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Disclosures

No disclosures

Objectives

- Review the role of I-131 therapy in distant metastatic disease
- I-131 therapeutic activity, preparation for therapy and other therapeutic considerations for treatment of lung, bone and brain metastases will be discussed

JNM

The Journal of Nuclear Medicine

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Locations and patterns of frequent, infrequent, and rare sites of metastasis secondary to well-differentiated thyroid cancer



Gauri Khorjekar¹, Douglas Van Nostrand¹, Elmo Acio¹, Shyam Chennupati¹,
Kalpna Prasad¹, Kanchan Kulkarni¹ and Kenneth Burman²

Sites of Distant Metastases

- Lung
- Bone
- Brain
- *Liver, spleen, bowel, pancreas, ovary, etc*

- Morbidity and mortality are increased in patients with distant metastases, but individual prognosis depends upon factors including
 - i. histology of the primary tumor,
 - ii. distribution and number of sites of metastasis (e.g., brain, bone, lung),
 - iii. tumor burden,
 - iv. age at diagnosis of metastases,
 - v. Tolerance to previous therapies
 - vi. Response to previous therapies
 - vii. 18FDG and RAI avidity.
- Mutation profiling?

- Improved survival is associated with responsiveness to directed therapy (surgery, EBRT, thermal ablation, etc.) and/or RAI
- Treatment of a specific metastatic area must be considered in light of the patient's performance status and other sites of disease; for example, 5%–20% of patients with distant metastases die from progressive cervical disease.
- Longitudinal re-evaluation of patient status and continuing reassessment of potential benefit and risk of intervention are required.
- Tertiary centers for multidisciplinary treatment

- **Empiric** fixed amounts,.
- Therapy determined by the upper limit of **blood and body dosimetry**, and quantitative tumor or lesional dosimetry .
-

Radioiodine Activity

Empiric

**29, 60, 75, 100, 150, 200, 300
mCi**

Dosimetric

**Lesion Dosimetry
Lesional
Maxon**

**“Maximal safe dose”
Whole Body
Benua-Leeper**

**Combination
of both**

- Dosimetric methods are often reserved for patients with distant metastases or unusual situations such as **renal insufficiency children, the elderly, and those with extensive pulmonary metastases** .
 - Comparison of outcomes among these methods from published series is difficult.
 - No prospective randomized trial to address the optimal therapeutic approach has been published.
 - One retrospective study concluded that patients with loco-regional disease were more likely to respond after dosimetric therapy than after empiric treatment. (*Klubo-Gweizdzinska et al*).
 - Another study demonstrated improved efficacy of administration of dosimetric maximal activity after failure of empiric dosage. (*Lee et al*).
 - Arguments in favor of higher activities cite a positive relationship between the total ¹³¹I uptake per tumor mass and outcome, while others have not confirmed this relationship.

Klubo-Gwiezdzinska et al Efficacy of dosimetric versus empiric prescribed activity of ¹³¹I for therapy of differentiated thyroid cancer. J Clin Endocrinol Metab 96:3217–3225.

Lee JJ, et al. Maximal safe dose of I-131 after failure of standard fixed dose therapy in patients with differentiated thyroid carcinoma. Ann Nucl Med 22: 727–734

- Mean radiation dose delivered to neoplastic foci and also to the radiosensitivity of tumor tissue.
- Radiosensitivity: The radiosensitivity is higher in patients who are younger, with small metastases from well-differentiated papillary or follicular carcinoma and with uptake of RAI but no or low ¹⁸F₂ uptake.

Empiric Doses for Metastasis

Advantages

- Long history of use
- Acceptable rate and severity of complications
- Permits treating without having to use I-131 diagnostically
- Convenient

Empiric Doses for Metastasis

Disadvantages

- The maximum tolerated radiation absorbed dose (MTRD), commonly defined as 200 rads (cGy) to the blood, is potentially exceeded in a significant number of patients undergoing empiric treatment with various amounts of ^{131}I .
- No attempt is made to determine either the dose to the tissue or the dose to the bone marrow.

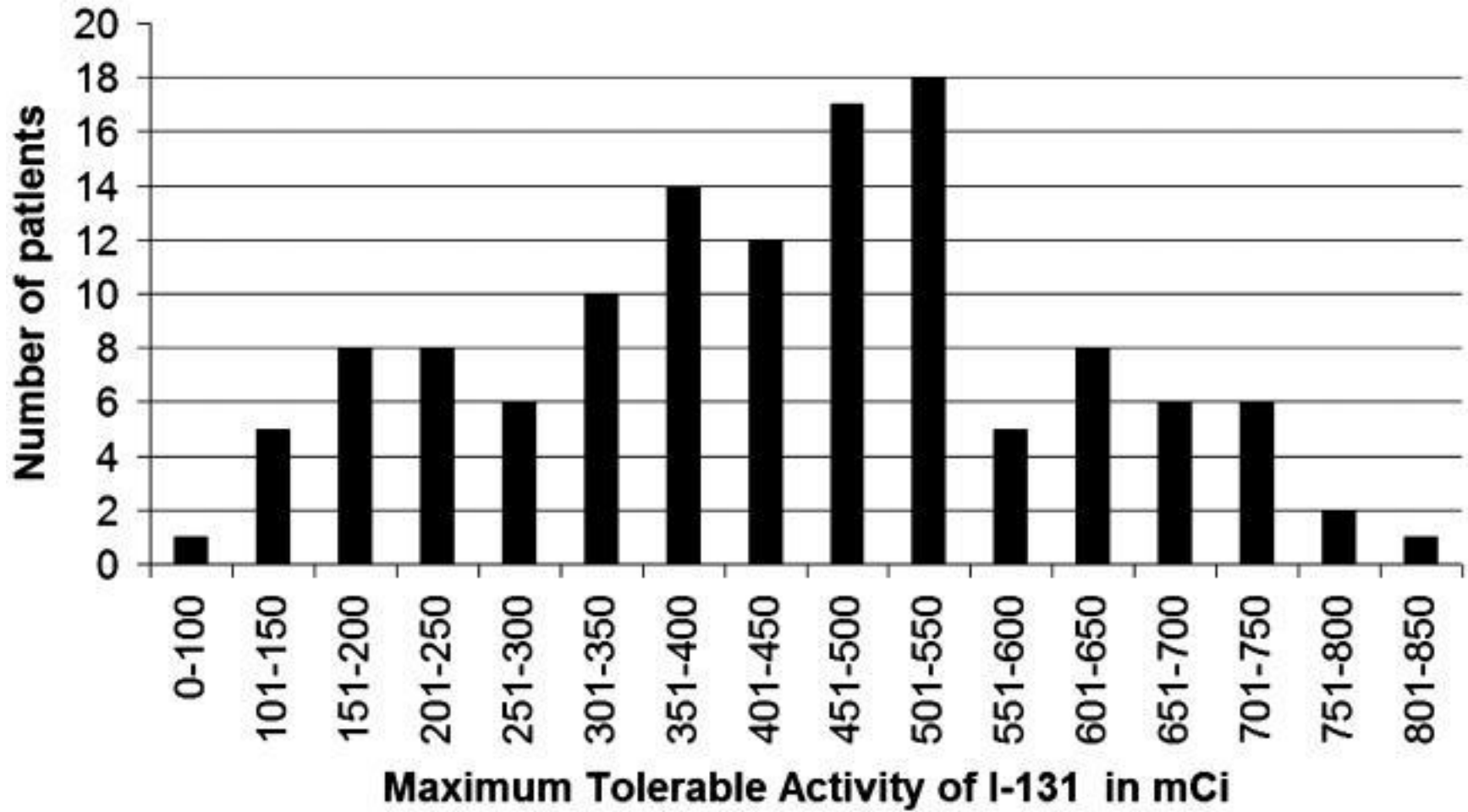
THYROID
Volume 16, Number 10, 2006
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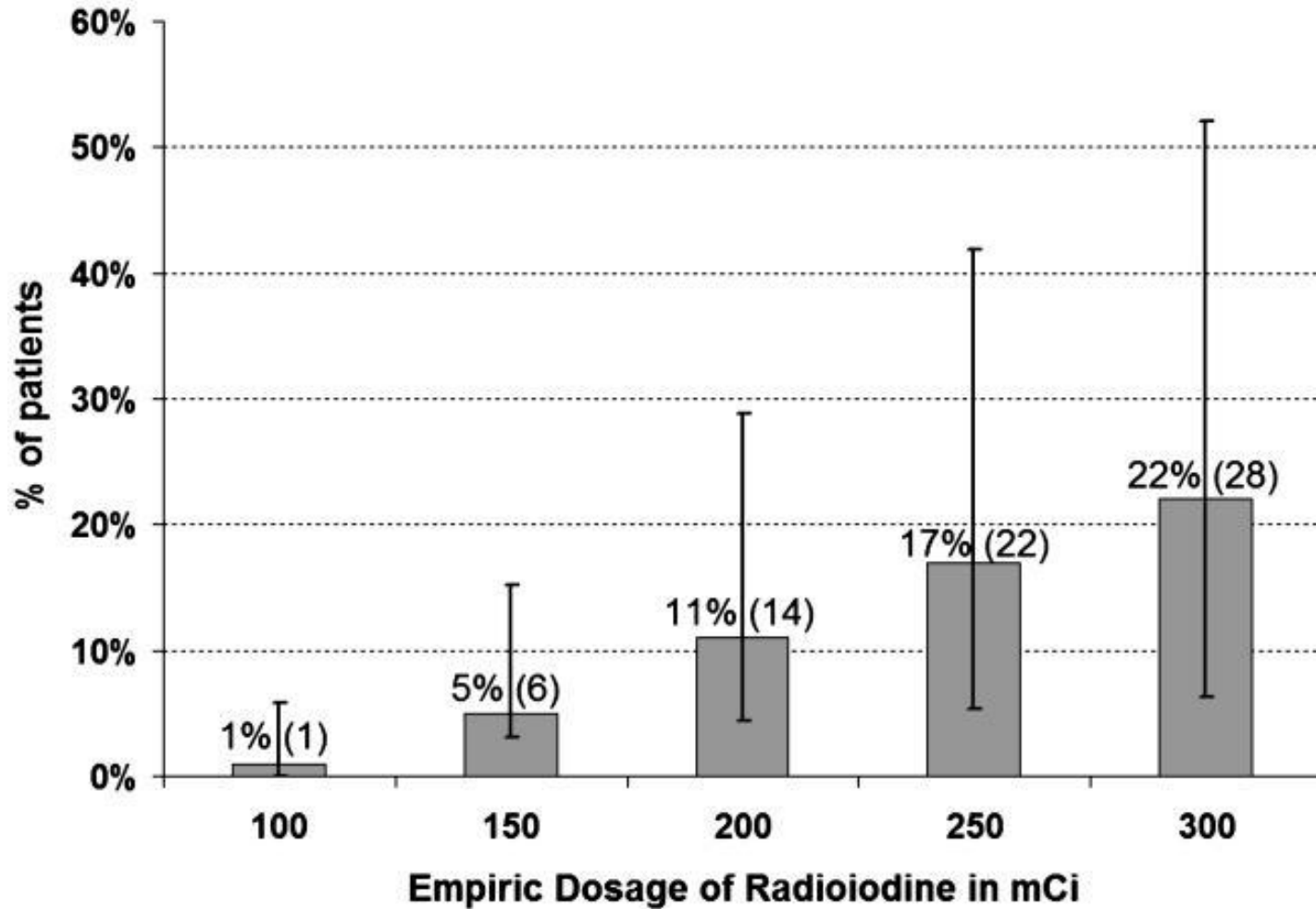
The Relative Frequency in Which Empiric Dosages of Radioiodine Would Potentially Overtreat or Undertreat Patients Who Have Metastatic Well-Differentiated Thyroid Cancer

K. Kulkarni,¹ D. Van Nostrand,¹ F. Atkins,¹ M. Aiken,¹ K. Burman,² and L. Wartofsky²

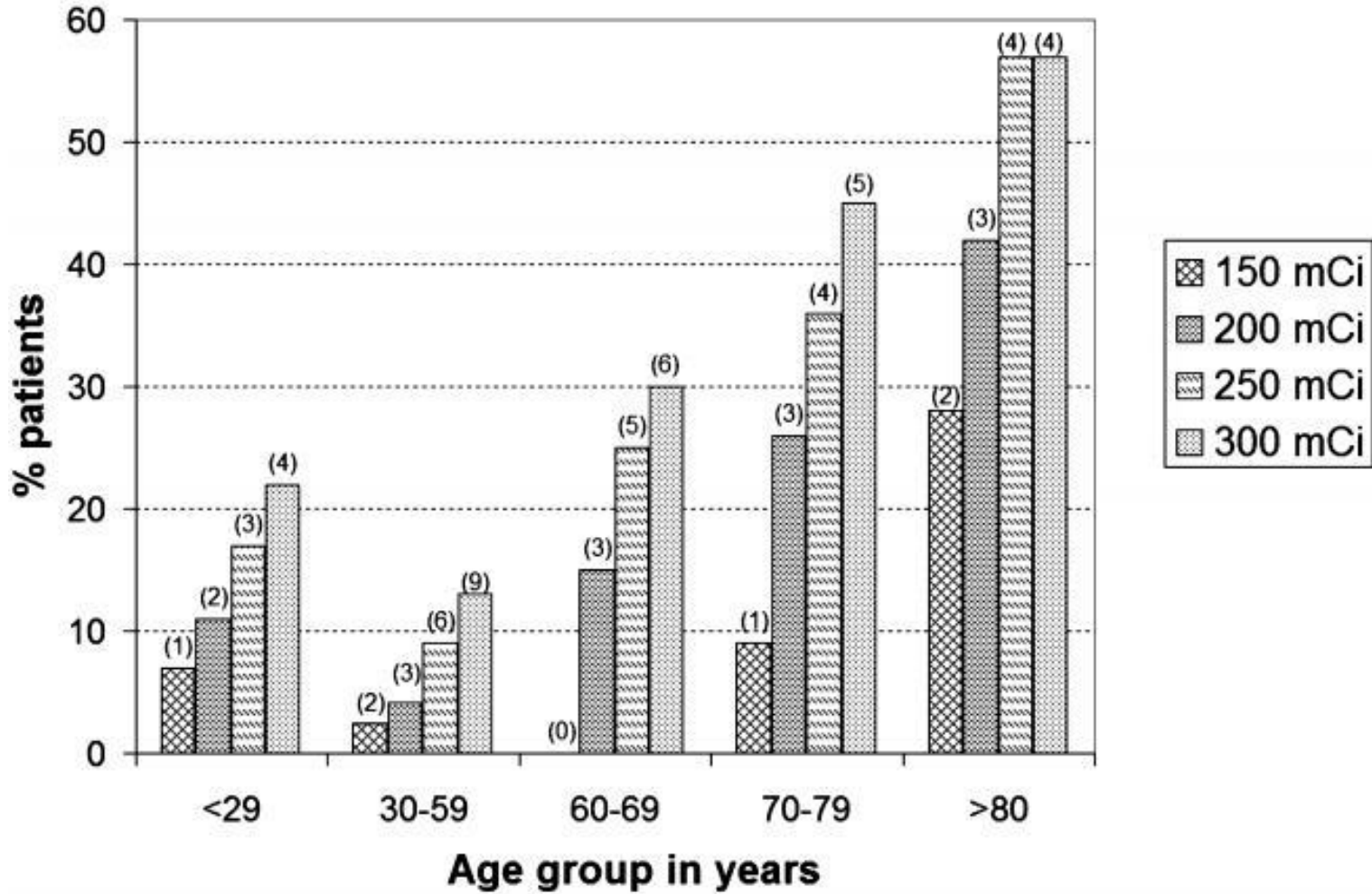
Range of Maximum Tolerated Activity (MTA)



Exceeding MTA



Exceeding MTA- Age adjusted



Empiric Radioactive Iodine Dosing Regimens Frequently Exceed Maximum Tolerated Activity Levels in Elderly Patients with Thyroid Cancer

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- *Another study found that an empirically administered ¹³¹I activity of 200 mCi would exceed the MTRD in 8%–15% of patients younger than age 70 and 22%–38% of patients aged 70 years and older.*
- *Administering 250 mCi empirically would have exceeded the MTRD in 22% of patients younger than 70 and 50% of patients 70 and older.*

■ RECOMMENDATION 73

(A) Although there are theoretical advantages to dosimetric approaches to the treatment of loco-regional or metastatic disease, no recommendation can be made about the superiority of one method of RAI administration over another (empiric high activity versus blood and/or body dosimetry versus lesional dosimetry).

(No recommendation, Insufficient evidence)

(B) Empirically administered amounts of ^{131}I exceeding 150 mCi that often potentially exceed the maximum tolerable tissue dose should be avoided in patients over age 70 years.

(Strong recommendation, Moderate-quality evidence)

RECOMMENDATION 74

There are currently insufficient outcome data to recommend rhTSH-mediated therapy for all patients with distant metastatic disease being treated with ¹³¹I. (No Recommendation, Insufficient evidence)

RECOMMENDATION 75

Recombinant human TSH-mediated therapy may be indicated in selected patients with underlying comorbidities making iatrogenic hypothyroidism potentially risky, in patients with pituitary disease whose serum TSH cannot be raised, or in patients in whom a delay in therapy might be deleterious. Such patients should be given the same or higher activity that would have been given had they been prepared with hypothyroidism or a dosimetrically determined activity. (Strong Recommendation, Low-quality evidence)

How long does thyroid hormone need to be withdrawn in preparation for RAI remnant ablation/treatment or diagnostic scanning?

■ RECOMMENDATION 53

(A) If thyroid hormone withdrawal is planned prior to RAI therapy or diagnostic testing, LT4 should be withdrawn for 3–4 weeks. Liothyronine (LT3) may be substituted for LT4 in the initial weeks if LT4 is withdrawn for 4 or more weeks, and in such circumstances, LT3 should be withdrawn for at least 2 weeks. Serum TSH should be measured prior to radioisotope administration to evaluate the degree of TSH elevation.

(Strong recommendation, Moderate-quality evidence)

(B) A goal TSH of >30 mIU/L has been generally adopted in preparation for RAI therapy or diagnostic testing, but there is uncertainty relating to the optimum TSH level associated with improvement in long-term outcomes.

RECOMMENDATION 57:

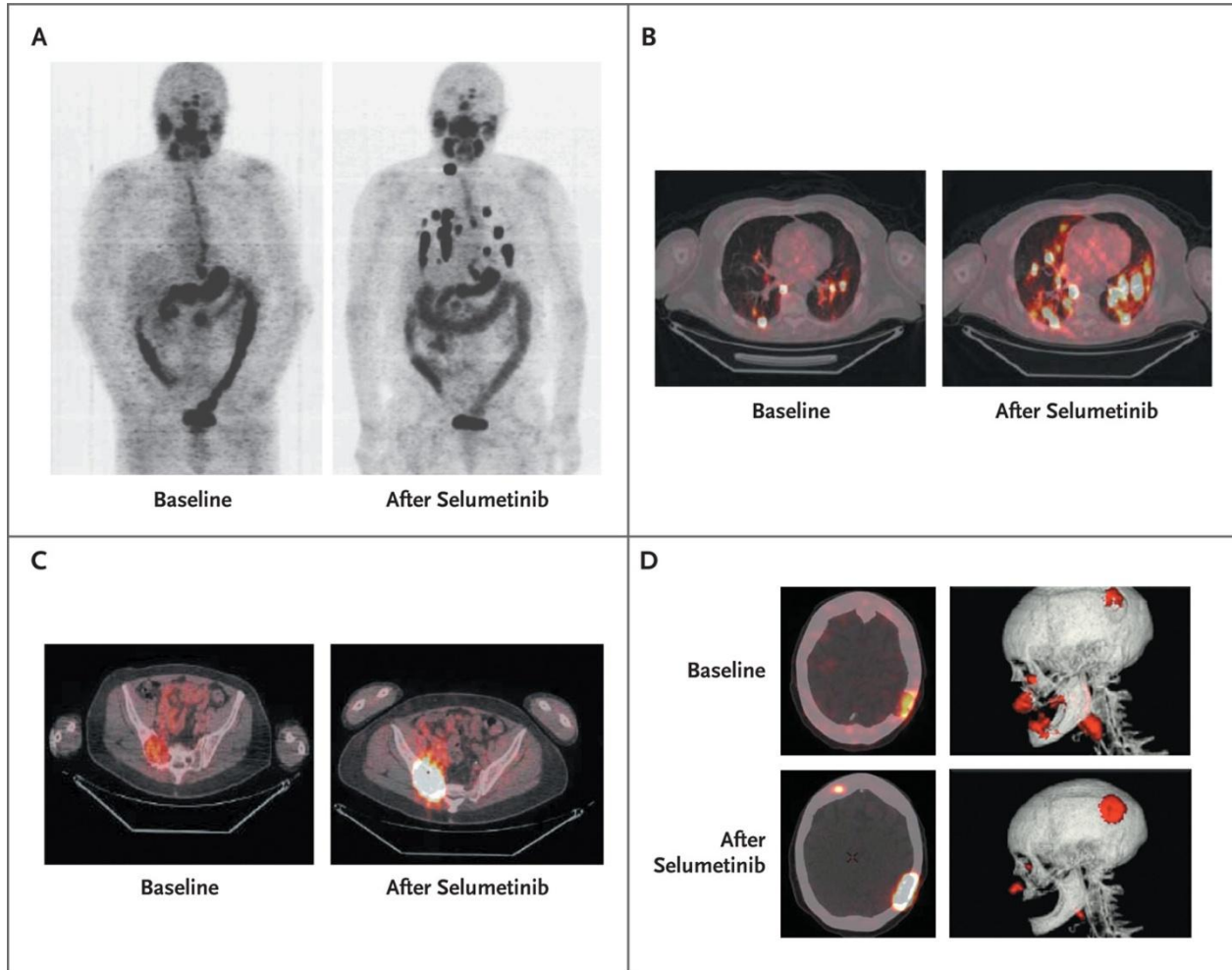
A low iodine diet (LID) for approximately 1–2 weeks should be considered for patients undergoing RAI remnant ablation or treatment.

(Weak recommendation, Low-quality evidence)

RECOMMENDATION 76

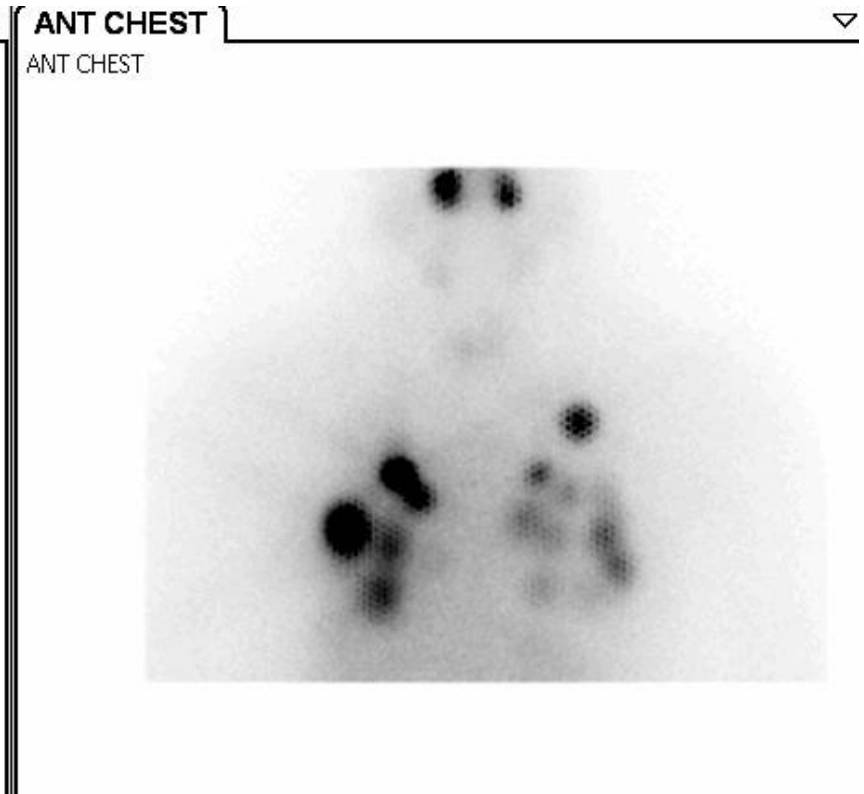
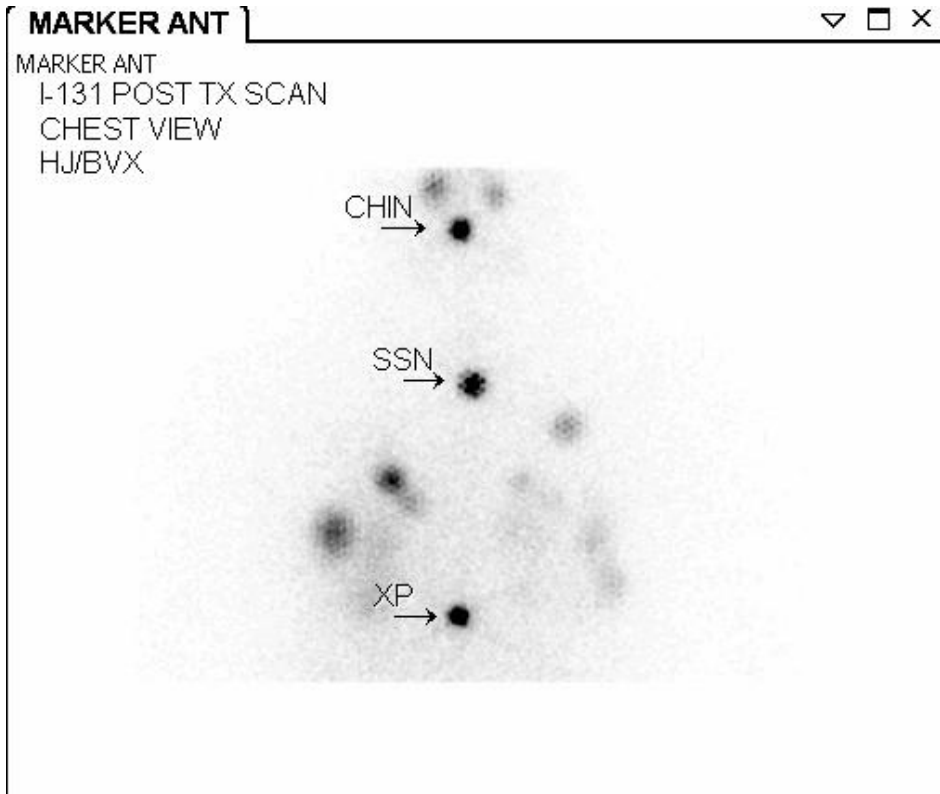
Since there are no outcome data that demonstrate a better outcome of patients treated with lithium as an adjunct to 131I therapy, the data are insufficient to recommend lithium therapy.

MEK Inhibitors

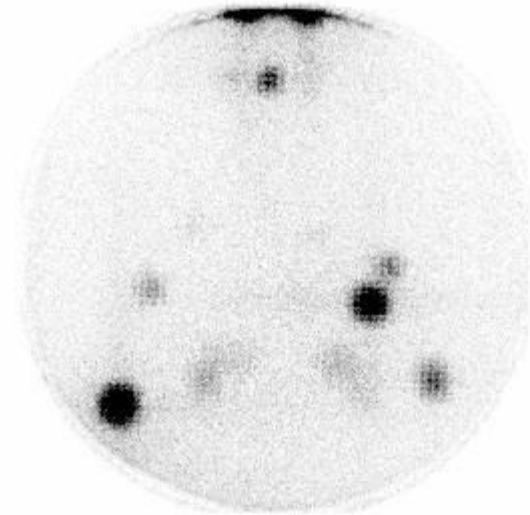


Selumetinib-Enhanced Radioiodine Uptake in Advanced Thyroid Cancer Ho et al. N Engl J Med 2013; 368:623-632

Pulmonary metastases



Pattern of Pulmonary Metastatic Disease



Pulmonary Metastases: Spectrum of Prognosis

	Best	Better	Good	Fair	Poor
RAI scan	Positive Micronodular	Positive Macronodular	Positive Macronodular	Positive Macronodular	Neg
Chest CT	Neg	Pos	Pos	Positive Micronodules	Positive Macronodules
FDG PET	Neg	Neg	Neg	Neg	Positive FDG

RECOMMENDATION 77

(A) Pulmonary **micrometastases** should be treated with RAI therapy and RAI therapy should be repeated every 6–12 months as long as disease continues to concentrate RAI and respond clinically because the highest rates of complete remission are reported in these subgroups.

(Strong recommendation, Moderate-quality evidence)

(B) The selection of RAI activity to administer for pulmonary micrometastases can be empiric (100–200 mCi, or 100–150 mCi for patients ≥ 70 years old) or estimated by dosimetry to limit whole-body retention to 80 mCi at 48 hours and 200 cGy to the bone marrow.

(Strong recommendation, Moderate-quality evidence)

RECOMMENDATION 78

- Radioiodine-avid **macronodular** metastases may be treated with RAI and treatment may be repeated when objective benefit is demonstrated (decrease in the size of the lesions, decreasing Tg), but complete remission is not common and survival remains poor.
- The selection of RAI activity to administer can be made empirically (100–200 mCi) or by lesional dosimetry or whole-body dosimetry if available in order to limit whole-body retention to 80 mCi at 48 hours and 200 cGy to the bone marrow.

(Weak recommendation, Low-quality evidence)

Pulmonary Metastases: Factors

- **Size** of metastatic lesions (macronodular typically detected by chest radiography, micronodular typically detected by CT, lesions beneath the resolution of CT)
- **Avidity for RAI** and, if applicable, **response** to prior RAI therapy
- **Stability** of metastatic lesions
- Pulmonary pneumonitis and fibrosis are rare **complications** of high-dose RAI treatment. Pulmonary function testing and consultation should be obtained.

Pulmonary Metastases: Other considerations

- The risks of **bone marrow suppression or pulmonary fibrosis** should generate caution when repeated doses of RAI are being considered.
- Absolute neutrophil count and platelet counts are the usual markers of bone marrow suppression, and pulmonary function testing including diffusing capacity of the lungs for carbon monoxide can be markers of pulmonary toxicity.
- **Other approaches should be considered** once maximal cumulative tolerable radiation doses have been administered.

Patients with **solitary pulmonary** DTC metastases may be considered for surgical resection, although the potential benefit weighed against the risk of surgery is unclear.

SBRT, IMRT, RFA

- Progression in a single lesion in patients with otherwise controlled disease during systemic treatment.
- In cases of lung metastases associated with
 1. insufficient respiratory reserve,
 2. poor patient clinical status, or
 3. after multiple previous surgical resections,
 4. local recurrence at the site of previous surgery, or
 5. refusal of additional surgery

- *Selective treatment*
- *Minimally invasive*
- *Well tolerated*
- In improving symptoms such as pain,
- In delaying the initiation of systemic treatments,
- In improving survival,
- These techniques can be a less aggressive alternative to surgery

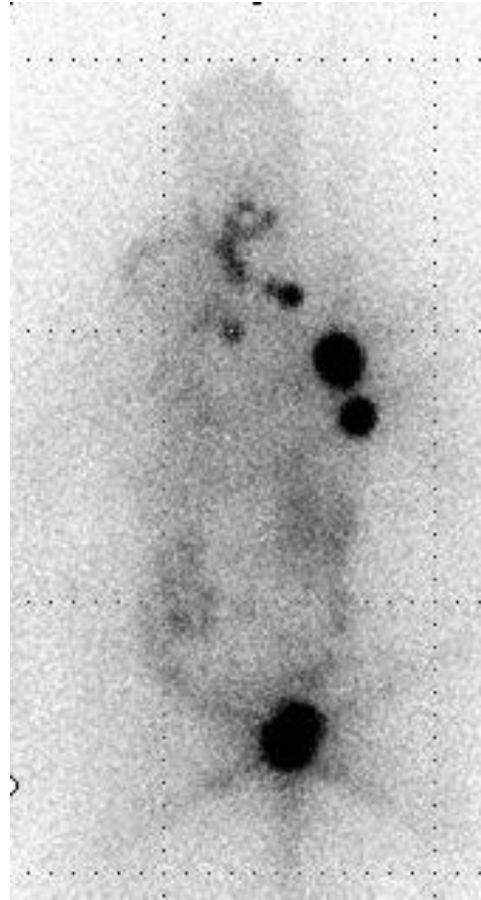
Directed therapy : Limitations

- Selection - *lesions < 3 cm without mediastinal and vascular invasion*
- Experience- *extrapolation from non thyroid cancers*
- Complications –*low and not life threatening*

must be individualized based on the

- Pattern of metastatic disease
- Response to treatment,
- RAI avidity,
- Age of the patient,
- Presence or absence of other metastatic lesions,
- Presence of significant side effects including complications: Bone marrow suppression and salivary gland damage ,risk of second malignancies after RAI treatment , *etc*

Bone metastases



- Improve the patient's quality of life by reducing pain
- Prolonging time to skeletal events,
- Delaying initiation of systemic treatment,
- Improving patient survival

- Rarely curative,
- Dosimetry
- **Directed therapy** of bone metastases that are visible on anatomical imaging - *surgery, external beam radiation therapy, and other focal treatment modalities.*
- Systemic therapy with bone-directed agents.

- RAI therapy of iodine-avid bone metastases has been associated with improved survival and should be employed, although RAI is rarely curative.
(Strong recommendation, Moderate-quality evidence)
- The RAI activity administered can be given empirically (100–200 mCi) or determined by dosimetry.
(Weak recommendation, Low-quality evidence)

RECOMMENDATION 93

- Both stereotactic radiation and thermal ablation (RFA and cryoablation) show a high efficacy in treating individual distant metastases with relatively few side effects and may be considered as valid alternatives to surgery.

(Weak recommendation, Moderate-quality evidence)

- Stereotactic radiation or thermal ablation should be considered prior to initiation of systemic treatment when the individual distant metastases are symptomatic or at high risk of local complications.

(Strong recommendation, Moderate-quality evidence)

Therapies:

- **Surgery**
- **Thermal ablations, Cement injections, SBRT, or IMRT** are the most frequently used techniques
- **Bisphosphonates** (especially zoledronic acid) and the
- **Ligand-directed agent denosumab**

Actions

- **To delay time to occurrence of subsequent skeletal-related adverse events** (fracture, pain, neurologic complications) and
- **To improve symptoms** of bone metastases .

I. Percutaneous thermal ablation is aimed at destroying tumor

- increasing (**RFA**) or
- decreasing (**cryoablation**) temperatures sufficiently to induce irreversible cellular damages.

II. RFA or cryoablation of bone lesions showed promising results with rapid (1–7 days) and long-lasting pain control

III. The association of **cryoablation and cementoplasty** seems promising in purely lytic bone metastases from thyroid cancer.

Role:

- Complement surgery in case of incomplete resection or be used alone
- Pain relief or palliation.

Major Limitation:

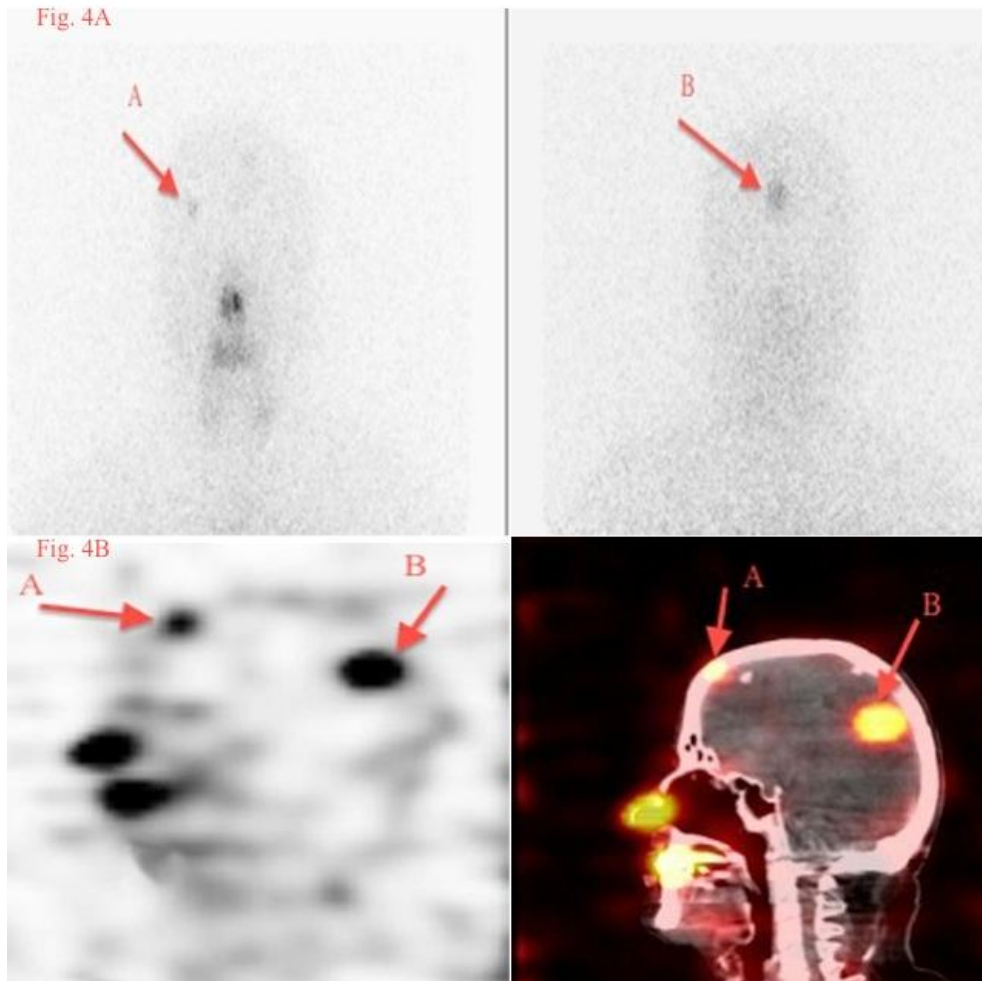
Radiotherapy of spine lesions due to the cumulative dose to the spinal cord.

Skeletal metastases that are painful or are a threat to life or function may, in addition to being treated with ^{131}I , be treated with **bone-seeking b-emitting radiopharmaceuticals (e.g., ^{89}Sr or ^{153}Sm -lexidronam)** if the bone scan is positive at the painful site, although these carry a greater risk of myelosuppression than ^{131}I , external radiotherapy, or surgery.

Multidisciplinary treatment for bone metastases

Combination of **surgery** with directed local therapy
(including, for example, **thermal ablation** (RFA or cryoablation)
and/or cementoplasty associated with systemic treatment
(**RAI, bone-directed agents, or chemotherapy**).

Brain Metastases



- While **surgical resection and stereotactic EBRT** are the mainstays of therapy for CNS metastases, RAI can be considered if CNS metastases concentrate RAI.
- If RAI is being considered, stereotactic EBRT and concomitant glucocorticoid therapy are recommended prior to RAI therapy to minimize the effects of a potential TSH-induced increase in tumor size and RAI-induced inflammatory response.
(Weak recommendation, Low-quality evidence)

- **MRI of the brain** and spine is recommended to detect the presence of critical metastases prior to treatment.
- When metastases are detected, institution of temporary **high-dose corticosteroid** therapy is recommended for trying to limit the risk of acute tumor swelling and compromised function.
- **Regimen:** Dexamethasone has been employed in doses of 2–4 mg every 8 hours starting 6–12 hours prior to rhTSH and RAI dosing or after 10–12 days of thyroid hormone withdrawal, with the steroids continued in a tapering dosage schedule for 1 week post therapy, for 48–72 hours after rhTSH administration, or for 72 hours after re-institution of thyroxine therapy when thyroid hormone withdrawal was employed.

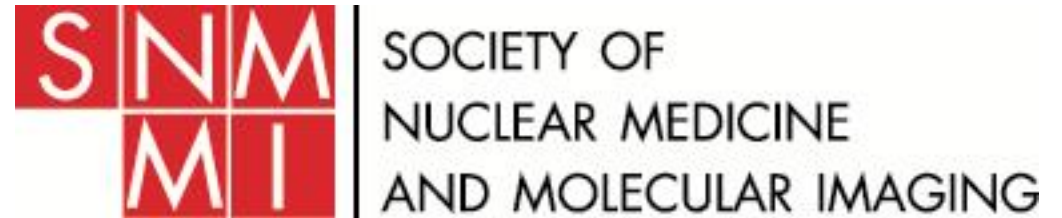
- In patients with these critical metastases, consideration should be given to preparation with either a **reduced dose of rhTSH** or to attenuating the degree and duration of endogenous TSH elevation after thyroid hormone withdrawal while monitoring serum TSH levels. This can be achieved by the temporary addition of LT3 therapy to thyroxine replacement.
- Satisfactory RAI treatment **with either empiric or dosimetric activities** should be feasible after achieving TSH levels of 30–50 mU/L.
- When thyroid hormone withdrawal has been employed, LT4 therapy should **recommence** once the dose of RAI is administered in order to reduce the duration of TSH elevation

- **SBRT** : high radiation doses in few fractions to the target tumoral lesion with a high degree of precision, minimizing the radiation of normal surrounding tissue.
- Indication: For patients with few (one to three) brain metastases,
- Efficacy: SBRT is as effective as surgery and repeatable
- Complications: Well tolerated, and brain necrosis that occurred in less than 10% of cases is usually limited and had no clinical consequences.

- **Corticosteroids** to prevent swelling may be required if central nervous system metastases are to be irradiated.
- The **use of external beam radiation beforehand, or alternating with 131I treatment**, has not been documented to be associated with a subsequent reduction in tumor uptake of radioactive iodine. Therefore, external-beam radiation, if clinically and emergently indicated, need not be delayed. The toxicity, acute and late, is likely to be additive within the field of irradiation.
- **Dosimetry calculations** are especially important if 131I therapy and external-beam radiotherapy are both being considered, or have previously been performed in patients with spinal metastases, to avoid potential radiation-induced spinal cord damage. A treatment planning method for combination external-beam therapy with radiopharmaceutical therapy is available .

- Surgery and
- External Radiation
- Systemic: RAI can alternate

- RAI avidity
- Response
- Side effects
- CBC, Chem profile, renal function, PFTS
- Dosimetry
- Counselling –pregnancy,side effects, prognosis
- Adeqaute preparation
- Patient desires...



Happy Birthday RAI!

Mar 31, 2018 — On this day in 1941, Dr. Saul Hertz administered the very first radioactive iodine therapy to a patient with Graves' Disease. This pivotal treatment was the index case for what we today know as radioactive iodine therapy for hyperthyroidism, and it validated the concept that is now known as theranostics.

Thank you

MAKE I-131 GREAT AGAIN !