



Workshop
**LA RADIOTERAPIA DEI TUMORI RARI
I TIMOMI : INDICAZIONI**

PIERA NAVARRIA Unità Operativa di Radioterapia e Radiochirurgia

Humanitas Cancer Center



Associazione
Italiana
Radioterapia
Oncologica

TIMOMI: INDICAZIONI

DEFINITIVE RECOMMENDATIONS FOR TREATMENT

- LOW **INCIDENCE** AND **INDOLENT** NATURAL HISTORY
- FEW PUBLISHED STUDIES
 - Small series
 - Long time** interval
 - Thymoma and Thymic Carcinoma
- NO RANDOMIZED **PROSPECTIVE** CLINICAL TRIAL PUBLISHED

TIMOMI: INDICAZIONI

- Retrospective Analysis Surveillance, Epidemiology and End Results (SEER) database
- Potential use of Radiotherapy in selected patients

- The mainstay of treatment is “en bloc resection”
- In the late 1980s adjuvant RT in all Thymic Neoplasms
- More recently stratification by Tumor Stage
Resection Characteristics

THYMOMA Masaoka Stage I
Macro- and Microscopically completely encapsulated

Recurrence rate 2-3% after Complete Resection (FU 32 years)

WHO *subtype A or AB*

A recent retrospective analysis adjuvant RT **no advantage in OS**

Forquer JA, IJROBP 2010

Surgery alone OS 10 years **92%** vs 88% with adjuvant RT

Zhang H, Chin Med J 1999



*In **Completely Resected** stage I adjuvant RT*
is NOT RECOMMENDED

THYMOMA Masaoka Stage II
THYMOMA Masaoka Stage III

Micro or macro invasion into surrounding fatty tissue
Macro invasion into neighboring organs

LOCAL CONTROL

Smaller mostly institutional series-not statistically significant

Curran WJ Jr. et al. J Clin Oncol 1988

68 patients after R0 Resection

Local Recurrence at 5 years **47%** without RT vs **0%** with RT

Urgesi A et al. Radiother Oncol 1990

33 patients

NO "in field" Recurrences and 3 out of field

EFFICACY ADJUVANT RT

THYMOMA Masaoka Stage II
THYMOMA Masaoka Stage III

Micro or macro invasion into surrounding fatty tissue
Macro invasion into neighboring organs

“PRO” RT



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CLINICAL INVESTIGATION

Thymus

POSTOPERATIVE RADIOTHERAPY AFTER SURGICAL RESECTION OF THYMOMA: DIFFERING ROLES IN LOCALIZED AND REGIONAL DISEASE

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LOC disease	274 pts	35% Surgery alone
REG disease	626 pts	65% PORT

THYMOMA Masaoka Stage II
THYMOMA Masaoka Stage III

Micro or macro invasion into surrounding fatty tissue
Macro invasion into neighboring organs

“PRO” RT

<u>ENTIRE COHORT</u>		
OS 5yrs	74.6%	Surgery
	77.1%	PORT
} ($p = 0.71$)		

<u>LOCALIZED Disease</u>		
OS 5yrs	87% Surgery alone	} ($p = 0.35$)
	81% PORT	
CSS 5yrs	98% Surgery alone	} ($p = 0.03$)
	91% PORT	

<u>REGIONAL Disease</u>		
OS 5yrs	66% Surgery alone	} ($p = 0.01$)
	76% PORT	
CSS 5yrs	86% Surgery alone	} ($p = 0.12$)
	91% PORT	

POSITIVE EFFECT IN REGIONAL DISEASE
after Surgery R1



doi:10.1016/j.ijrobp.2011.03.010

CLINICAL INVESTIGATION

EVALUATION OF THE ROLE OF RADIATION THERAPY IN THE MANAGEMENT OF MALIGNANT THYMOMA

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From 1973 to 2003 ;1254 patients; median FU 41 months; Thymoma
63% complete excision
18% partial excision
18% no surgery

64% (800 pts) RT

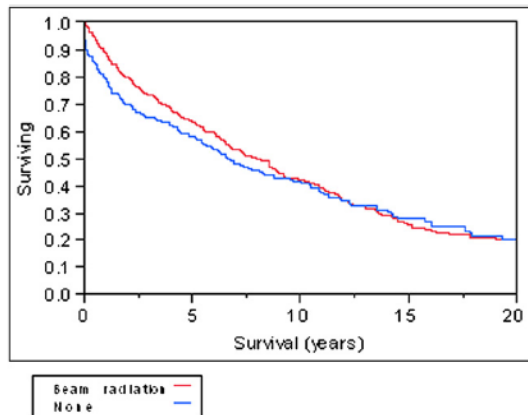
THYMOMA Masaoka Stage II
THYMOMA Masaoka Stage III

Micro or macro invasion into surrounding fatty tissue
Macro invasion into neighboring organs

“PRO” RT

ALL STAGE

OS 5-10-15-yr
64%, 42%, and 26% with RT
59%, 41%, and 28% without RT

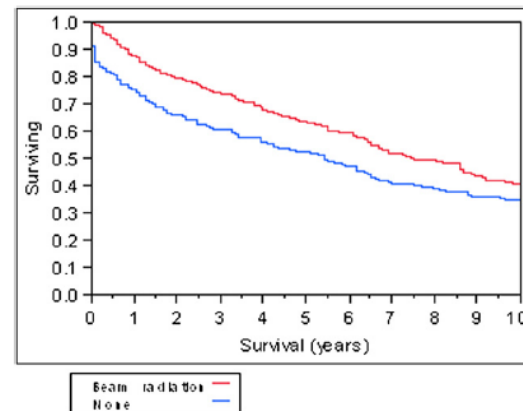


$p = 0.06$

Fig. 1. OS is shown as a function of the presence or absence of RT.

STAGE II–III

OS 5-10 yrs
64% and 41% with RT
53% and 35% without RT



$p = 0.002$

Fig. 3. OS is shown as a function of the presence or absence of RT in patients with regional spread of disease.

THYMOMA Masaoka Stage II
THYMOMA Masaoka Stage III

Micro or macro invasion into surrounding fatty tissue
Macro invasion into neighboring organs

“CONTRA” RT

International report 1320 thymoma (115 institutes) no difference in OS between surgery alone and adjuvant RT in patients with stage II-III totally resected
Kondo K, Ann Thorac Surg 2003

Smaller domestic report 167 patients no benefit in OS from adjuvant RT in margin negative stage II disease
Singhal S SJ, Ann Thorac Surg 2003

Meta-analysis 592 patients no benefit of adjuvant RT on recurrence rates after complete resection of stage II and/or III thymic epithelial tumors
Korst et al.27 Ann Thorac Surg 2009

NO RT IN MARGIN-NEGATIVE SURGICAL RESECTION

The use of radiation remains an area of
Debate and institutional norms

THYMOMA Masaoka Stage III

THYMOMA Masaoka Stage IV

Macroscopic invasion into neighboring organs

Pleural or Pericardial dissemination

ADJUVANT RADIOTHERAPY in **INCOMPLETE RESECTION**

- Resectable Disease
- Widely believed to be **the standard of care** for residual disease

MULTIMODALITY TREATMENT in **UNRESECTABLE DISEASE**

- Chemotherapy + Definitive Radiotherapy
- Chemotherapy + Surgery + Radiotherapy
- Radiotherapy + Surgery
- Concomitant Chemoradiotherapy + Surgery

THYMOMA Masaoka Stage III

Macroscopic invasion into neighboring organs

THYMOMA Masaoka Stage IV

Pleural or Pericardial dissemination

MULTYMODALITY TREATMENT

CHEMOTHERAPY + DEFINITIVE RADIOTHERAPY

A Prospective Phase II intergroup study

CDDP, Doxorubicin, and Cyclophosphamide x 4 cycles
Radiotherapy 54 Gy to the primary tumor and lymph nodes

Median survival time 93 months

OS 5 years 52.5%

Loehrer PJ J Clin Oncol 1997

THYMOMA Masaoka Stage III

Macroscopic invasion into neighboring organs

THYMOMA Masaoka Stage IV

Pleural or Pericardial dissemination

MULTYMODALITY TREATMENT

CHEMOTHERAPY + SURGERY + RADIOTHERAPY

A phase II Study

22 Locally advanced unresectable malignant Thymoma

Induction chemotherapy (3 cycles), Surgical resection, adjuvant RT and consolidation chemotherapy (3 cycles)

After CT: 3 CR 14 PR 5 SD

21/22 Surgery 16 R0 5 R1

OS 95% PFS 77% at 5 years

Kim ES Lung Cancer 2004

THYMOMA Masaoka Stage III

Macroscopic invasion into neighboring organs

THYMOMA Masaoka Stage IV

Pleural or Pericardial dissemination

MULTYMODALITY TREATMENT

PREOPERATIVE RADIOTHERAPY + SURGERY

21 patients with Masaoka stage III thymoma

*Preoperative RT of 12 to 20 Gy + surgical resection 1 to 3 weeks later
+ postoperative RT 40 Gy (range 22-66.8Gy)*

Surgery in all patients: 19 R0 2R1
OS 5 years 91% 10 years 78% DFS 10 years 84%

Onuki TJ Thorac Oncol 2008

THYMOMA Masaoka Stage III

Macroscopic invasion into neighboring organs

THYMOMA Masaoka Stage IV

Pleural or Pericardial dissemination

MULTYMODALITY TREATMENT

CONCURRENT CHEMORADIOOTHERAPY + SURGERY

A retrospective review of 10 patients treated from 1997 to 2006
7 stage III and 3 stage IVA

2 cycles of cisplatin and etoposide with concurrent RT (33-49 Gy)
followed +/- CT

4 PR 6 SD

8 R0 resection 2 R1 resection

4 necrosis >90%

median FU 41 months 3 had recurrences
OS 5-year 69%

Wright CD Ann Thorac Surg 2008

THYMOMA Masaoka Stage III

Macroscopic invasion into neighboring organs

THYMOMA Masaoka Stage IV

Pleural or Pericardial dissemination

MULTYMODALITY TREATMENT



PHASE II STUDY OF TRIMODALITY THERAPY FOR PATIENTS WITH THYMOMA OR THYMIC CARCINOMA AT SIGNIFICANT RISK FOR RECURRENCE

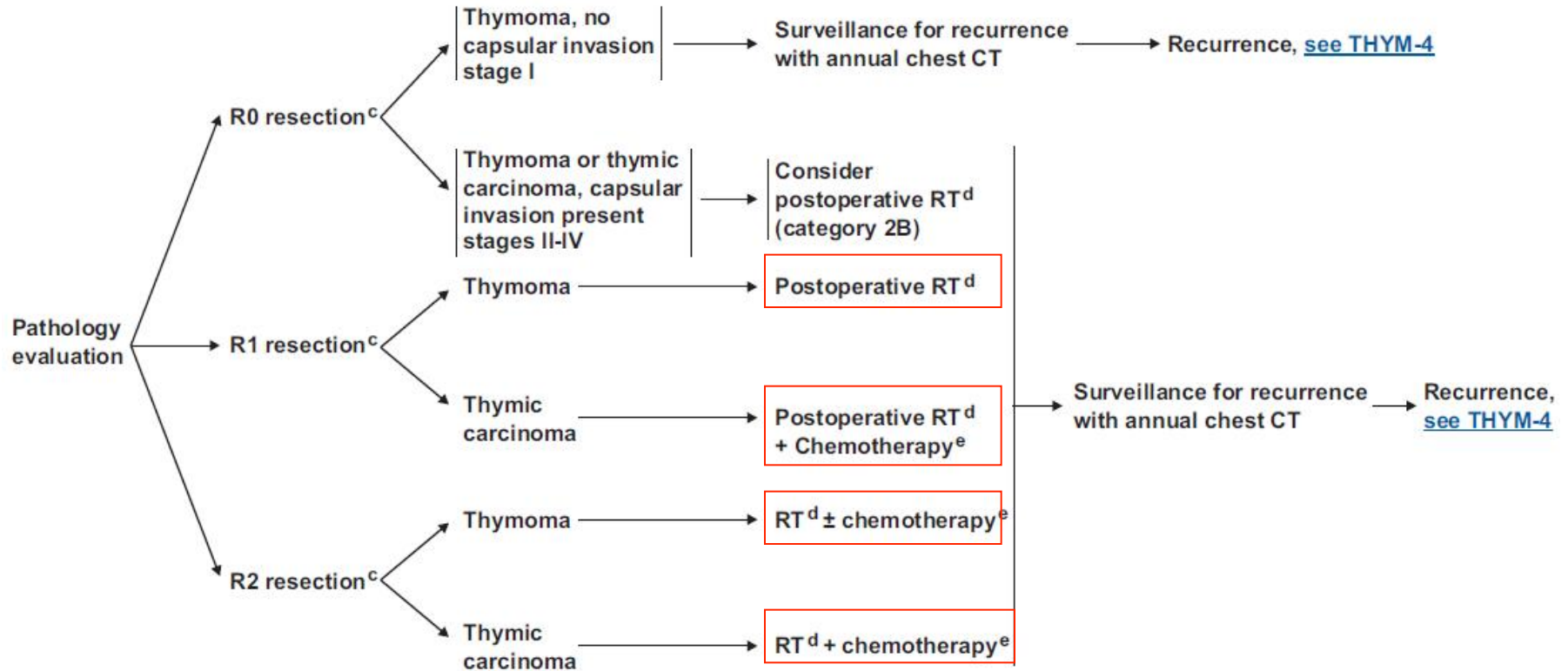
Primary End point To determine the **complete pathologic response** rate to preoperative cisplatin and etoposide given concurrently with radiation in patients with **thymoma** thought to be at high risk for recurrence

Secondary End point **Radiographic response**, Rate of **complete resection**, **Toxicities** of preoperative treatment

Estimated Enrollment: 30 patients

RESECTABLE DISEASE^b

POSTOPERATIVE MANAGEMENT



LOCALLY ADVANCED, ADVANCED
OR RECURRENT DISEASE

TREATMENT

Thymoma or thymic carcinoma:
All patients should be managed by a multidisciplinary team with experience in the management of thymoma and thymic carcinoma

