

Initial Staging and Management of Medullary Thyroid Carcinoma

Monitoring and Adjuvant Standard Treatment Options

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Disclosures

None relevant to this presentation

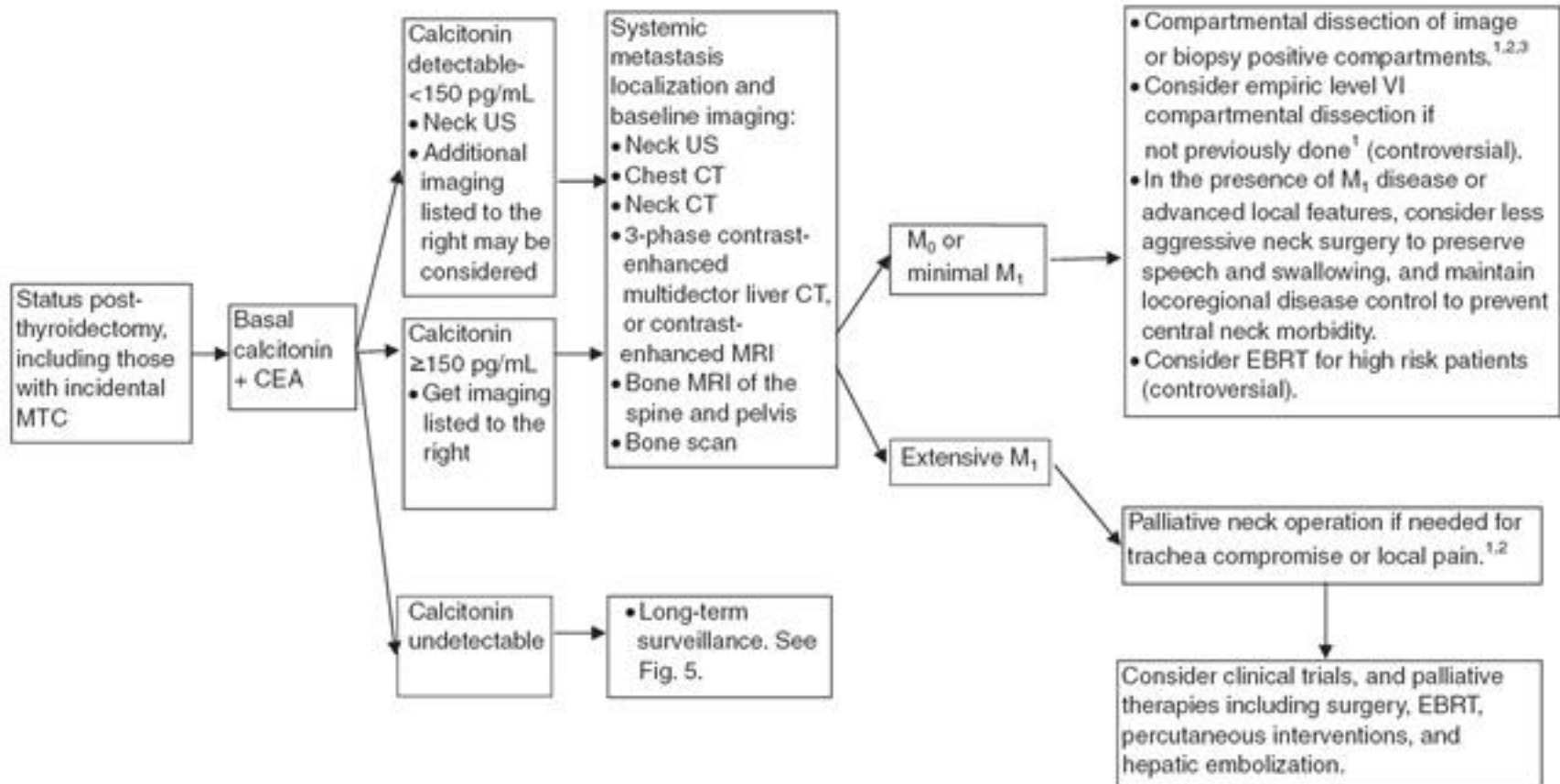
55 year old male

- Age 40
 - Felt a right neck lump; FNA “tumor cells”; Calcitonin 30 pg/mL (<8); CEA 302.8 ng/mL (<3); Tg 38 ng/mL.
 - Total Tx with bilateral Level VI dissection: 2.6 cm MTC right lobe, no ETE, bilateral C-cell hyperplasia; 0.5 cm FV Papillary Ca; 0/7 right VI+, 0/7 left VI+, 0/1 paratracheal LN+ (Stage II [pT2,pN0,Mx]).
FHx – for MEN, FMTC, HPT, Pheo; RET – no mutations
 - 1.5 months post-op CT <1 pg/mL, CEA 39 ng/mL
 - 2 months post-op CEA 17.7 ng/mL, Tg 0.9 ng/mL
 - 3 months post-op CT <1pg/mL, CEA 5.5 ng/mL;urine fractionated metanephrines, catecholamines, VMA nl
 - 6 months post-op calcium stim test – all CT values <1 pg/mL
- Followed by primary care physician

Questions

- How should he be followed?
- How often do patients with negative central compartment LN and post-op undetectable CT experience persistent/recurrent disease?

Kloos et al. Medullary Thyroid Cancer: Management Guidelines of the American thyroid Association. Thyroid 19:565, 2009



¹Parathyroid glands resected or devascularized should be autografted in the neck in *RET*-negative, MEN 2B, and FMTC patients, while MEN 2A glands should be autografted to a heterotopic site.

²Consider external beam radiation of T₄ disease to prevent recurrent local disease.

³Observation of nonthreatening locoregional disease <1 cm may be considered.

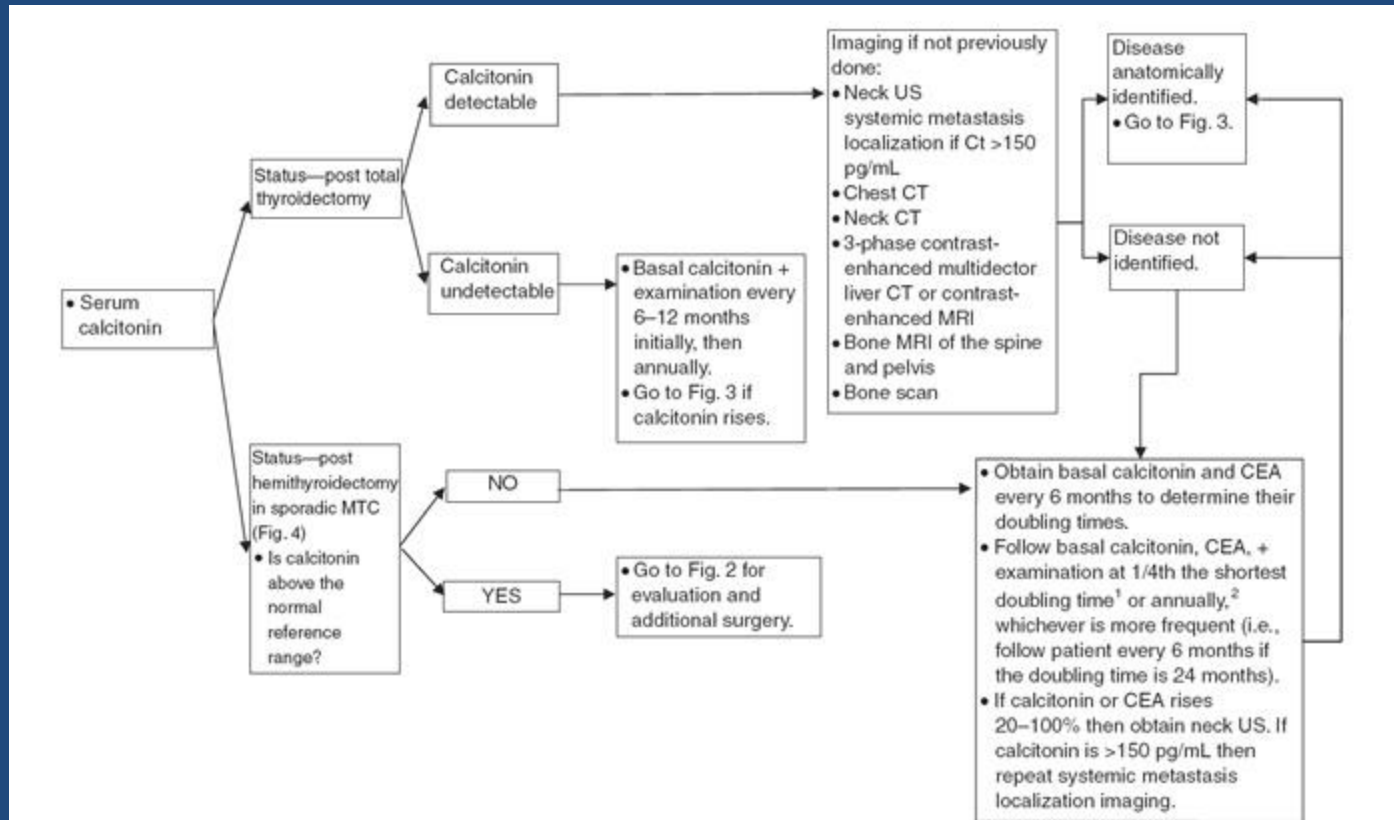
FIG. 3. Initial evaluation and treatment of postoperative patients.

How often do patients with negative central compartment LN and post-op undetectable CT experience persistent/recurrent disease?

- Patients with 0+, 1-3+, 4 or more + Level VI LN have: **10.1, 77, 98%** ipsilateral lateral LN metastases
- With 0+,1-9+, 10 or more + Level VI LN, there were **4.9, 38, 77%** contralateral lateral LN metastases
Machens et al Br J Surg 95:586, 2008
- When both basal and stimulated serum calcitonin level is undetectable (biochemical remission)
 - **3.3%** chance of recurrent disease during follow-up at an average of 3.2 years (range 0.7-7.5) after surgery
Franc et al. Clin Endocrinol 55:403, 2001

- Age 44
 - CT 14.4 pg/mL (repeat 12 pg/mL), CEA 0.7 ng/mL
 - Neck ultz, neck + chest CT -; Octreotide scan-low level activity in mid neck (?post surgical vs residual disease)
 - Right functional neck dissection of levels II, III, IV and part of V: 0/32 nodes +
 - 10 days post-op CT 16 pg/mL
- Age 45
 - Left functional neck dissection of levels II, III, IV: 0/21 nodes +
 - 4 months post-op CT 28 pg/mL
- Ages 46-53
 - CT rose from 49 pg/mL to 384 ng/mL (DT=1.9 years)
 - CEA rose from 1.7 ng/mL to 6.7 ng/mL (DT=1.9 years)
 - 14 Ultz; 4 neck MRI; 4 Chest MRI; 3 Abd MRI; 5 chest CT; 4 neck CT; 2 octreotide scans; 4 FDG-PET scans; 1 bone scan; 1 ¹⁸F-DOPA PET scan; and 4 ULTZ guided FNA of nodes—ALL NEG

Kloos et al. Medullary Thyroid Cancer: Management Guidelines of the American Thyroid Association. Thyroid 19:565, 2009



¹Doubling time may be estimated or optimally calculated by fitting data to single exponentials by nonlinear least-square analysis (calculator available at www.thyroid.org).

²Patients with *RET* mutations associated with PHEO or primary hyperparathyroidism should be screened annually beginning at age 8 years in MEN 2B and mutated *RET* codons 634 and 630, and from age 20 years in carriers of other MEN 2A *RET* mutations, while those associated only with FMTC should be screened at least periodically.

FIG. 5. Long-Term surveillance.

Imaging Studies in Patients with Persistent Hypercalcitoninemia

Approximate % + Detection From Multiple Studies

- ^{18}F -DOPA-PET* 73%
- MRI/CT 60%
- ^{18}F -FDG-PET 59%
- SSR-scintigraphy** 40%
- DMSA-V scan*** 26%
- ^{131}I -MIBI scan**** 7.5%

* ^{18}F -dihydroxyphenylalanine PET; **somatostatin receptor scintigraphy; ***V-di-mercaptosuccinic acid scintigraphy; **** ^{131}I -metaiodobenzylguanidine

(Baudin 1996;Hoegerle 2001;Szakall 2002;Mirallie 2005;Ong 2007;Rubello 2008;Beheshti 2009;Marzola 2010)

Regional Sensitivity of Imaging Modalities

Giraudet et al. JCEM 92:4185, 2007

Prospective Study; N=55; 82% disease found, 18% none found

	<u>Neck</u>	<u>Mediastinum</u>	<u>Lung</u>	<u>Liver</u>	<u>Bone</u>
Disease Present	58%	31%	35%	61%	45%
Ultrasound	93%	--- ---	85%	---	
CT	70%	100%	100%	90%	---
¹⁸F-FDG-PET	55%	65%	42%	55%	76%
MRI	---	--- ---	100%	88%	
Bone Scan	---	---	---	---	88%

Most Effective Work-Up:

- Neck Ultrasound
- Chest CT
- Liver MRI
- Bone Scan or Axial skeletal MRI

¹⁸F-FDG-PET – low sensitivity and low prognostic value (better for DT<12 months, calcitonin >1000)

- Age 54
 - Ultz showed a right thyroid bed lesion and some right level III abnormal lymph nodes
 - FNA of thyroid bed lesion + for MTC and needle washout CT 84,400 pg/mL
 - Right level II, III, IV and VI reoperation: right thyroid bed nodule was MTC invading skeletal muscle, 2/16 nodes + for MTC
 - 4 months post-op CT 173 pg/mL

Questions

- What is his prognosis?
- How should he be managed?
- How should localized disease in general be managed?

Prognostic Factors for CSS

- Age
 - <40 y, 5 & 10y DSS 95 and 75%
 - >40 y, 5 & 10y DSS 65 and 50%
 - But age may not be a factor when adjusted for age-specific mortality as older people die earlier
- MEN 2B or exon 16 mutation in sporadic tumors
- Surgical pathology
 - Extra Thyroidal Extension
 - Stage
 - Paucity of calcitonin immunostaining of tumor cells
- Calcitonin Doubling Time <2 years
- Rapidly ↑CEA with stable calcitonin

Saad, Medicine 63:319,1984; Kebebew, Cancer 88:1139,2000; O’Riordain, Surgery 116:1017,1994; Lippman JCEM 54:233,1982; Romei, JCEM 81:1619,1996; Kouvaraki Thyroid 15:531,2005; deGroot, Clin Endo65:729, 2006; Clarke, Laryngoscope 115:1445, 2005.

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CALCITONIN AND CARCINOEMBRYONIC ANTIGEN (CEA) DOUBLING TIME CALCULATOR



Please note: Due to HIPAA regulations, the information entered into the calculator is not retained by the ATA system. Once you exit the calculator page, any calculated data and results will no longer be available. However, you may enter a non-HIPAA patient identifier and print the calculator results to maintain for your record-keeping purposes.

The monitoring of calcitonin levels play an important role in the follow-up and management of patients with medullary thyroid cancer. Calcitonin doubling times of > 2 years seem to be associated with a better long term prognosis than those < 6 months. The calculator is intended for use by healthcare providers as appropriate medical training and clinical experience is required for interpretation of the results and application to care of individual patients. Providers are referred to the recently published ATA Guidelines on Medullary Thyroid Cancer.

Based on available data, it is recommended to use a minimum of 4 calcitonin values preferably spread over a 2 year period. For a valid result, it is essential that all the calcitonin results have been obtained from the same laboratory and assay.

(One record per line. The two tables should have equal number of records.)

(One record per line. The two tables should have equal number of records.)

Patient Reference

Date of Test

(mm/dd/yyyy)

Calcitonin

(must be number)

CEA

(must be number)

Print

Calculate

Days:

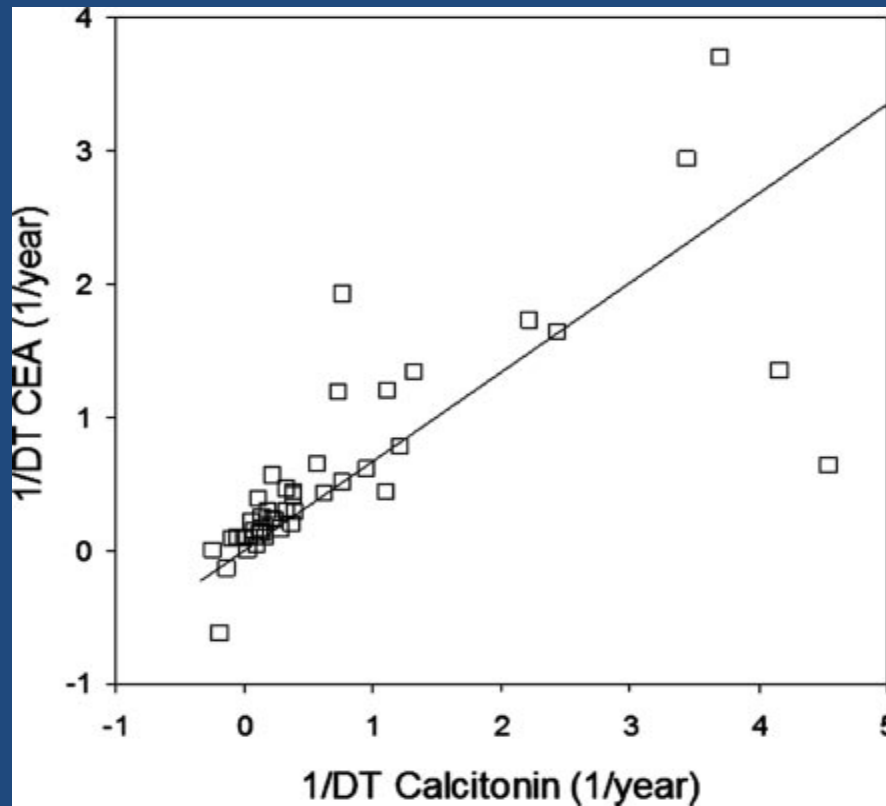
Months:

Years:

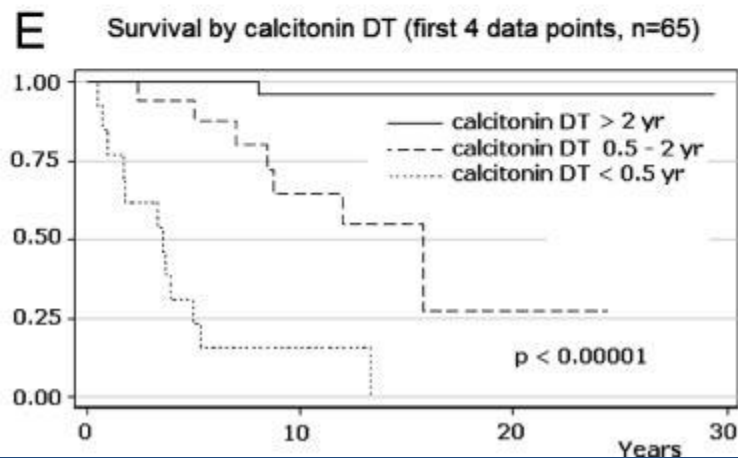
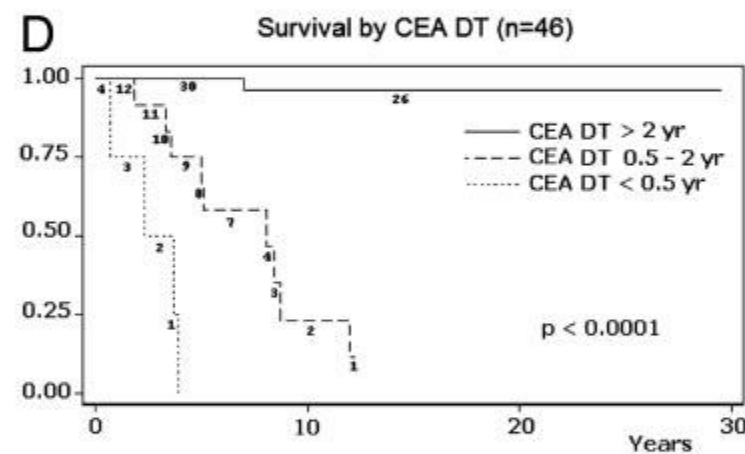
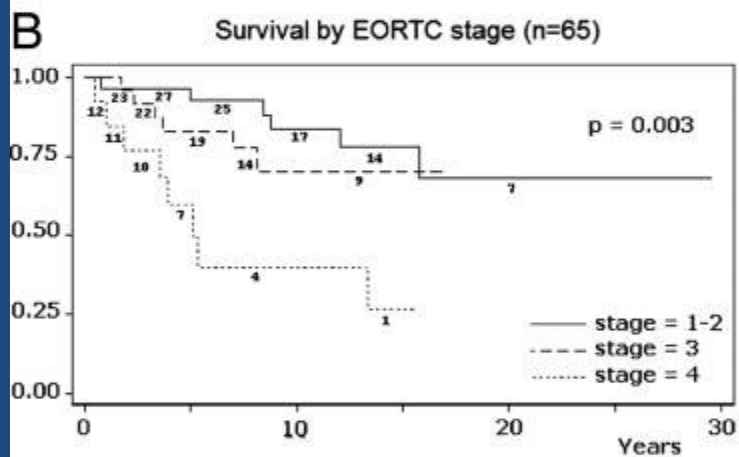
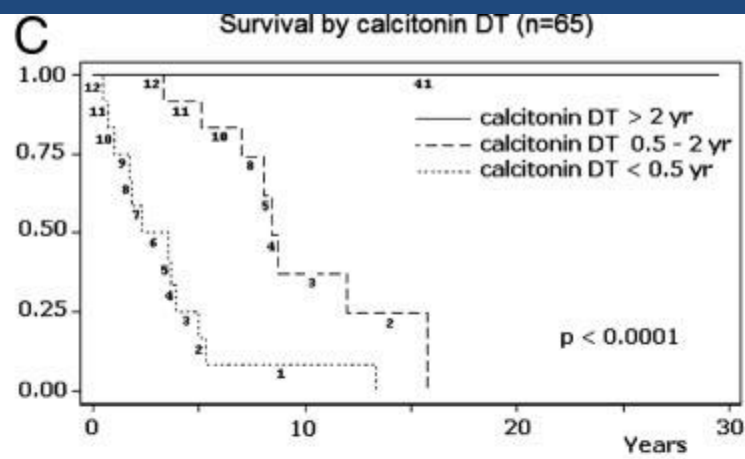
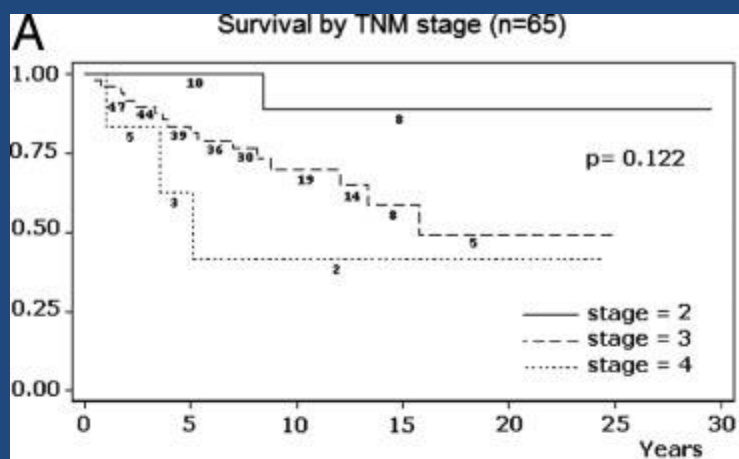
<http://www.thyroid.org/thyroid-physicians-professionals/calculators/thyroid-cancer-carcinoma/>

Relationship Between CT DT and CEA DT

Barbet et al. JCEM 90:6077, 2005



Barbet et al.
JCEM
90:6077, 2005



Calcitonin DT and 3-year Survival

Miyauchi et al. Ann Surg 199:461, 1984

T2 (year)	Number of Survivors	Number of Deaths	Total
<0.5	0	5	5
>0.5	13	0	13
Total	13	5	18

$\chi^2 = 13.360; p < 0.001.$

How should he be managed?

Goals of Treatment (ATA Guidelines)

- Provide Locoregional control
- Palliate symptoms of hormonal excess (e.g. flushing, diarrhea, ectopic ACTH)
- Palliate symptomatic distant metastases
- Control distant metastases that threaten to cause harm

How should localized disease in general be managed?

- Small volume disease with DT>2 years: may observe
- Neck disease only
 - Repeat surgery: ~10-25% cured
 - EBRT (only after optimal surgery has failed; for gross ETE, +margins, nodal disease esp. ENE): no survival benefit; may provide locoregional control
 - Ethanol injection or radiofrequency ablation: limited information
- Brain metastases: Surgery; EBRT

How should localized disease in general be managed?(Contd)

- Bone metastases
 - Surgery for weight bearing areas with fracture or impending fracture
 - Palliative resection
 - Radiofrequency ablation, cryosurgery, arterial embolization, EBRT: limited data for MTC; may control bone pain
 - IV bisphosphonates (zoledronic acid, pamidronate) or SubQ denosumab: data based on other solid tumor experience

How should localized disease in general be managed? (Contd)

- Paraneoplastic symptoms
 - Diarrhea
 - Antimotility agents (loperamide or codeine)
 - Somatostatin analogues: \pm response
 - Somatostatin analogues with interferon α (Vitale et al, JCEM 85:983, 2000 – 5/6 patients improved)
 - Hepatic surgery or chemoembolization: \pm response
 - Ectopic ACTH
 - Debulking liver metastases
 - Medical therapy (ketoconazole, mifepristone, aminoglutethamide, metyrapone, mitotane)
 - Adrenalectomy

References in Kloos et al. Medullary Thyroid Cancer: management guidelines of the American Thyroid Association. Thyroid 19:565, 2009.