

WORKSHOP

La radioterapia transcutanea dei tumori tiroidei

La radioterapia adiuvante nel trattamento dei carcinomi ad alto rischio: Pro

Gabriele Simontacchi – AOU Careggi, Firenze



RADIOTERAPIA

SOPPRESSIONE
DEL TSH

CHIRURGIA

TERAPIA
RADIOMETABOLICA

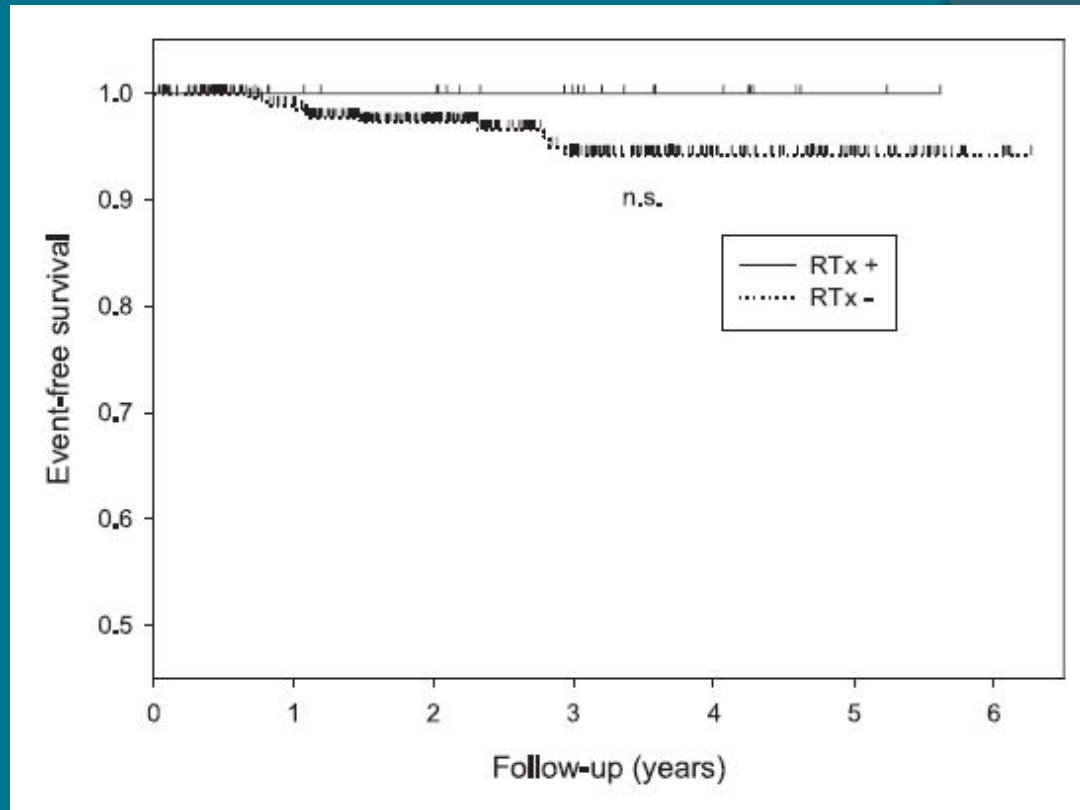
EBRT ADIUVANTE: STUDI RANDOMIZZATI

2 studi randomizzati... falliti per scarso accrual!!

*Taylor, AnnIntMed 1998: ...
nessun beneficio da EBRT... solo
46 paz. trattati con RT (18,5%),
effetto RT detrimentalmente...*

EBRT ADIUVANTE: STUDI RANDOMIZZATI

*Biermann, Nuklearmedizin
2009: 351 paz. inclusi... 35
randomizzati... 17 braccio
RT... solo 6 l'hanno fatta...
più 20 non randomizzati...*



EBRT ADIUVANTE: STUDI RETROSPETTIVI

PUNTI CRITICI

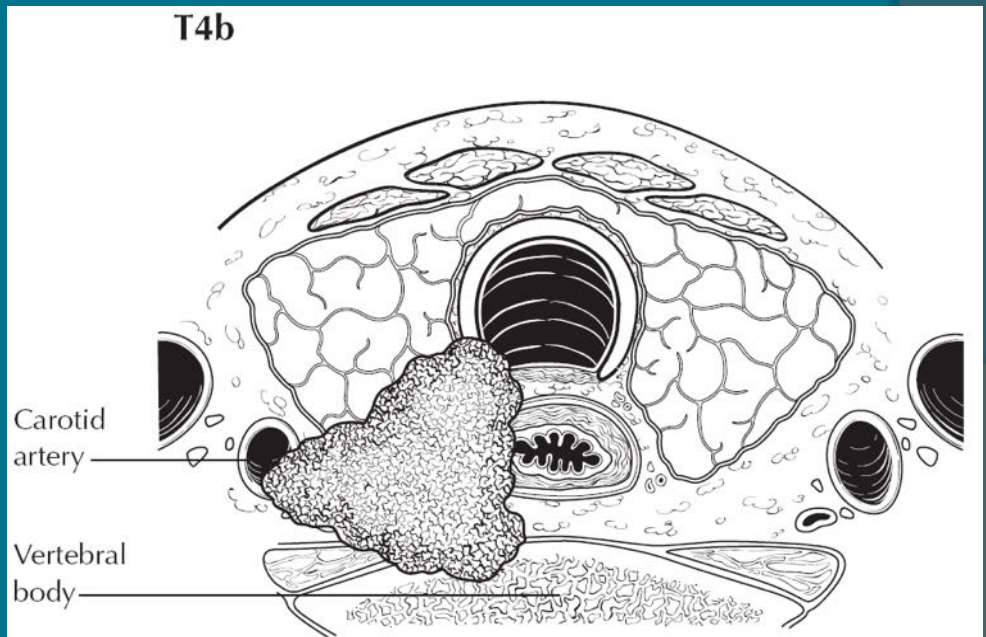
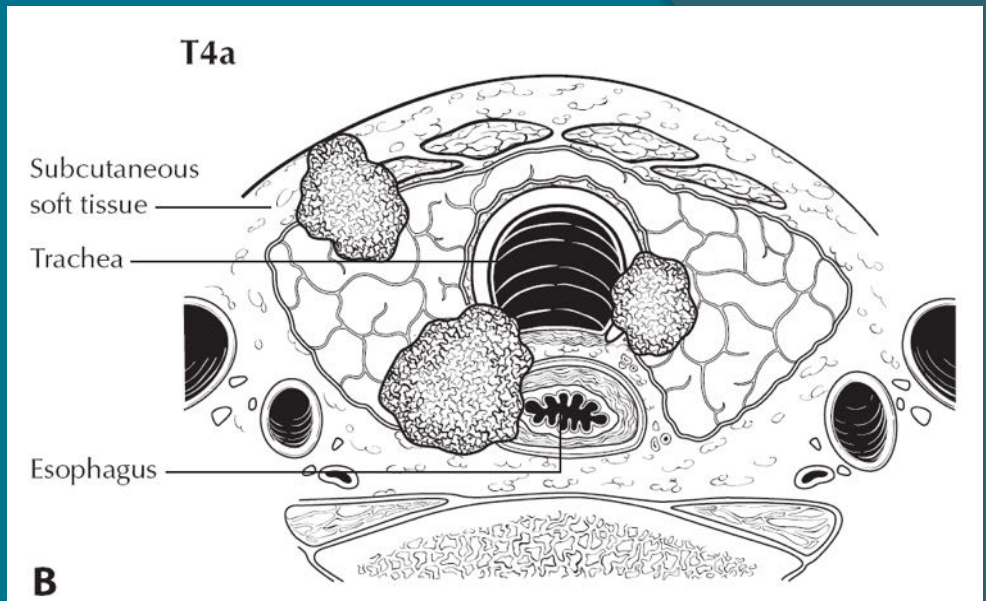
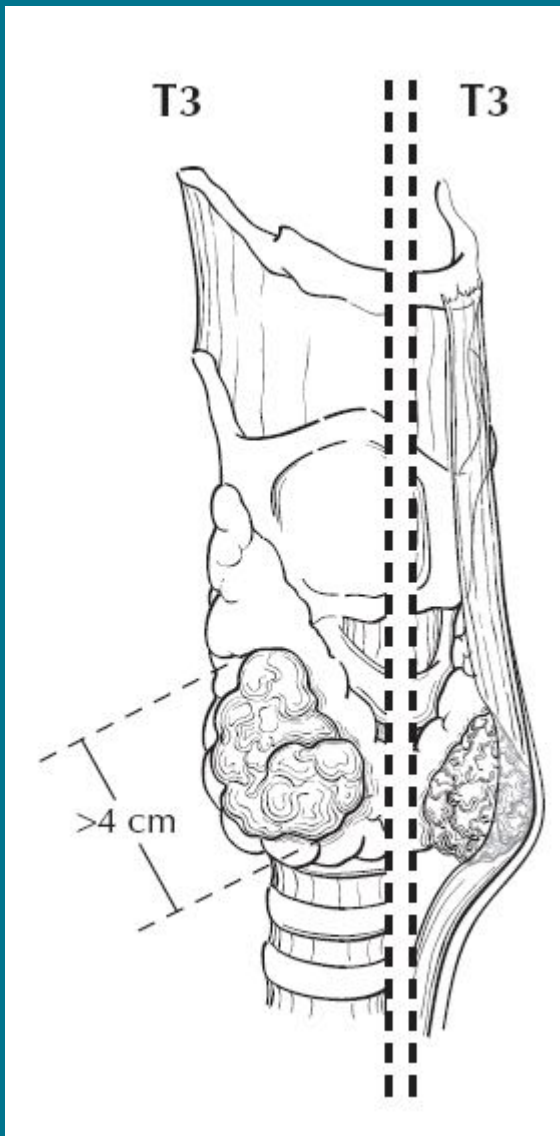
- criteri di inclusione poco definiti
- bias di selezione (avviati a RT i pazienti con maggiori fattori di rischio)
- iter terapeutici non definiti (tipo chirurgia, \pm 131I, timing RT)
- standard radioterapici non omogenei o obsoleti
- mancanza di un braccio di controllo
- differenti modalità di stadiazione (diverso TNM!!)

DEFINITION OF TNM

Primary Tumor (T)

Note: All categories may be subdivided: (a) solitary tumor, (b) multifocal tumor (the largest determines the classification).

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Tumor 1 cm or less in greatest dimension limited to the thyroid
- T2 Tumor more than 1 cm but not more than 4 cm in greatest dimension limited to the thyroid
- T3 Tumor more than 4 cm in greatest dimension limited to the thyroid
- T4 Tumor of any size extending beyond the thyroid capsule



EBRT ADIUVANTE: STUDI RETROSPETTIVI

Table 1 Local Regional Control Rate in High-Risk Differentiated Thyroid Cancer in Patients with No Gross Residual Disease After Surgery: 10-Year Local Recurrence-Free Rates

First Author	Year of Publication	Surgery Radioactive Iodine and External Beam Radiotherapy	Surgery and Radioactive Iodine
Tubiana et al ⁵	1985	86%	79%
Simpson et al ¹⁰	1988	86%	82%
Philips et al ¹¹	1993	97%	79%
Farahati et al ¹²	1996	90%*	50%*
Tsang et al ¹³ (papillary only)	1998	93%	78%
Ford et al ¹⁴ †	2003	82%	37%
Kim et al ¹⁵ (papillary only)†	2003	95.2%	63.5%
Brierley et al ¹⁶ (<60 years of age)	2005	86.4%	65.7%
Keum et al ¹⁷ *	2006	72%	11%
Meadows et al ¹⁸ †	2006	89%	No patients reported
Terezakis et al ¹⁹ **	2009	75%	No patients reported
Schwartz et al ²⁰ **	2009	79%	No patients reported

*Includes distant failures.

†5-year local recurrence-free rate.

**4-year local recurrence-free rate.

Brierley, SemRadOncol 2012

EBRT ADIUVANTE: STUDI RETROSPETTIVI

- Studi che hanno mostrato un aumento del controllo locale: Tubiana 1985, Faharati 1996, Chow 2002, Kim 2003, Bierley 2005, Chow 2006, etc.
- Studi che hanno mostrato un aumento della sopravvivenza: Leisner 1982, Kim 2003, Chow 2006



EBRT ADIUVANTE... QUANDO?!?

FATTORI PROGNOSTICI: N

Table 6. Multivariable analysis for local–regional relapse-free rate endpoint

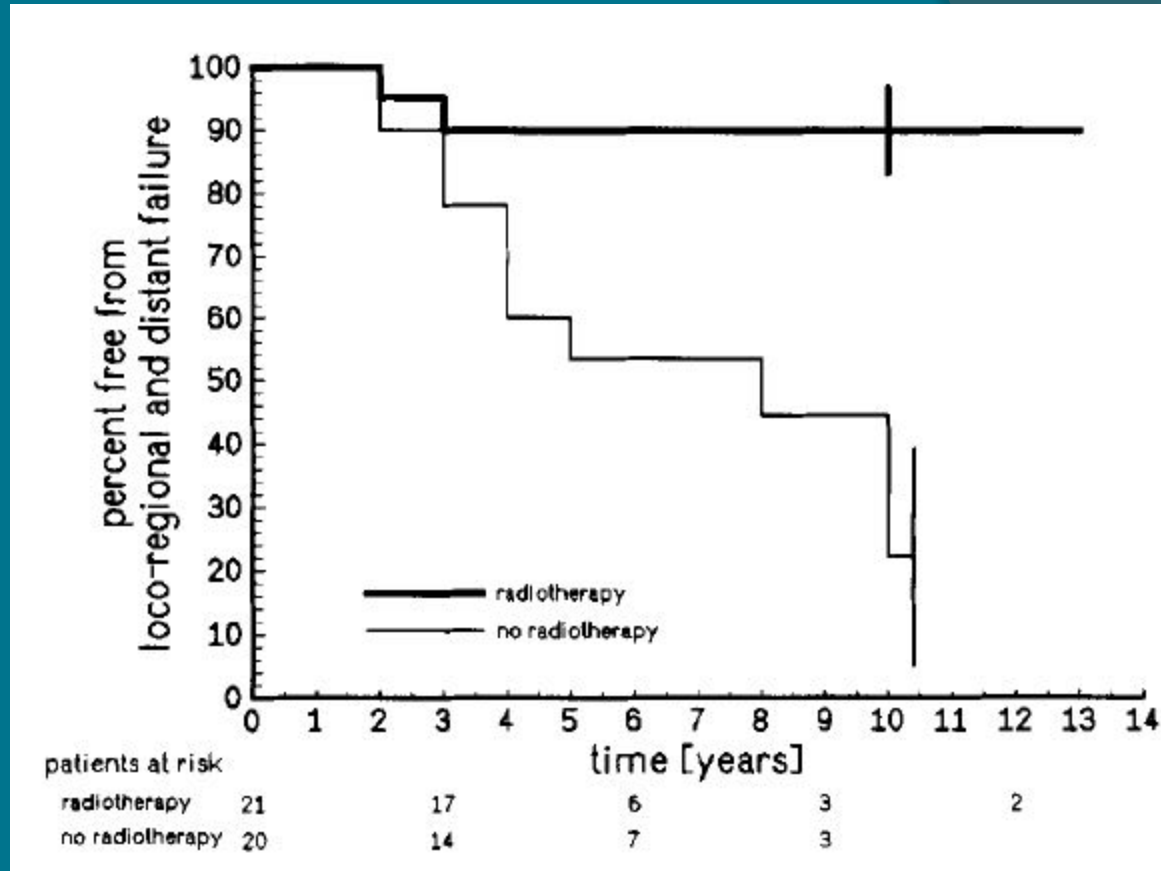
Variable	Description	Parameter estimate	Standard error	P-value	HR (95% CI)
Tumour size (cm)	> 4 vs. Other	+0.56	0.22	0.009	1.8 (1.1–2.7)
Age	> 60 vs. Other	+0.66	0.27	0.015	1.9 (1.1–3.3)
Neck metastasis	Yes vs. No	+0.55	0.20	0.007	1.7 (1.2–2.6)
<i>Model testing each treatment variable concurrently (adjusted for baseline variables) and stratified by time period (1958–71; 1972–85; 1986–98)</i>					
Surgery	Total/Near total vs. Other	–0.30	0.25	0.24	0.7 (0.5–1.2)
RAI	Yes vs. No	–0.65	0.24	0.007	0.5 (0.3–0.8)
RT	Yes vs. No	+0.26	0.22	0.25	1.1 (0.7–1.8)
Likelihood ratio χ^2 -test of joint treatment effect; $P = 0.01$					

Brierley, Clin Endocr 2005

FATTORI PROGNOSTICI: N

Effetto della radioterapia adiuvante negli N1

“...lymph node involvement was associated with a higher rate of metastasis at staging and in follow-up...”



Farahati, Cancer 1996

FATTORI PROGNOSTICI: N

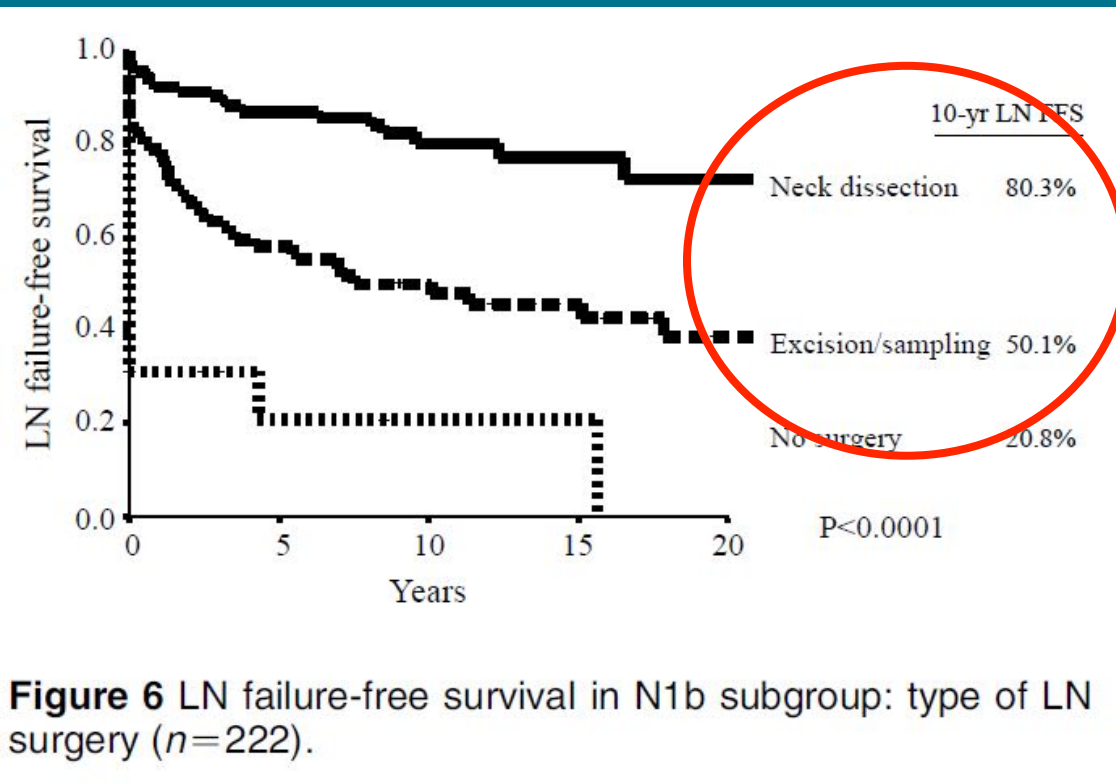
Endocrine-Related Cancer (2006) 13 1159–1172

Local and regional control in patients with papillary thyroid carcinoma: specific indications of external radiotherapy and radioactive iodine according to T and N categories in AJCC 6th edition

Sin-Ming Chow, Stephen Yau, Chung-Kong Kwan, Patricia C M Poon and Stephen C K Law

RAI, radioactive iodine; EXT, external radiotherapy. * $P < 0.05$.

FATTORI PROGNOSTICI: N



“...in pN1b patients multivariate analysis showed that more radical surgery... improved local control...”

Chow, Clin Endocr 2006

FATTORI PROGNOSTICI: N

Dimensione dei linfonodi

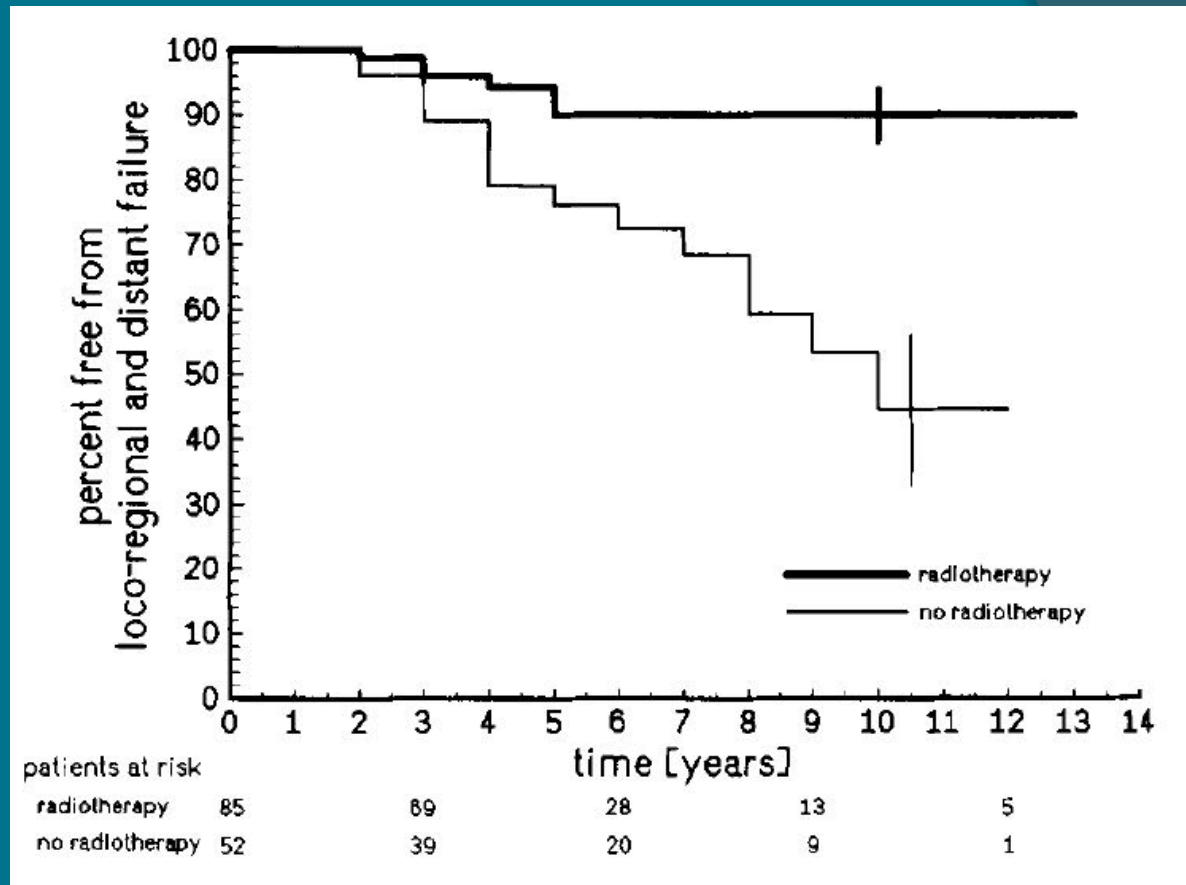
LN relapse according to size of metastatic LN

	≤ 1 cm ($n=87$) (%)	<i>P</i>	> 1 to ≤ 2 cm ($n=95$) (%)	<i>P</i>	> 2 cm ($n=114$) (%)	<i>P</i>
LN surgery		0.30		0.002*		$<0.001^*$
Excision	12.5		35.3		48.9	
Selective LN dissection	25		6.1		12.3	
RAI		0.38		0.003*		$<0.001^*$
No	23.1		70		73.9	
Yes	12.2		21.2		25.3	
EXT		0.87		0.79		0.008*
No	9.6		27.8		44.4	
Yes	9.8		21.7		19	

FATTORI PROGNOSTICI: T

pT4 N0-1

p=0,0009

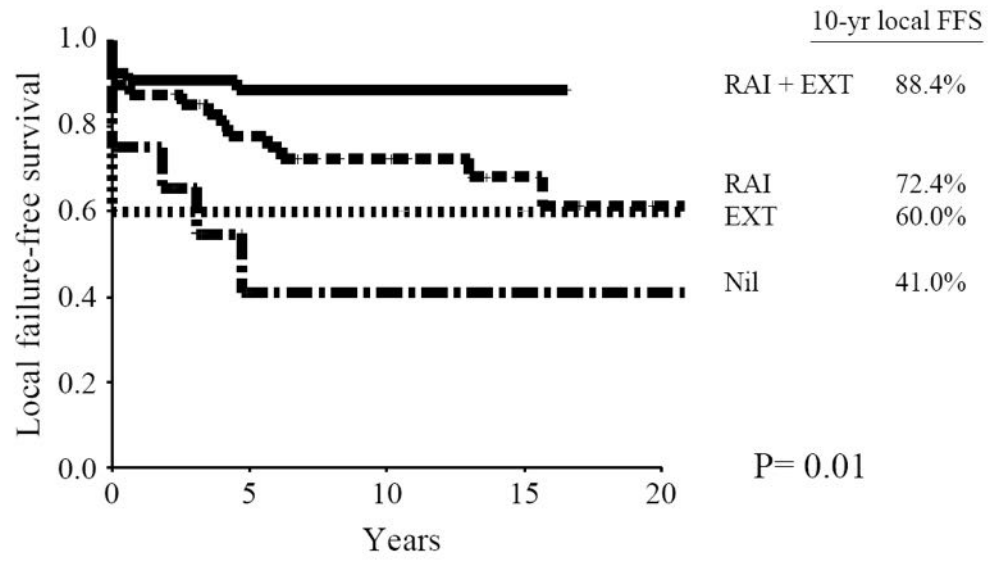


Farahati, Cancer 1996

FATTORI PROGNOSTICI: T

Local relapse				Local relapse according to RAI treatment					Local relapse according to EXT				
T stage	No.	(%)	<i>P</i>	No RAI		RAI		<i>P</i>	No EXT		EXT		<i>P</i>
				No.	(%)	No.	(%)		No.	(%)	No.	(%)	
T1	3/413	0.7		2/116	1.7	1/297	0.3	0.19	3/404	0.7	0/9	0	1.0
T2	8/163	4.9		4/29	13.8	4/134	3.0	0.03*	7/158	4.4	1/5	20	0.22
T3	22/391	5.6		5/26	19.2	17/365	4.7	0.01*	21/328	6.4	1/63	1.6	0.23
T4	36/154	23.4		10/19	52.6	26/135	19.3	0.003*	24/67	35.8	12/87	13.8	0.002*

<0.0001*

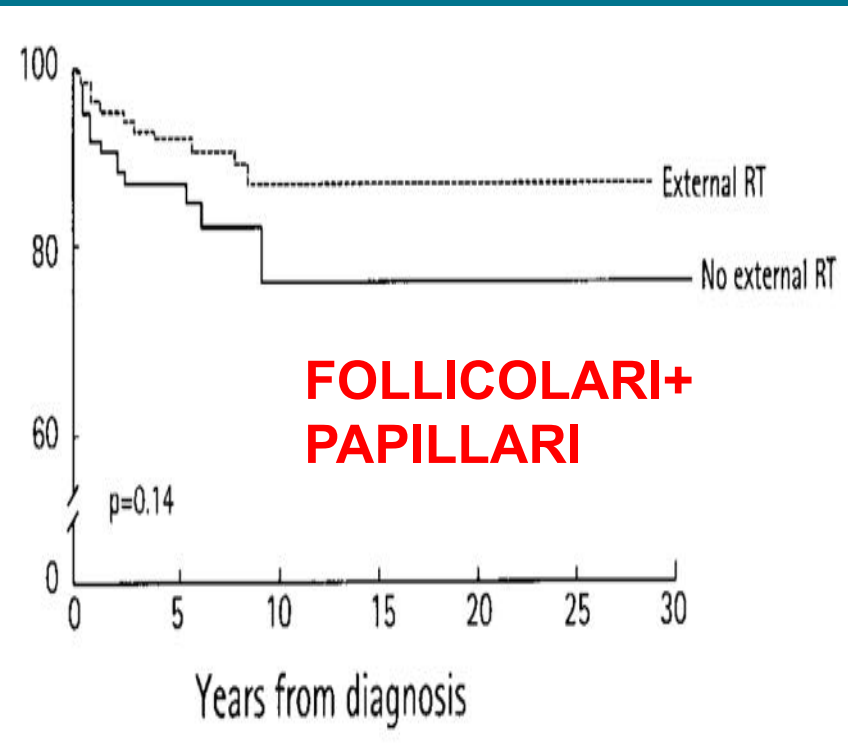


Chow, Clin Endocr 2006

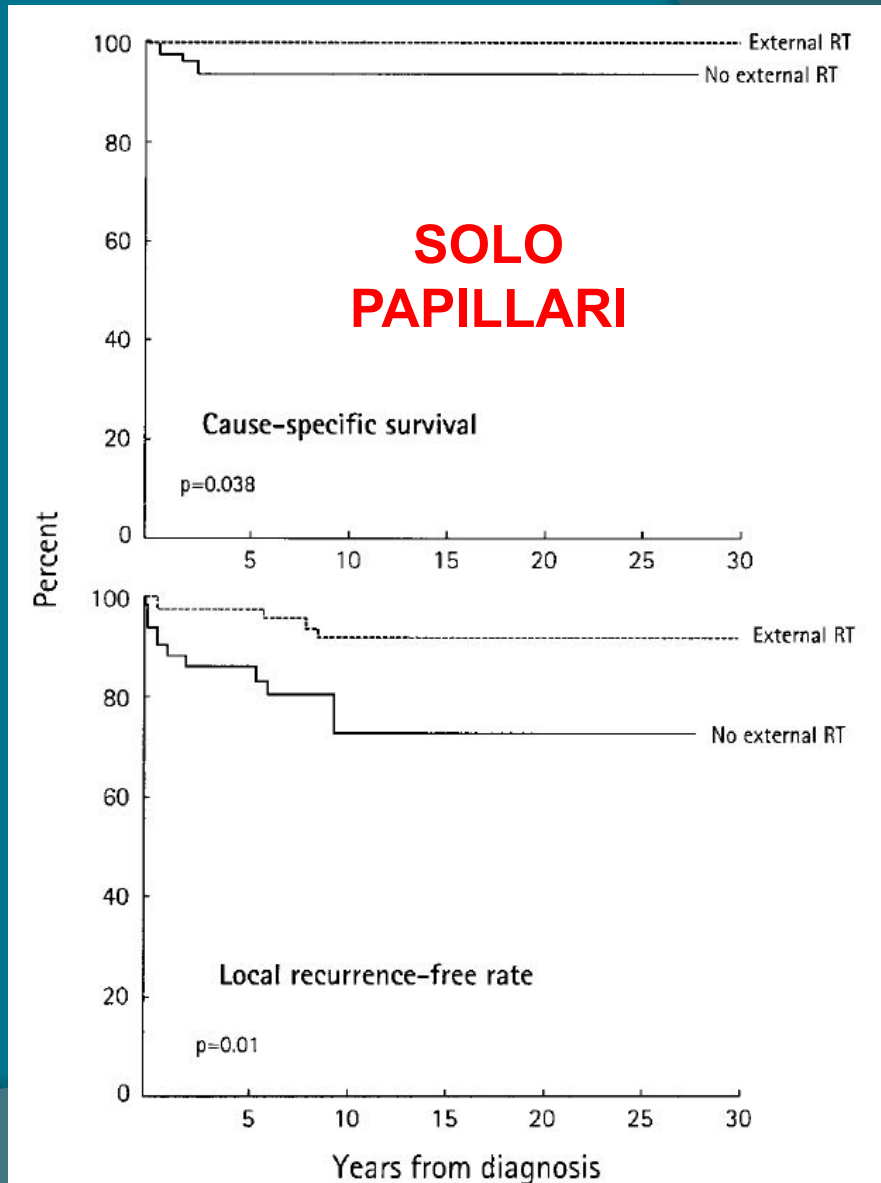
Figure 4 Local failure-free survival in T4a disease after total thyroidectomy: role of RAI and EXT (*n*=131).

FATTORI PROGNOSTICI: MARGINI

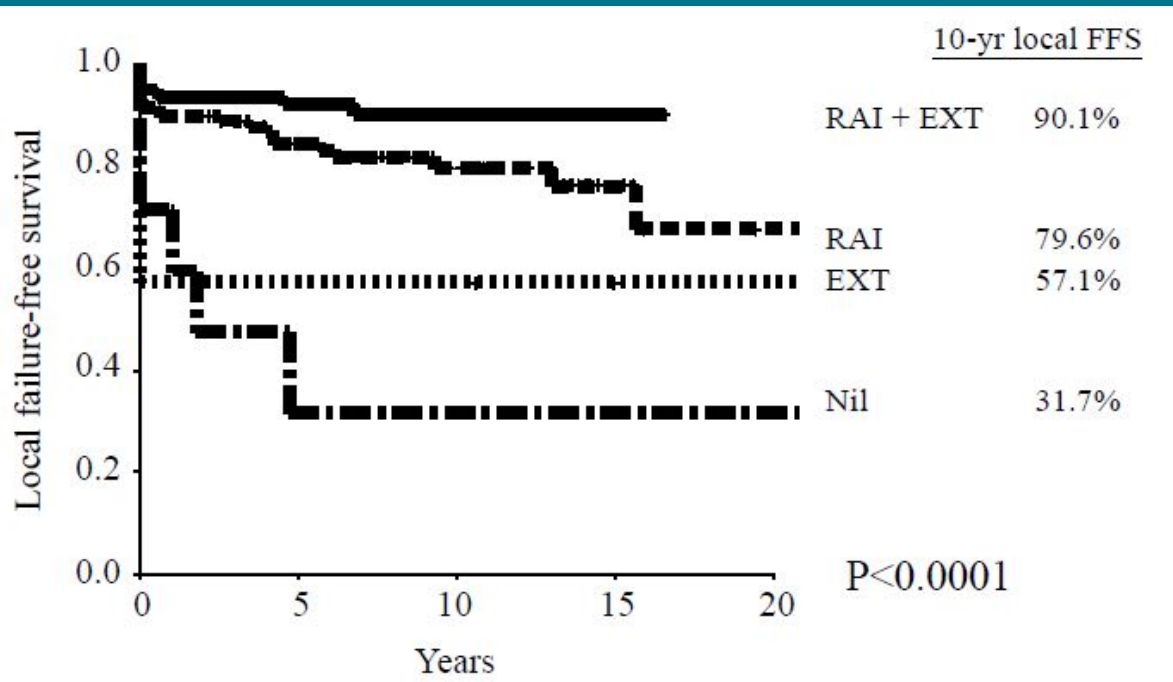
R1



Tsang, Cancer 1998



FATTORI PROGNOSTICI: MARGINI



“...for R1 patients there was significant benefit in local control by EBRT only in T4 disease...”

Figure 2 Local failure-free survival in patients with ‘positive’ resection margins after total thyroidectomy: role of RAI and EXT (n=251).

FATTORI PROGNOSTICI: T

... e i pT3b, magari R1?!?

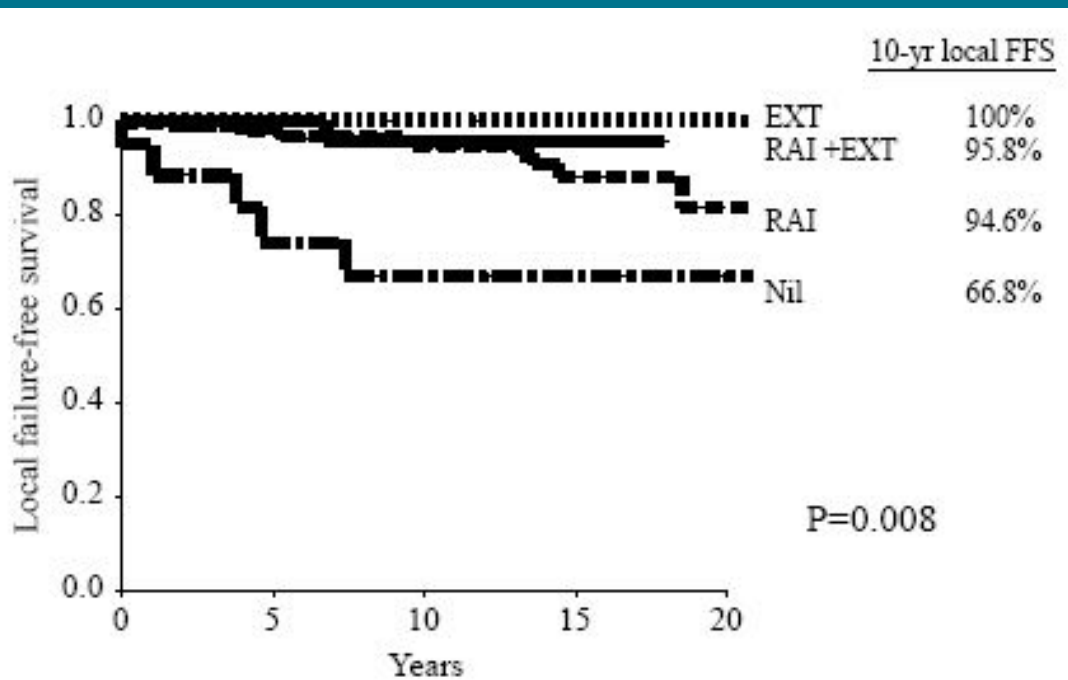
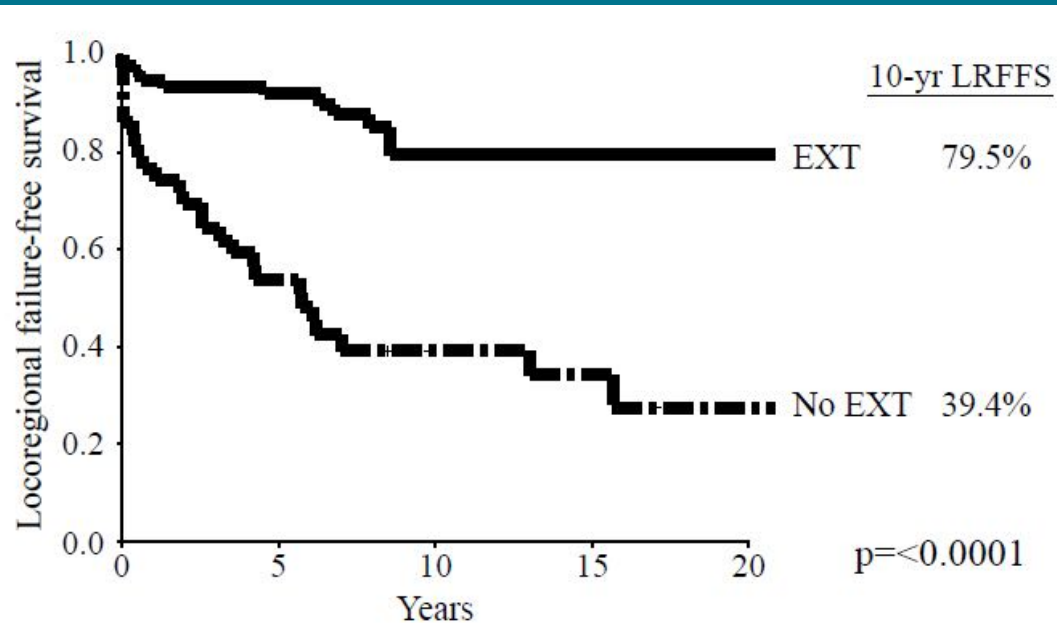


Figure 3 Local failure-free survival in T3b disease after total thyroidectomy: role of RAI and EXT ($n=352$).

“...therefore we may try RAI in T1 to T3 also with positive resection margin, while reserving EBRT to those with T4...”

FATTORI PROGNOSTICI: RESIDUO MACROSCOPICO



Chow, Clin Endocr 2006

17.5% had no radiation therapy. In this subgroup, EXT not only improved LR control as observed in our previous publication (Chow *et al.* 2002c), it also improved CSS. The 10-year LR FFS was improved from 24 to 63.4% ($P < 0.0001$) while the 10-year CSS was improved from 49.7 to 74.1% ($P = 0.01$).

FATTORI PROGNOSTICI: ETA'

STAGE GROUPING

Separate stage groupings are recommended for papillary or follicular, medullary, and anaplastic (undifferentiated) carcinoma.

Papillary or Follicular

Under 45 years

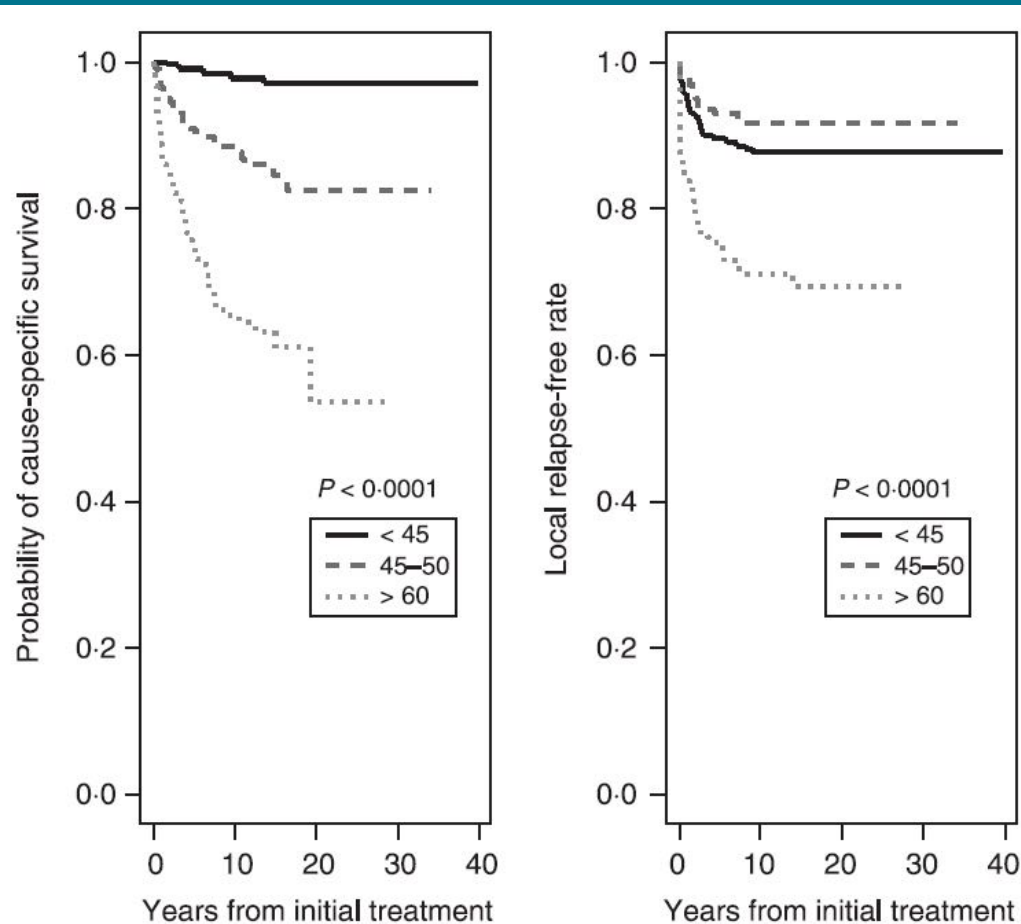
I	Any T	Any N	M0
II	Any T	Any N	M1

Papillary or Follicular

45 years and older

I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0

FATTORI PROGNOSTICI: ETA'

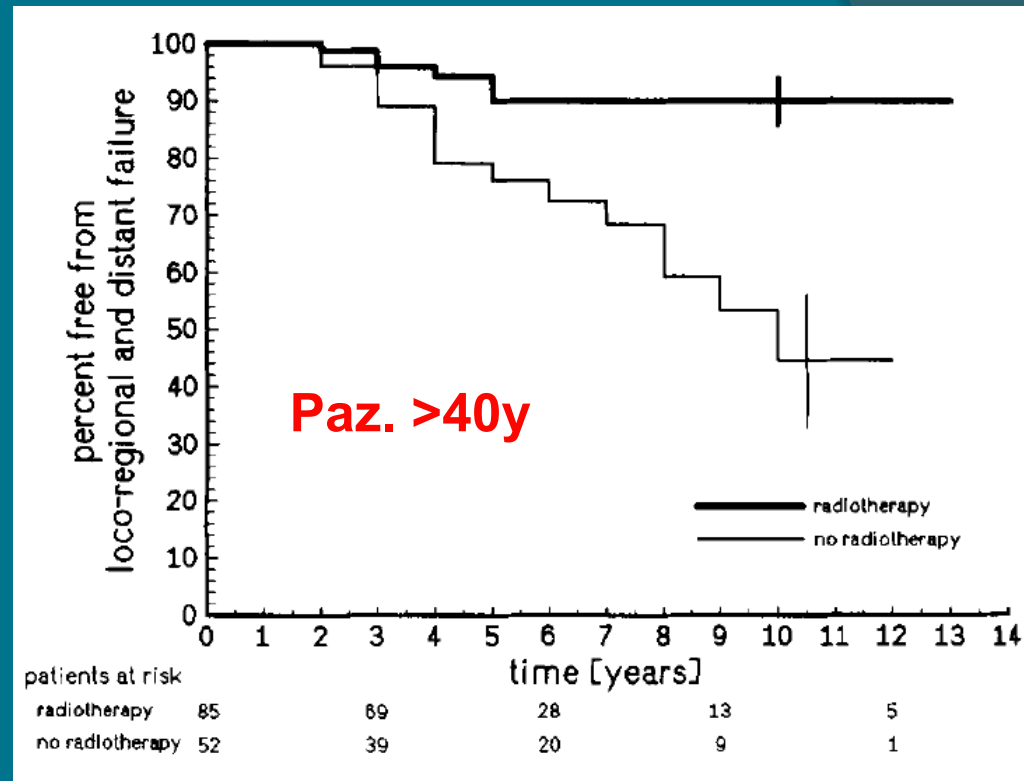


Brierley, Clin Endocr 2005
Sia, J Thy Res 2010

Fig. 2 Cumulative incidence of cause-specific survival and local-regional relapse-free rate by age.

FATTORI PROGNOSTICI: ETA'

“...because none of the patients younger than age 40 years died due to the disease nor had progressive disease during follow up, we reassessed our results in patients older than 40 years...”



Farahati, Cancer 1996

FATTORI PROGNOSTICI: ETA'

Prognostic factors	Total patients in group	Patients dead of disease		Cause-specific survival		
		No.	(%)	Univariate analysis	Multivariate analysis	
				<i>p</i>	Relative risk (95% CI)	<i>p</i>
Age				<0.0001		<0.001
Age ≤45	446	9	(2.0%)		1	
Age >45	396	55	(13.9%)		5.4 (2.6–11.3)	
Gender				0.05		NS
Female	689	47	(6.8%)			
Male	153	17	(11.1%)			
Cervical LN met				0.2		NS
No	549	33	(6.0%)			
Yes	280	28	(10.0%)			
Not stated	13	3	(23.0%)			

Chow, IJROBP 2002
Chow, Clin Endocr 2006

CONCLUSIONI

La Radioterapia adiuvante a fasci esterni è da considerare in caso di

- ✓ R2
- ✓ T4 in pazienti >45 anni con presenza di fattori di rischio di persistenza di malattia
- ✓ In caso di associazione di multipli fattori di rischio di persistenza di malattia o di non efficacia del 131I:
 - pT3b esteso
 - R1
 - N1b esteso con grosse masse linfonodali o estesa estensione extracapsulare
 - istotipi sfavorevoli o aree di dedifferenziazione
 - chirurgia sui linfonodi inadeguata