

ROMA

Associazione Italiana Radioterapia Oncologica

XXII CONGRESSO 17-20 novembre 2012

**LA RADIOTERAPIA ADIUVANTE
NEL TRATTAMENTO DEI CARCINOMI
AD ALTO RISCHIO DELLA TIROIDE: CONS**



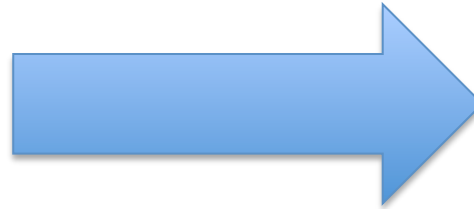
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Department of Radiation Oncology

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DIFFERENTIATED THYROID CANCER



TIPICAL THERAPEUTIC APPROACH



RADIOACTIVE IODINE THERAPY

- **Staging**
- **Follow-Up**
- **Treatment**



Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM. *Thyroid*. 2009 Nov;19(11):1167-214.

RADIOACTIVE IODINE THERAPY

TABLE 5. MAJOR FACTORS IMPACTING DECISION MAKING IN RADIOIODINE REMNANT ABLATION

Factors	Description	Expected benefit			RAI ablation usually recommended	Strength of evidence
		Decreased risk of death	Decreased risk of recurrence	May facilitate initial staging and follow-up		
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	1–2 cm, intrathyroidal	No	Conflicting data ^a	Yes	Selective use ^a	I
T2	>2–4 cm, intrathyroidal	No	Conflicting data ^a	Yes	Selective use ^a	C
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	<45 years old	No	Conflicting data ^a	Yes	Yes	B
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	Any size, any age, minimal extrathyroidal extension	No	Inadequate data ^a	Yes	Selective use ^a	I
T4	Any size with gross <u>extrathyroidal extension</u>	Yes	Yes	Yes	Yes	B
Nx,N0	No metastatic nodes documented	No	No	Yes	No	I
N1	<45 years old	No	Conflicting data ^a	Yes	Selective use ^a	C
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M1	Distant metastasis present	Yes	Yes	Yes	Yes	A



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ADJUVANT EXTERNAL BEAM RADIOTHERAPY



ERT
or
NOT ERT

that is the question



Hamlet by William Shakespeare

ADJUVANT EXTERNAL BEAM RADIOTHERAPY

“La radioterapia esterna (RTE) ha, rispetto alla chirurgia e al ^{131}I , un ruolo limitato”

“Non vi è un consenso generale su quali pazienti debbano essere candidati al trattamento radiante esterno e centri con lunga tradizione seguono approcci anche molto diversi”



ADJUVANT EXTERNAL BEAM RADIOTHERAPY

- **About 5% of patients die to due the disease**
- **Risk factors:**
 - age
 - histology
 - tumor extension



ADJUVANT EXTERNAL BEAM RADIOTHERAPY

WHY?

EXTRATHYROID DISEASE



radioactive iodine may not be distributed well in areas with a local invasion and in the surgical bed where the surgery may have destroyed the normal vasculature

(Vassilopolou – 2006)

ELDERLY PATIENTS



in elderly patients the uptake of iodine may be lower for a lower tumor differentiation

(Coburn – 1995)



- Age correlates with increased frequency of high risk factors in elderly patients with thyroid cancer. Coburn MC, Wanebo HJ. Am J Surg. 1995 Nov;170(5):471-5.
- Clinical outcome of patients with papillary thyroid carcinoma who have recurrence after initial radioactive iodine therapy. Vassilopoulou-Sellin R, Schultz PN, Haynie TP. Cancer. 1996 Aug 1;78(3):493-501.

ADJUVANT EXTERNAL BEAM RADIOTHERAPY RETROSPECTIVE ANALYZES

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%
Phlips 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.



The role of external beam radiation and targeted therapy in thyroid cancer.
Brierley J, Sherman E. Semin Radiat Oncol. 2012 Jul;22(3):254-62

ADJUVANT EXTERNAL BEAM RADIOTHERAPY RANDOMIZED CLINICAL TRIALS

MSDS-trial



Original article

Clinical outcomes of adjuvant external-beam radiotherapy for differentiated thyroid cancer

Results after 874 patient-years of follow-up in the
MSDS-trial

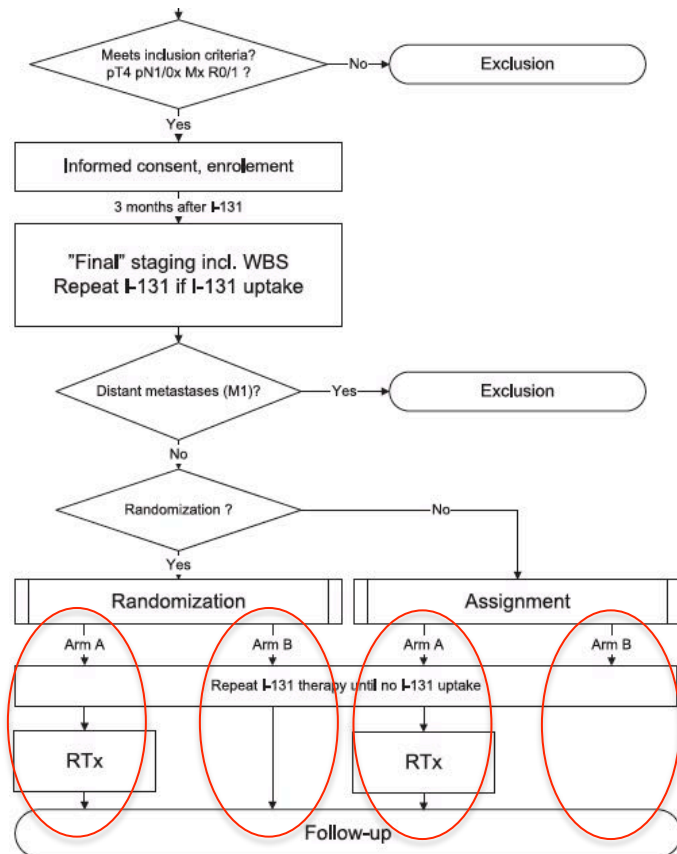
M. Biermann^{1,*}; M. K. Pixberg^{2,*}; B. Riemann^{2,*}; A. Schuck^{3,*}; A. Heinecke^{4,*};
K. W. Schmid^{5,*}; N. Willich^{3,*}; H. Dralle^{6,*}; O. Schober^{2,*}



Clinical outcomes of adjuvant external-beam radiotherapy for differentiated thyroid cancer - results after 874 patient-years of follow-up in the MSDS-trial. - Biermann M, Pixberg M, Riemann B, Schuck A, Heinecke A, Schmid KW, Willich N, Dralle H, Schober O; MSDS study group. Nuklearmedizin. 2009;48(3):89-98; quiz N15. Epub 2009 Mar 23

ADJUVANT EXTERNAL BEAM RADIOTHERAPY RANDOMIZED CLINICAL TRIALS

MSDS-trial



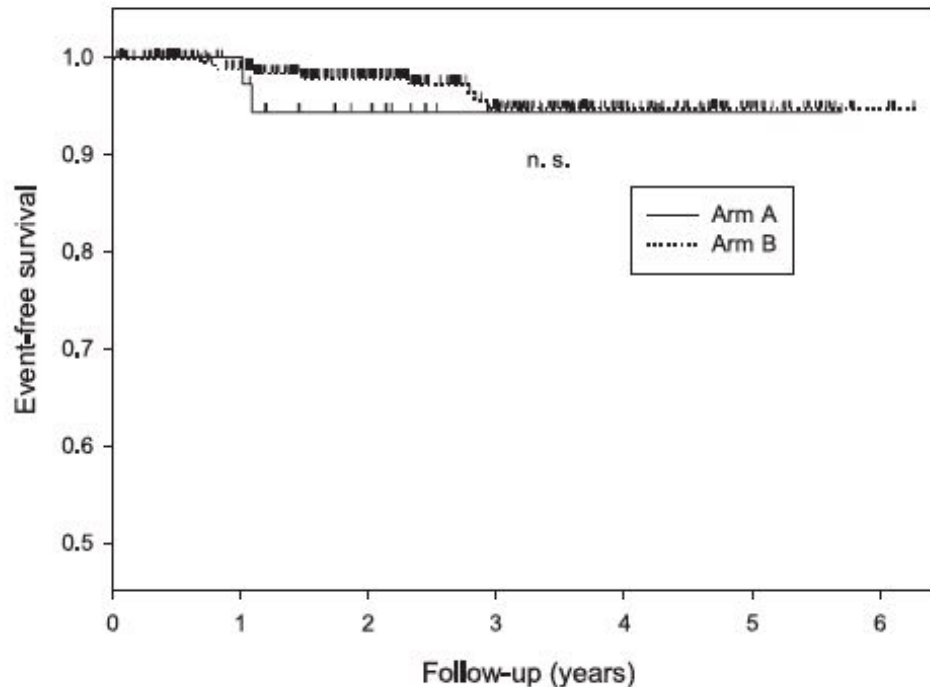
the study was closed early because of poor accrual and although started as a **randomized study**, it was changed to a **observational prospective cohort study**



Clinical outcomes of adjuvant external-beam radiotherapy for differentiated thyroid cancer - results after 874 patient-years of follow-up in the MSDS-trial. - Biermann M, Pixberg M, Riemann B, Schuck A, Heinecke A, Schmid KW, Willich N, Dralle H, Schober O; MSDS study group. Nuklearmedizin. 2009;48(3):89-98; quiz N15. Epub 2009 Mar 23

ADJUVANT EXTERNAL BEAM RADIOTHERAPY RANDOMIZED CLINICAL TRIALS

MSDS-trial



Intention-to-treat-analysis (Arm A – RTx+ v. Arm B – RTx-) of patients meeting the trial’s inclusion criteria (“included” pts.). Product-limit estimate (Kaplan-Meier)



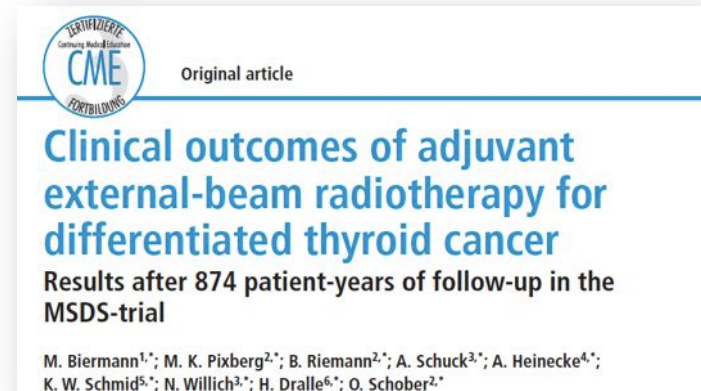
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ADJUVANT EXTERNAL BEAM RADIOTHERAPY RANDOMIZED CLINICAL TRIALS

MSDS-trial

Conclusion

Mortality and recurrence rate in the MSDS trial have been low. Data show a weak benefit of RTx in terms of local control and chronic RTx toxicity in a similar order of magnitude even though none of the observed effects reached statistical significance. Based on the MSDS data, routine RTx in patients with locally invasive DTC can no longer be recommended. Further follow-up of the MSDS-cohort is planned.



NO ERT!!!



Clinical outcomes of adjuvant external-beam radiotherapy for differentiated thyroid cancer - results after 874 patient-years of follow-up in the MSDS-trial. - Biermann M, Pixberg M, Riemann B, Schuck A, Heinecke A, Schmid KW, Willich N, Dralle H, Schober O; MSDS study group. Nuklearmedizin. 2009;48(3):89-98; quiz N15. Epub 2009 Mar 23

ADJUVANT EXTERNAL BEAM RADIOTHERAPY TOXICITY

MEMORIAL SLOAN-KETTERING CANCER CENTER EXPERIENCE

- **acute mucositis grade 3 in 18%**
- **dysphagia in 32%**
- **29%** of patients were subjected to a short-term **percutaneous endoscopic gastrostomy** tube
- **5%** required enteral feeding for long-term support.



Role of external beam radiotherapy in patients with advanced or recurrent nonanaplastic thyroid cancer: Memorial Sloan-Kettering Cancer Center experience. Terezakis SA, Lee KS, Ghossein RA, Rivera M, Tuttle RM, Wolden SL, Zelefsky MJ, Wong RJ, Patel SG, Pfister DG, Shaha AR, Lee NY. Int J Radiat Oncol Biol Phys. 2009 Mar 1;73(3):795-801.

ADJUVANT EXTERNAL BEAM RADIOTHERAPY NEW TECHNOLOGY

MD ANDERSON EXPERIENCE

- in patients treated before IMRT
 - 12% had late toxicity
 - 9% required dilatation for esophageal stricture
- with IMRT treatment
 - 2% of patients had significant late morbidity of equivalent severity



Postoperative external beam radiotherapy for differentiated thyroid cancer: outcomes and morbidity with conformal treatment. Schwartz DL, Lobo MJ, Ang KK, Morrison WH, Rosenthal DI, Ahamad A, Evans DB, Clayman G, Sherman SI, Garden AS. Int J Radiat Oncol Biol Phys. 2009 Jul 15;74(4):1083-91. Epub 2008 Dec 25.

DIFFERENTIATED THYROID CANCER

synthesis

NO ERT

ERT



DIFFERENTIATED THYROID CANCER

synthesis

NO ERT

ERT



EXTRATHYROID DISEASE

ELDERLY PATIENTS



DIFFERENTIATED THYROID CANCER synthesis

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N0/N0	No metastatic nodes documented	No	No	No	No	
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EXTRATHYROID DISEASE

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RETROSPECTIVE ANALYZES

EXTRATHYROID DISEASE

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MSDS TRIAL

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DIFFERENTIATED THYROID CANCER synthesis

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NEW TECHNOLOGY

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EXTRATHYROID DISEASE

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DIFFERENTIATED THYROID CANCER

conclusion

- The role of external beam radiotherapy in high risk thyroid cancers **is an issue of debate**
- On one hand we have a number of retrospective studies that suggest a benefit in selected cases of patients, while the **randomized German trial**, though containing a series of bias, does **not recommend the use of EBRT**
- The external beam radiotherapy **is not free from toxicity**



DIFFERENTIATED THYROID CANCER

conclusion



Seminars in
**RADIATION
ONCOLOGY**

**The Role of External Beam Radiation
and Targeted Therapy in Thyroid Cancer**

James Brierley, MB, FRCP, FRCR, FRCPC,* and Eric Sherman, MD^{†,‡}



EXTRATHYROID DISEASE ELDERLY PATIENTS

“it is important to note that EBRT is not without toxicity and should be reserved for patients at high risk of locoregional recurrence in whom the potential benefit will outweigh the toxicity of the therapy and in whom no further surgery is possible”



The role of external beam radiation and targeted therapy in thyroid cancer.
Brierley J, Sherman E. Semin Radiat Oncol. 2012 Jul;22(3):254-62

DIFFERENTIATED THYROID CANCER

conclusion

- In all likelihood **new technologies** will play an important role in helping to conform the dose accurately.
- It is hoped that either **a multicenter randomized trial** will be started to definitively clarify the role of this therapy.



DIFFERENTIATED THYROID CANCER conclusion

INTERNATIONAL LARGE-DATABASE



Il futuro della Radioterapia Oncologica: la “Knowledge Based Oncology”

V. Valentini (ESTRO president)



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