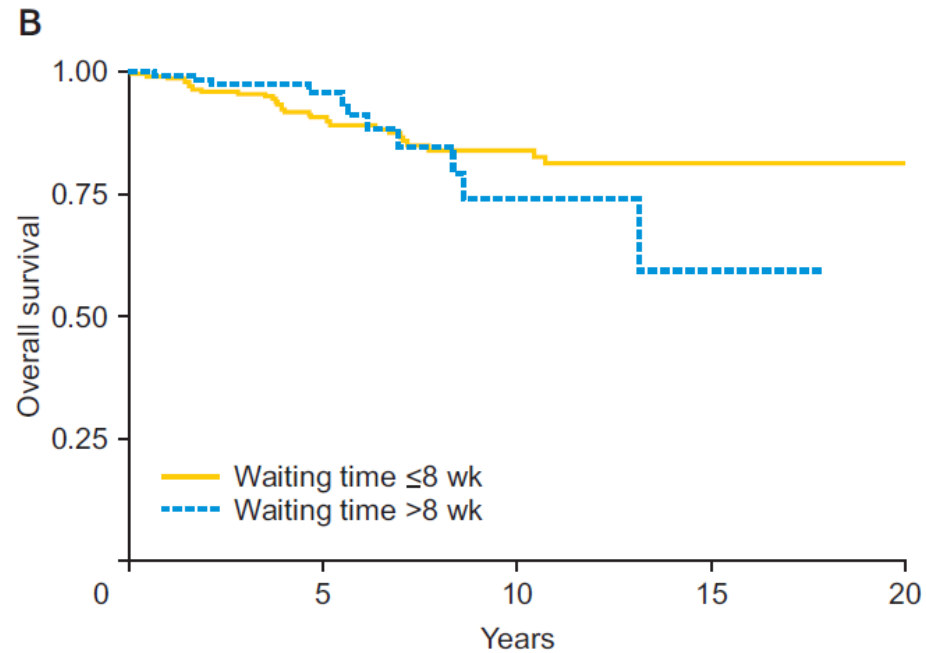
Recurrence-free survival
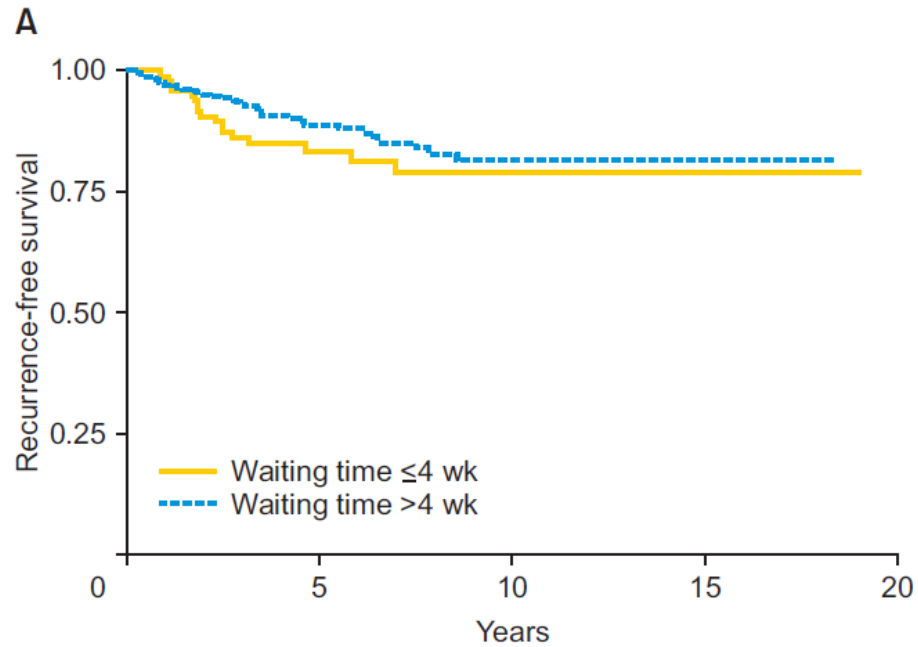
4 weeks   8 weeks

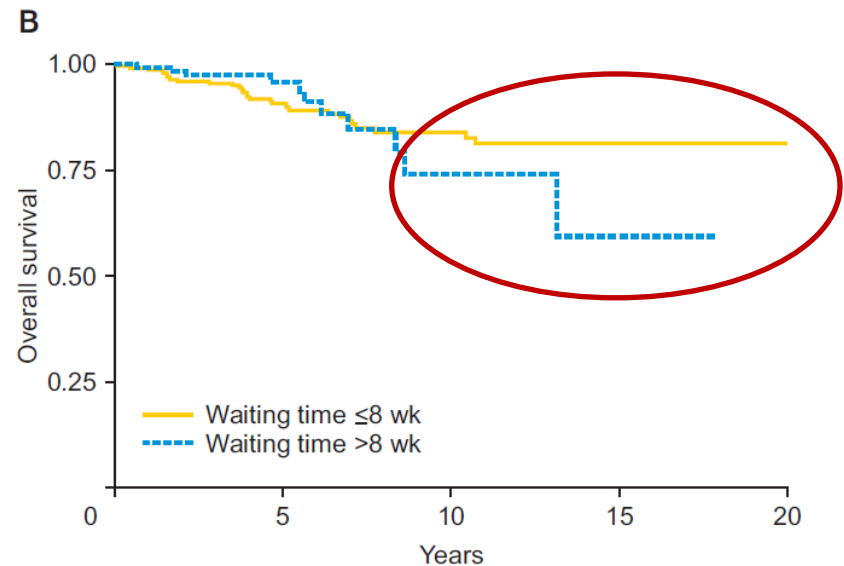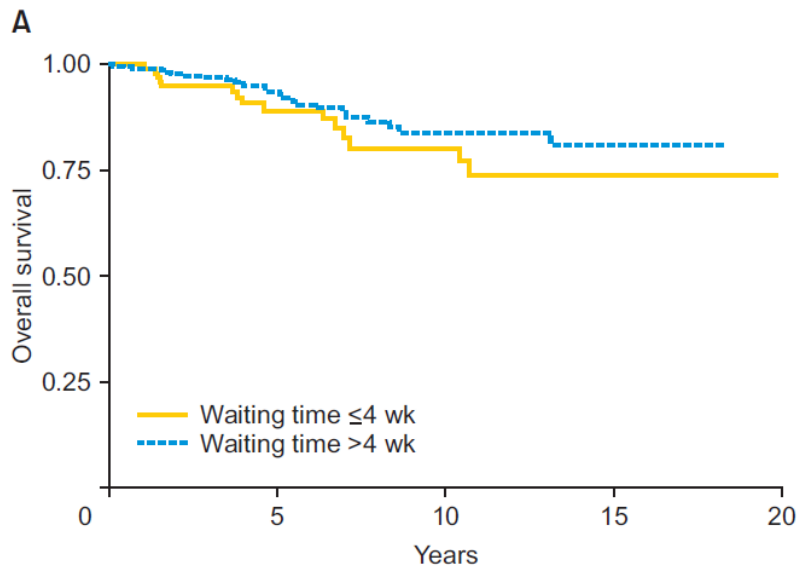# Overall survival

4 weeks

8 weeks

Their conclusion

- Longer surgical waiting time <u>was</u> associated with diminished long-term OS of early stage cervical cancer patients.

Explanation for conflicting data?

- Canada   Impact on survival   No impact?

- Japan   No impact   Impact on RFS?

- Israel   No impact

- Thailand Impact on survival   After 8 years

Modelling study

Original Article

An Audit of Delays Before and During Radical Radiotherapy for Cervical Cancer – Effect on Tumour Cure Probability

C. E. Coles, L. Burgess, L. T. Tan

Oncology Centre, Addenbrooke's Hospital, Cambridge, U.K.

Calculated TCP

- Radiosensitvity (SF2)   0.49, 0.43, 0.38

- Tpot   2.5, 7.5, 15 days

- Initial size   2, 4, 6 cm sphere

- Vol doubling times   15, 50, 100 days

- Used actual OTT and WT in 1996, 1998 and 2001

Days

Gaps during EBRT

Overall treatment time

Waiting time

p = 0.001

p = 0.001

p = 0.007
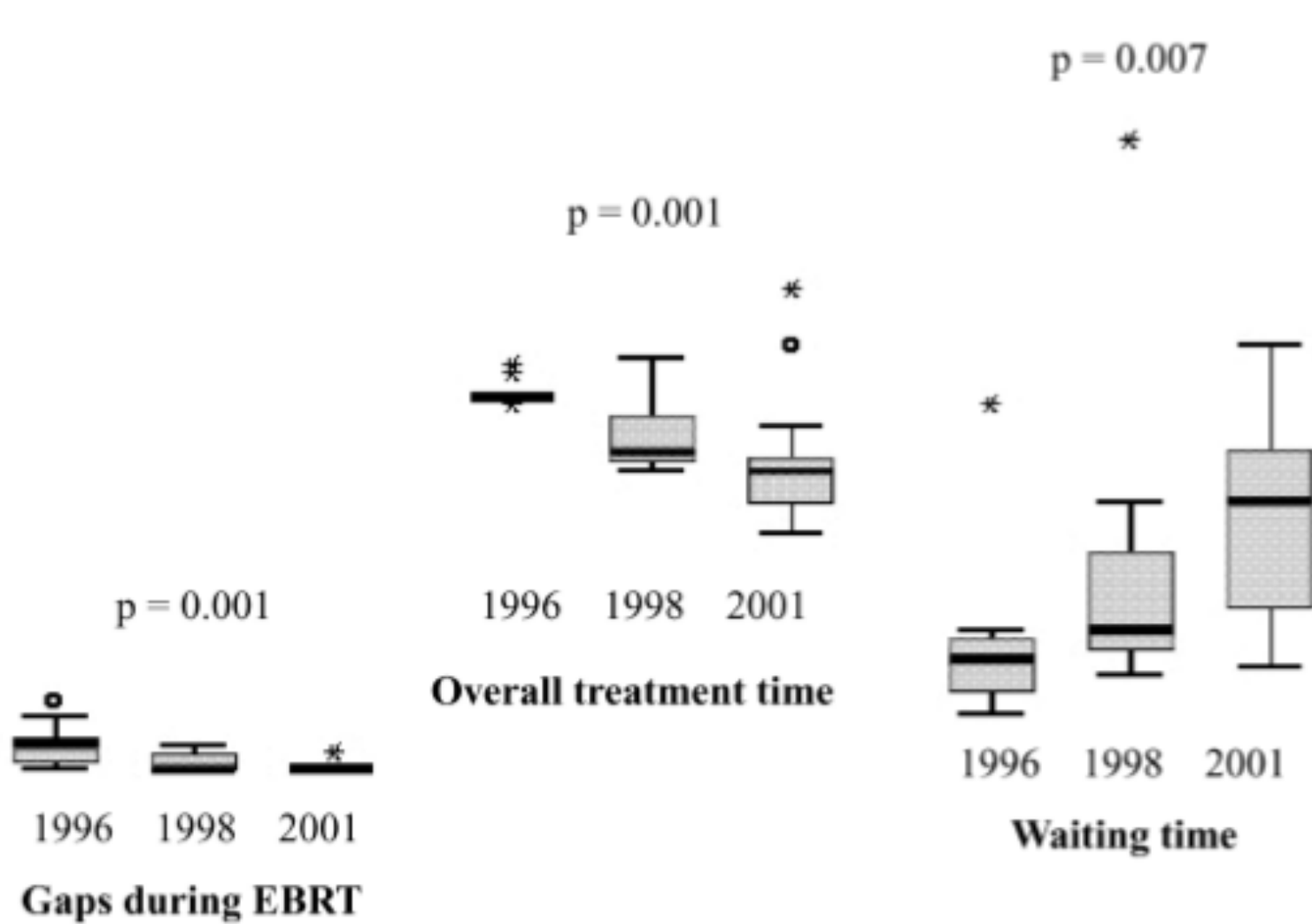
Our conclusions

- Tumours more likely to be affected by long WT if
    - Shorter volume doubling times
    - Medium chance of tumour control at outset.

- Adverse effect of long WT is diluted if heterogenous population of tumours is considered.
    - For individual patients, loss in TCP resulting from long WT could be substantial.

Our conclusions

- Any potential gain in TCP resulting from shorter OTT could be offset entirely by adverse effect of increasing WT.

Summary

- Some evidence that longer WT has a detrimental effect on outcome in cervix cancer.

  – Impact greater in advanced tumours?

- How much delay is acceptable before clinical outcome is affected?

UK cancer waiting time targets

- Referral to treatment   62 days

- Consult to treatment   31 days

- Consult to RT   17 days