



Management of Thyroid Anaplastic Carcinoma

ATC: External Radiation Therapy and Systemic Therapy

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Roma, 9-12 novembre 2017

Conflitti di interesse



ITALIAN CHAPTER



Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- Bayer Healthcare advisory board



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ATC: External Radiation Therapy and Systemic Therapy



ITALIAN CHAPTER



- Introduction
- Multidisciplinary team
- NCCN Guidelines
- Adjuvant Radiotherapy and Chemotherapy
- Neoadjuvant Radiotherapy and Systemic Therapy
- IMRT
- Role of Systemic Therapy combined with Radiation Therapy
- Clinic Cases
- NATURE - Multicentric Prospective Study of Radiotherapy
- Take At Home Messages



Introduction



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- **Anaplastic thyroid carcinoma is one of the most aggressive malignancies of the head and neck;**
- **Although rare (only 1-2% of thyroid cancers) it is related to 40% of all thyroid cancer-related deaths with a median survival from 3 months to 10 months;**
- **For this reason treatment is generally multimodal;**
- **In resectable patients surgery is the first option, but complete surgical resection is rarely feasible so radiation therapy with concurrent chemotherapy is considered;**



Introduction



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- One of the most important thing is to induce **local tumor control** in order to prevent airway obstruction, severe dysphagia and death caused by local tumor burden.
- All Anaplastic Thyroid Carcinoma are **stage IV**.
 - **IVA** lesions are intrathyroidal, N0, M0
 - **IVB** the primary tumor has gross extrathyroidal extension, any N, M0.
 - **IVC** patients have distant metastases.



Multidisciplinary Team



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- **Composition:**
 - Endocrinologist,
 - ENT,
 - Surgeon,
 - Pathologist,
 - Radiologist,
 - Nuclear physician,
 - Radiotherapist,
 - Oncologist,
 - I.P. Case manager
- **Personalized care path**

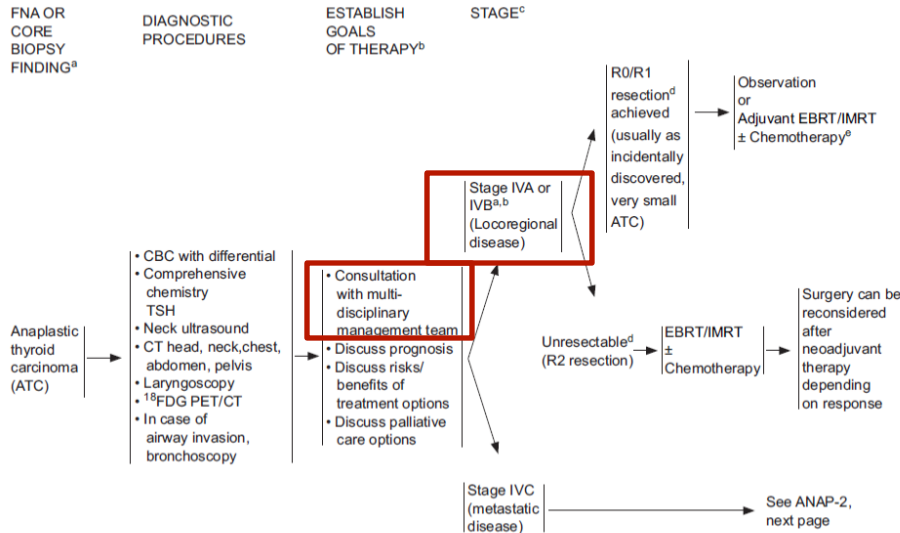


NCCN :treatment STAGE IV A or IV B



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Stage IVA or IVB: When it is possible, surgery is always the first option

When the cancer is unresectable (or R2 resection), surgery can be reconsidered after neoadjuvant therapy

^aConsider core or open biopsy if FNA is "suspicious" for ATC or is not definitive. Morphologic diagnosis combined with immunohistochemistry is necessary in order to exclude other entities such as poorly differentiated thyroid cancer, medullary thyroid cancer, squamous cell carcinoma, and lymphoma.

^bPreoperative evaluations need to be completed as quickly as possible and involve integrated decision making in a multidisciplinary team and with the patient. Consider referral to multidisciplinary high-volume center with expertise in treating ATC.

^cSee Staging (ST-1; available online, in these guidelines, at NCCN.org).

^dResectability for locoregional disease depends on extent of involved structures, potential morbidity, and mortality associated with resection. In most cases, there is no indication for a debulking surgery. See Staging (ST-1; available online, in these guidelines, at NCCN.org) for definitions of R0/R1/R2.

^eSee Systemic Therapy for Anaplastic Thyroid Carcinoma (ANAP-A, next page).

NCCN

Anaplastic Thyroid Carcinoma, Version 2.2015

Clinical Practice Guidelines in Oncology

Robert I. Haddad, MD; William M. Lydiatt, MD; Douglas W. Ball, MD; Naifa Lamki Bussidy, MD; David Byrd, MD; Glenda Callender, MD; Paxton Dickson, MD; Quan-Yang Duh, MD; Hormoz Ehyia, MD; Megan Haymart, MD; Carl Hoh, MD; Jason P. Hunt, MD; Andrei Iagaru, MD; Fouad Kandeel, MD, PhD; Peter Kopp, MD; Dominick M. Lamonica, MD; Judith C. McCaffrey, MD; Jeffrey F. Moley, MD; Lee Parks, MD;



NCCN: treatment STAGE IV C



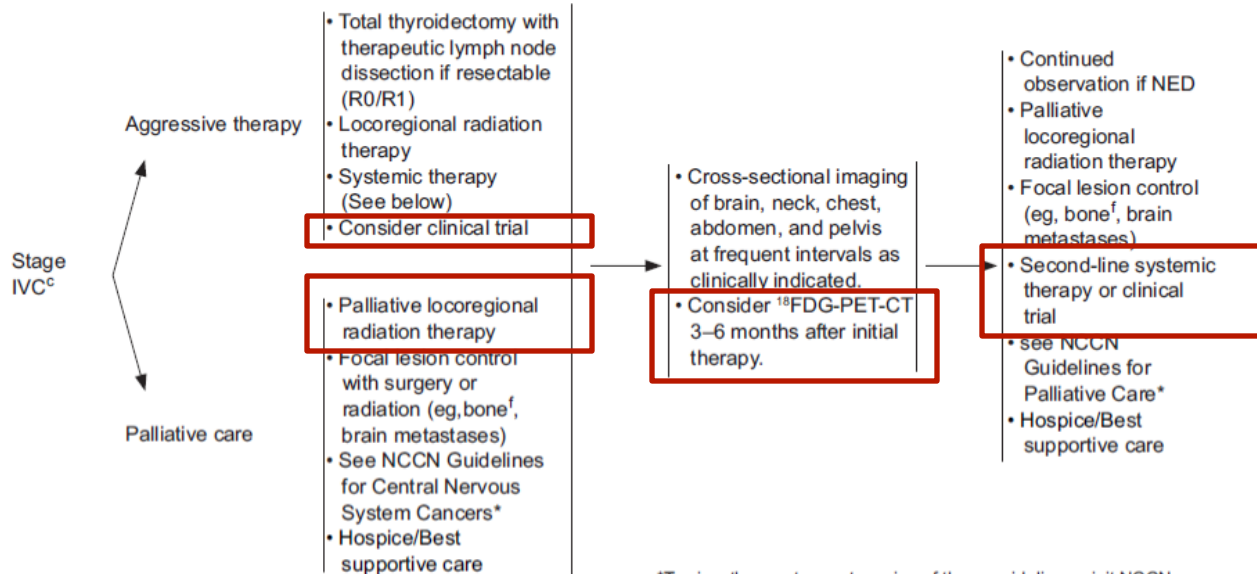
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METASTATIC DISEASE

TREATMENT

SURVEILLANCE AND MANAGEMENT



Consider clinical trial in every phase
Close surveillance

Consider Palliative Care

^cSee Staging (ST-1; available online, in these guidelines, at NCCN.org).

^fConsider use of intravenous bisphosphonates or denosumab. Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.

NCCN

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NCCN guidelines: - Systemic Therapy



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SYSTEMIC THERAPY¹

Regimen	Agents/Dosages	Frequency
Paclitaxel/carboplatin	Paclitaxel 60–100 mg/m ² , carboplatin AUC 2 mg/m ² IV	Weekly
Paclitaxel/carboplatin	Paclitaxel 135–175 mg/m ² , carboplatin AUC 5–6 mg/m ² IV	Every 3–4 weeks
Docetaxel/doxorubicin	Docetaxel 60 mg/m ² IV, doxorubicin 60 mg/m ² IV (with pegfilgrastim)	Every 3–4 weeks
	or Docetaxel 20 mg/m ² IV, doxorubicin 20 mg/m ² IV	Weekly
Paclitaxel	60–90 mg/m ² IV	Weekly
Paclitaxel	135–200 mg/m ² IV	Every 3–4 weeks
Doxorubicin	60–75 mg/m ² IV	Every 3 weeks
Doxorubicin	20 mg/m ² IV	Weekly

NCCN

Anaplastic Thyroid Carcinoma, Version 2.2015

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¹Reprinted with permission from Mary Ann Liebert, Inc., Smallridge RC, et al. American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer. Thyroid 2012;22:1124.



ATA: Adjuvant Therapy

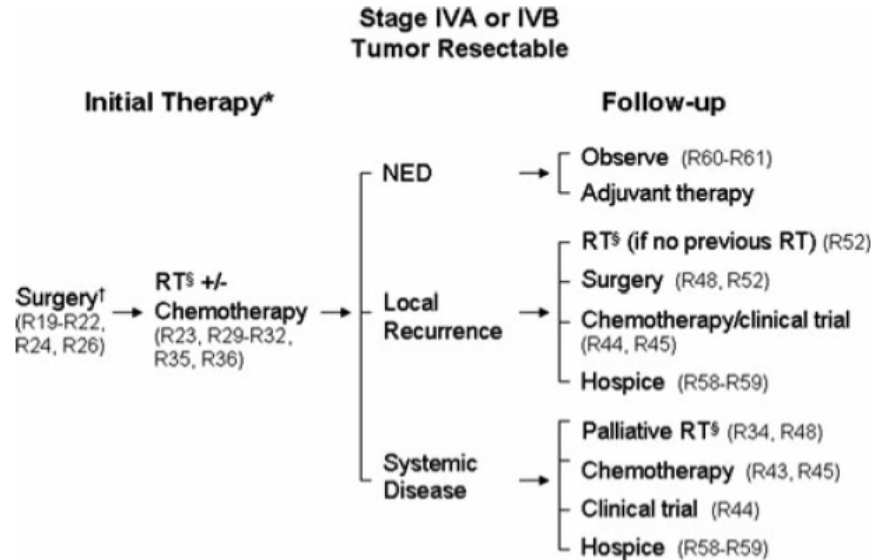


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American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer

Robert C. Smallridge,^{1,*} Kenneth B. Ain,^{2,3} Sylvia L. Asa,^{4,5} Keith C. Bible,⁶ James D. Brierley,^{4,5}
Kenneth D. Burman,⁷ Electron Kebebew,⁸ Nancy Y. Lee,⁹ Yuri E. Nikiforov,¹⁰ M. Sara Rosenthal,¹¹
Manisha H. Shah,¹² Ashok R. Shaha,⁹ and R. Michael Tuttle⁹



RECOMMENDATION 29

Following an R0 or R1 resection patients with good performance status with no evidence of metastatic disease who wish an aggressive approach should be offered definitive radiation therapy (with or without concurrent chemotherapy)

RECOMMENDATION 30

Treatment should be planned and radiation started as soon as the patient is sufficiently recovered from neck surgery, usually within 2 to 3 weeks after surgery

RECOMMENDATION 31

Systemic chemotherapy can begin as soon as the patient is sufficiently recovered from surgery, potentially even within 1 week of surgery, depending upon postoperative course and treatment goals.



Adjuvant Therapy



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Treatment and Prognosis of Anaplastic Thyroid Carcinoma: A Clinical Study of 50 Cases

Tian-Run Liu^{1*}, Zhi-Wen Xiao^{1*}, Hai-Neng Xu^{2*}, Zhen Long¹, Fan-Qin Wei¹, Shi-Min Zhuang¹, Xiao-Mei Sun¹, Liang-En Xie¹, Jia-Sheng Mu^{3,4}, An-Kui Yang^{5,6*}, Guan-Ping Zhang^{1*}, Yi Fan^{1*}

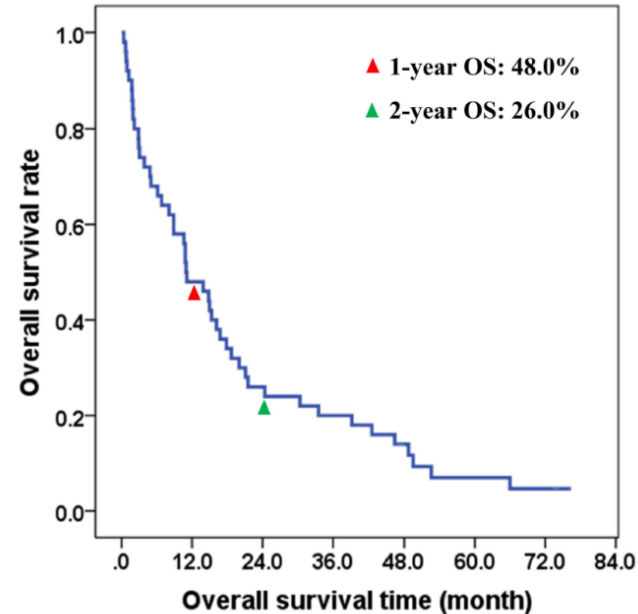
¹ Department of Otorhinolaryngology-Head and Neck Surgery, Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. ² Department of Radiation Oncology, University of Pennsylvania Perelman School of Medicine, Philadelphia, United States of America. ³ Department of General Surgery, Xinhua Hospital, affiliated to School of Medicine, Shanghai Jiao Tong University, Shanghai, China. ⁴ Institute of Biliary Tract Disease, Shanghai Jiao Tong University School of Medicine, Shanghai, China. ⁵ State Key Laboratory of Oncology in South China, Guangzhou, China. ⁶ Department of Head and Neck Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China

Table 2. Treatment methods of the 50 ATC patients.

Treatment group	Case(s)
Surgery only	21
Surgery plus radiotherapy or chemotherapy	17
Chemoradiotherapy	1
Chemotherapy only	2
Tracheotomy, biopsy or other	9

Survival conditions:

- 3 Alive
- 47 Died
 - 35 Primary tumor
 - 12 Metastases





Adjuvant Therapy



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1 Department of Otorhinolaryngology-Head and Neck Surgery, Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. 2 Department of Radiation Oncology, University of Pennsylvania Perelman School of Medicine, Philadelphia, United States of America. 3 Department of General Surgery, Xinhua Hospital, affiliated to School of Medicine, Shanghai Jiao Tong University, Shanghai, China. 4 Institute of Biliary Tract Disease, Shanghai Jiao Tong University School of Medicine, Shanghai, China. 5 State Key Laboratory of Oncology in South China, Guangzhou, China. 6 Department of Head and Neck Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China

Effect of radical surgery on overall survival:

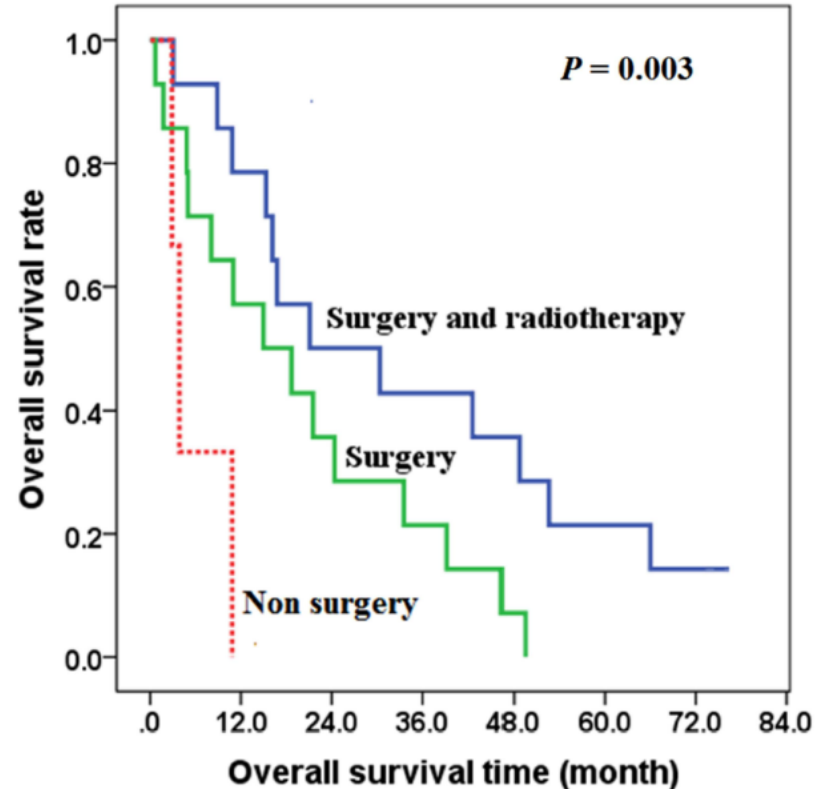
At 2 Years are alive:

- 58% Patients R0
- 31% Patients R1
- 0% No Surgery

Effect of radical surgery on overall survival (stage IV A and IV B)

At 2 Years are alive:

- 50% Surgery + Adjuvant RT
- 35% Only Surgery



ATA: Neoadjuvant Radiation and Systemic Therapy



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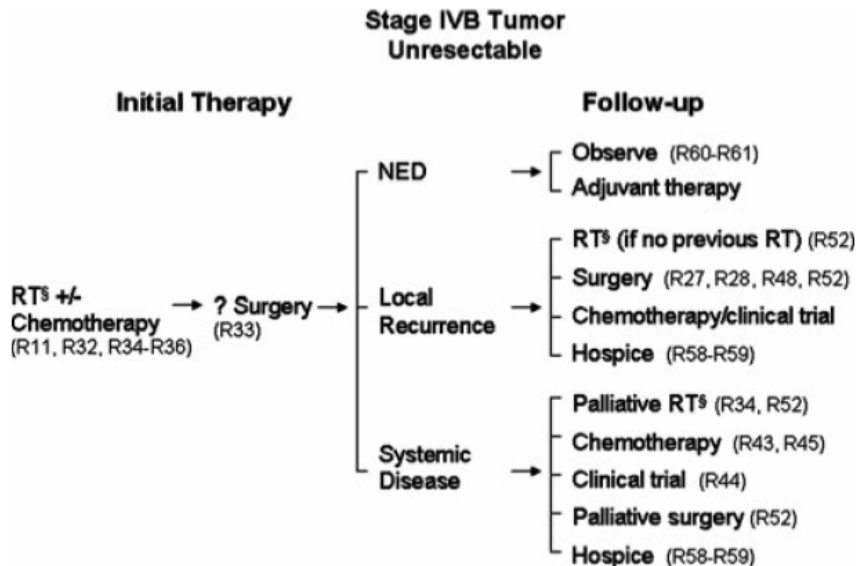


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for the American Thyroid Association Anaplastic Thyroid Cancer Guidelines Taskforce



RECOMMENDATION 32

Patients who have undergone R2 resection or have unresected disease with good performance status and who wish an aggressive approach should be offered definitive radiation (with or without concurrent chemotherapy)

RECOMMENDATION 33

Surgical resection may be reconsidered in patients when radiation (with or without chemotherapy) renders the tumor potentially resectable.



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ATA: Role of Systemic Therapy combined with Radiation Therapy



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Some chemotherapeutic agents when given concurrently with radiation can potentiate the antitumor effects of radiation and thereby act as “**radiation sensitizers**”.

This therapeutic advantage may be at the cost of **increased toxicity**, and in some regimen a reduction of the radiation dose may be required.

The aim of chemotherapy given concurrently with radiation is **to increase the chance of local control** of the tumor.

RECOMMENDATION 36

The use of cytotoxic chemotherapy involving some combination of **taxane** (paclitaxel or docetaxel), and/or **anthracyclines** (doxorubicin) and/or **platin** (cisplatin or carboplatin) therapy should be considered in combination with radiation therapy or altered fractionated radiotherapy in good performance status patients with nonmetastatic ATC who desire aggressive therapy.

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Radiation Therapy: which dose?



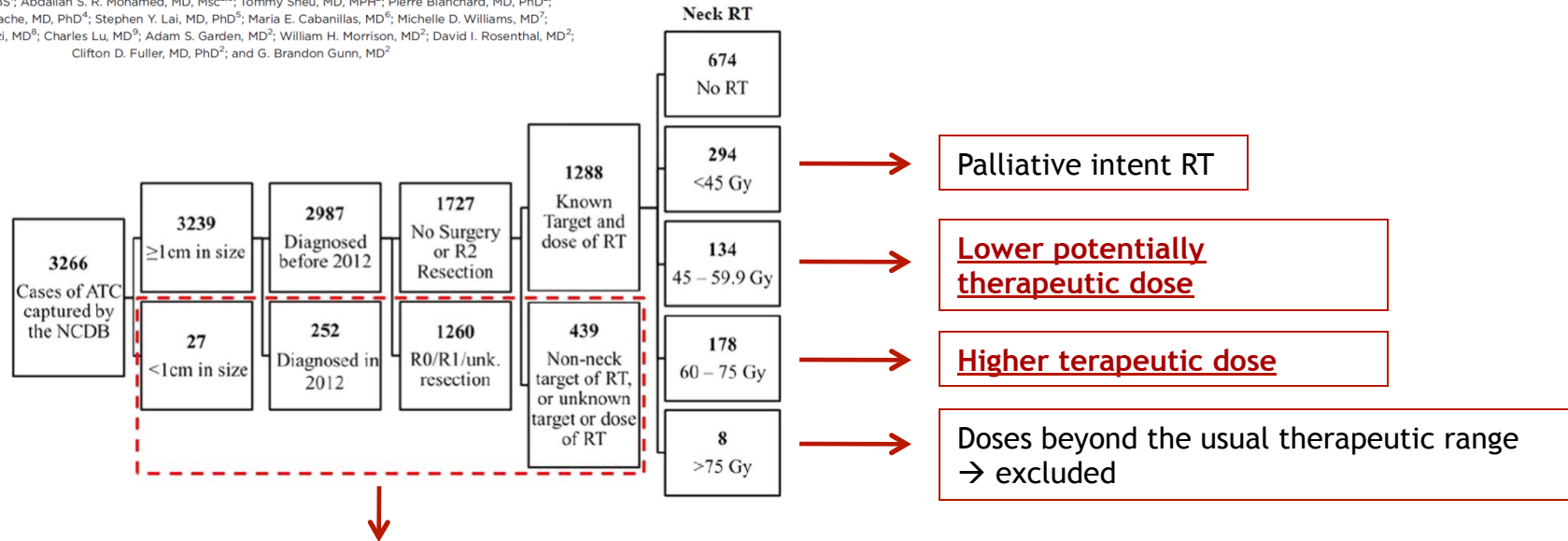
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Radiation Therapy Dose Is Associated With Improved Survival for Unresected Anaplastic Thyroid Carcinoma: Outcomes From the National Cancer Data Base

Todd A. Pezzi, BS¹; Abdallah S. R. Mohamed, MD, MSc^{2,3}; Tommy Sheu, MD, MPH²; Pierre Blanchard, MD, PhD²; Vlad C. Sandulache, MD, PhD⁴; Stephen Y. Lai, MD, PhD⁵; Maria E. Cabanillas, MD⁶; Michelle D. Williams, MD⁷; Christopher M. Pezzi, MD⁸; Charles Lu, MD⁹; Adam S. Garden, MD²; William H. Morrison, MD²; David I. Rosenthal, MD²; Clifton D. Fuller, MD, PhD²; and G. Brandon Gunn, MD²

Patients with ATC reported to NCDB from 1998 to 2012



Patients with tumors measuring < 1 cm, and those who underwent complete surgical resection of macroscopic disease were excluded



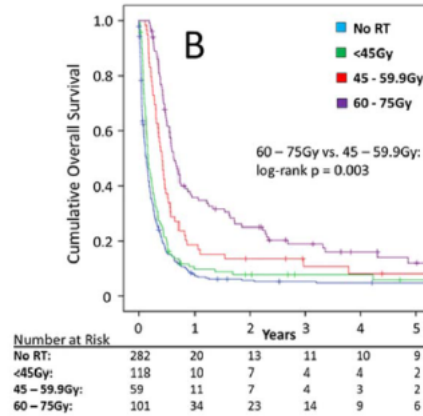
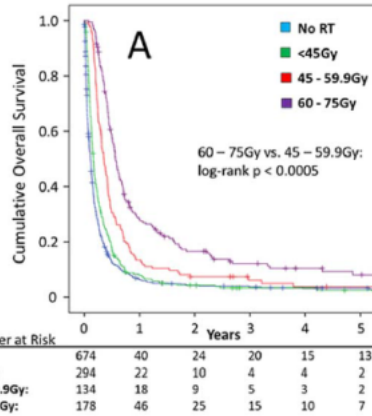
Radiation Therapy: which dose?



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Overall Study Cohort



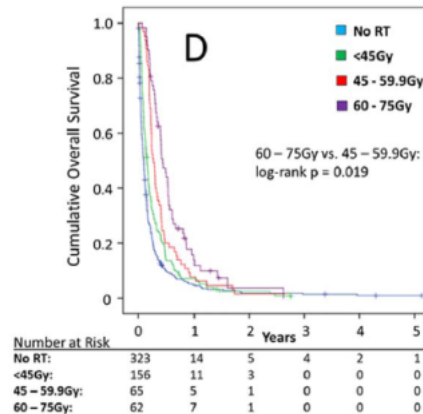
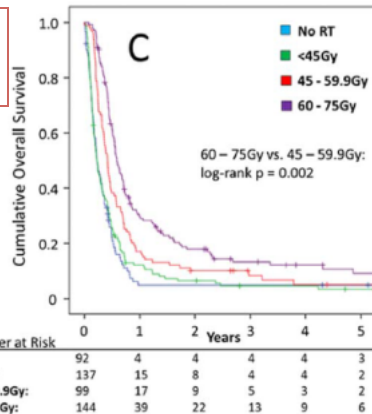
IV A - IV B

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Survival in patients with unresected anaplastic thyroid carcinoma is illustrated according to neck radiation therapy

Systemic Therapy



IV C



Radiation Therapy: which dose?



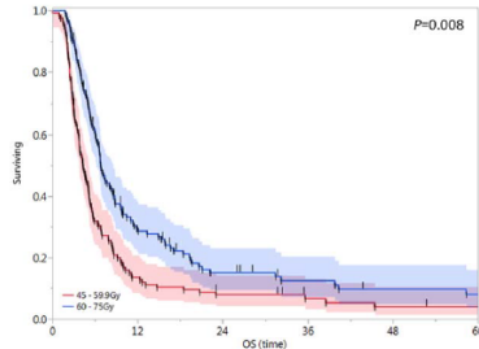
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TABLE 2. Correlates of Survival in Patients With Unresected Anaplastic Thyroid Cancer: Results From the Univariate and Multivariable Models

Variable	Univariate P	Multivariable P	HR	95% CI	
				Lower	Upper
Age ≥ 65 y vs < 65 y	< .001	< .001	1.317	1.137	1.526
Women vs men	.008	.696	1.026	0.902	1.167
White vs not white	.124	—	—	—	—
≥ 1 Comorbidity vs none	< .001	< 0.001	1.587	1.379	1.827
T4b vs T4a	.609	—	—	—	—
N+ vs N0	.811	.324	1.066	0.939	1.210
M1 vs M0	< .001	< .001	1.385	1.216	1.578
R2 resection vs no surgery	.604	.019	0.786	0.643	0.962
Chemotherapy vs none	< .001	< .001	0.637	0.547	0.742
RT dose (reference, no RT [0 Gy])	—	—	—	—	—
<45 Gy	.001	.035	0.843	0.718	0.988
45-59.9 Gy	< .001	< .001	0.596	0.479	0.743
60-75 Gy	< .001	< .001	0.419	0.339	0.517

Abbreviations: CI, confidence interval; Gy, grays; HR, hazard ratio; RT, radiation therapy.



Red: 45 - 59.9 Gy
 Blu: 60 - 75 Gy

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Patients who received treatment that incorporated higher dose RT to the neck had incontrovertibly **extended survival**, even for patients with distant metastatic disease.



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Radiation Therapy: which technique ?

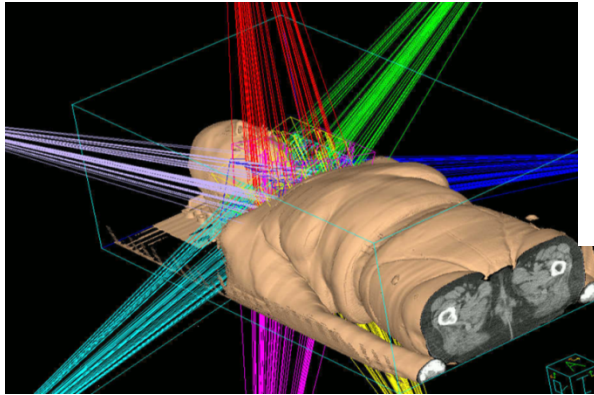
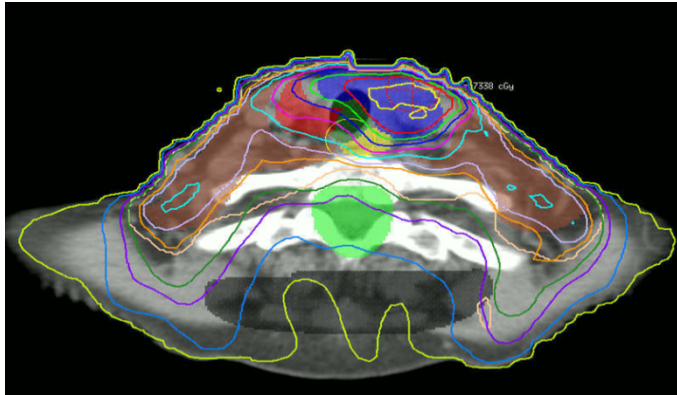


ITALIAN CHAPTER

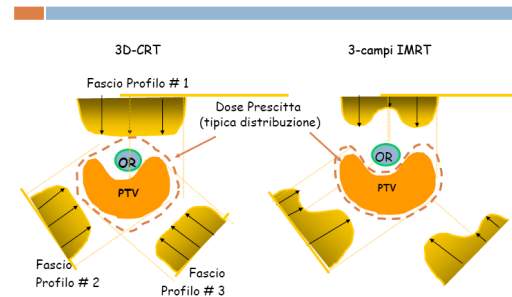
By modulation of the intensity of the radiation fields as well as shape of the fields, the radiation can be made more conformal, thereby reducing toxicity to normal structures further and potentially enabling a higher radiation dose to be given to the tumor areas.

RECOMMENDATION 35

Patients who have to receive radiation for unresectable thyroid cancer or in the postoperative setting should, where available, be treated with IMRT; however, treatment should not be delayed because of lack of availability of IMRT.



3D CRT versus IMRT



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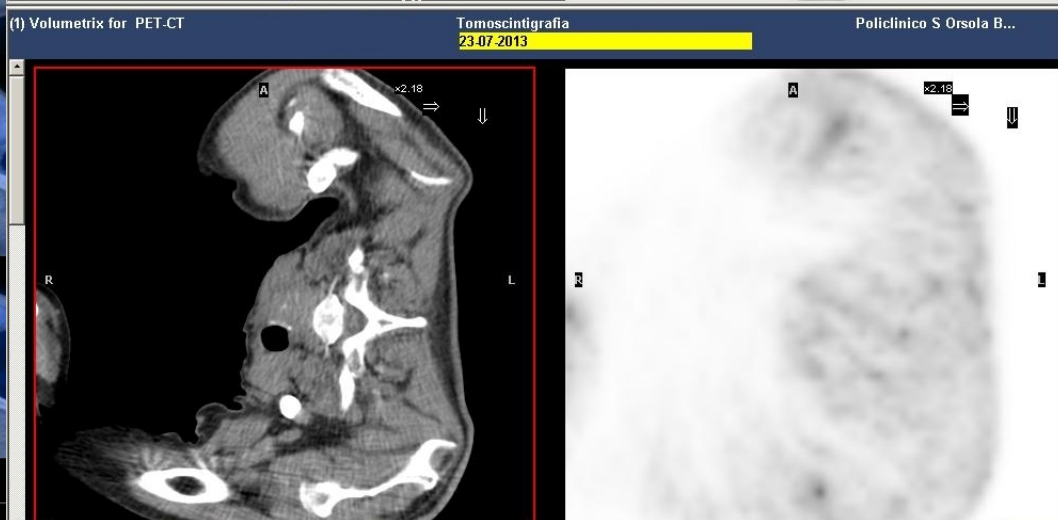
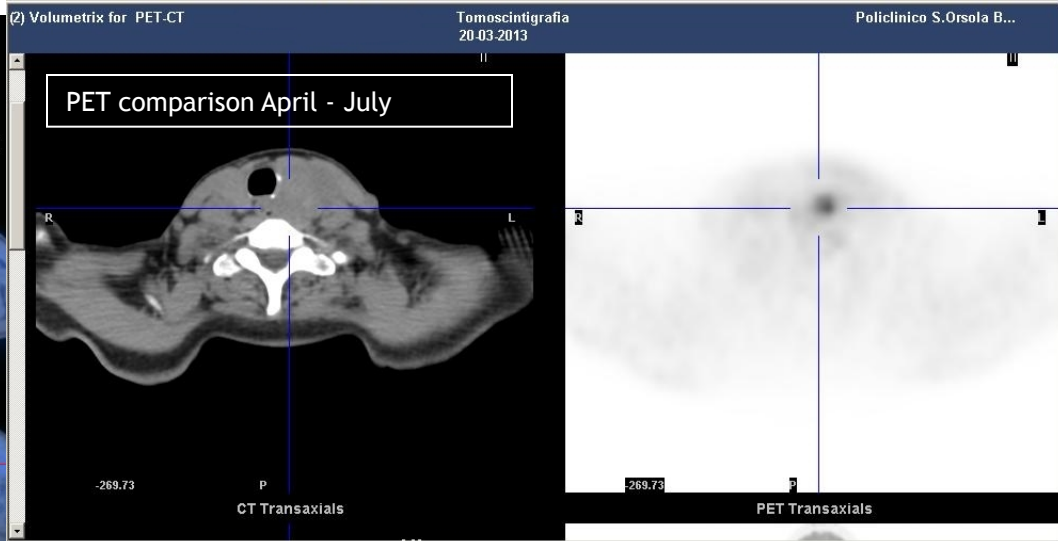
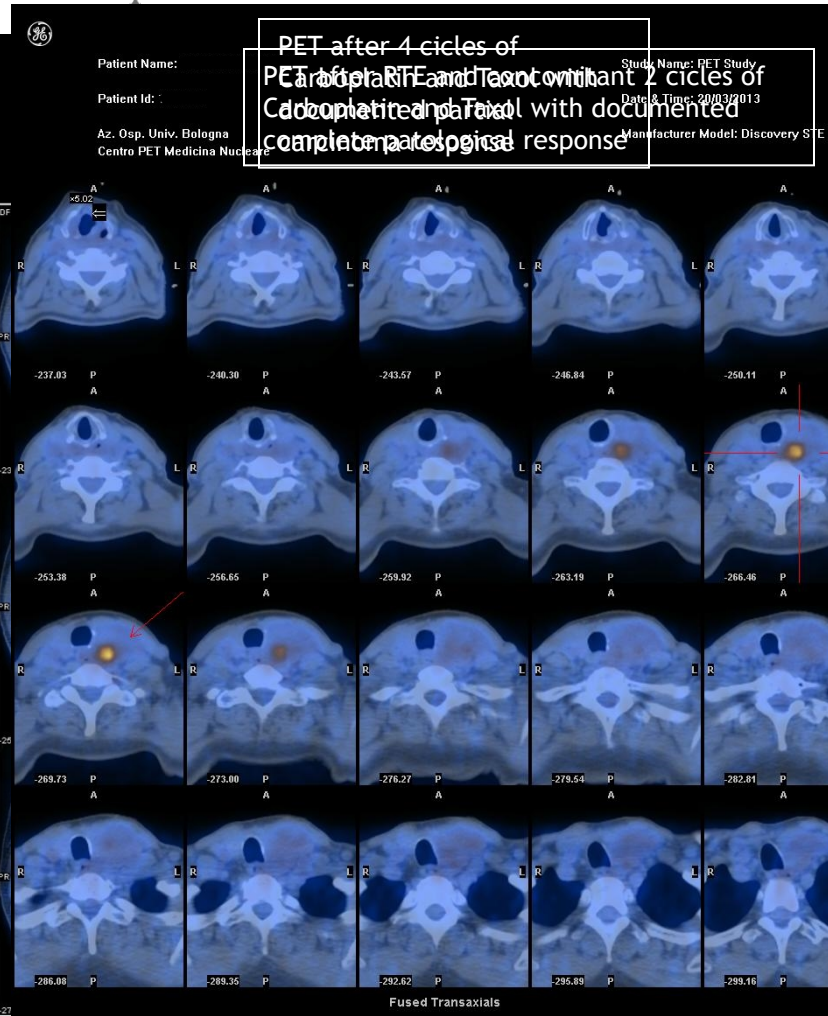
Clinic Case 1 - Neoadjuvant



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- A.M.F. Woman 72 years old. Considered unresectable by the surgeon for the involvement of vessels of the neck.
- Biopsy DI: **locally advanced anaplastic thyroid cancer** of the left thyroid lobe that dislocates and compresses the trachea in close proximity to the large vessels of the neck. **Stage cTIVb**.
- 26/11/2012 - 01/02/2013 IV cycles Carboplatin e Taxol. Biopsy documented partial Carcinoma Response. *image
- 08/04/2013 - 25/05/2013 RTE - IMRT with concomitant II cycles Carboplatin + Taxol.
 - 6600 cGy 30 fx GTV PET +;
 - 6000 cGy 30 fx bilateral laterocervical lymph nodes IIB - VII.
 - No G3 toxicity
- 23/07/2013 PET-FDG: metabolic normalization. *image
- 03/09/2013 Total thyroidectomy with recurrent left nerve sacrifice that was completely infiltrated by cancer.
- DI: **full pathological response**.
- At present no signs of loco-regional or distant disease.





PET comparison April (below) - July (above) 2013 After neoadjuvant RTE - CT

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Az. Osp. Univ. Bologna Einstein.DBPatientSelectorStyle: TerraSmall

Study Name: Tomoscintigrafia Globa

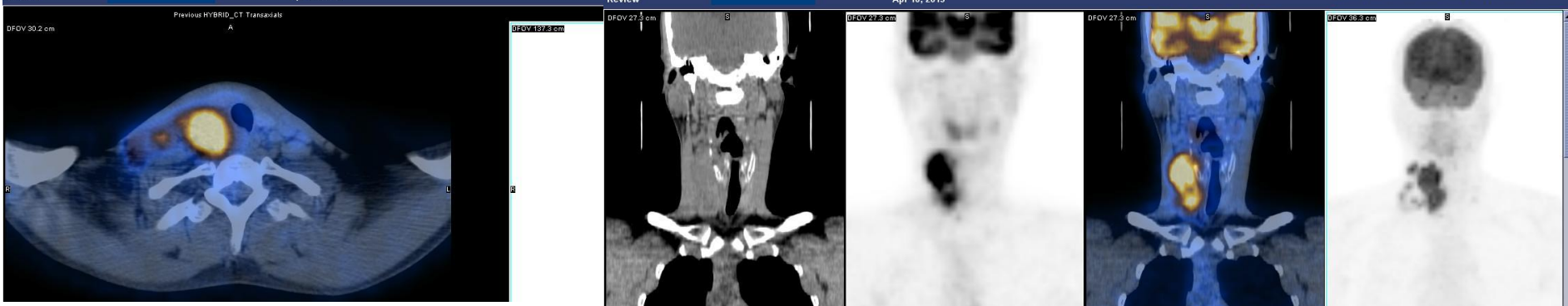
Date & Time: Jul 18, 2013

Manufacturer Model: Discovery STE, Discovery STE

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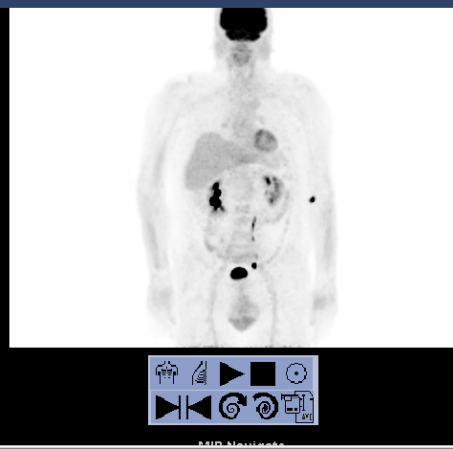
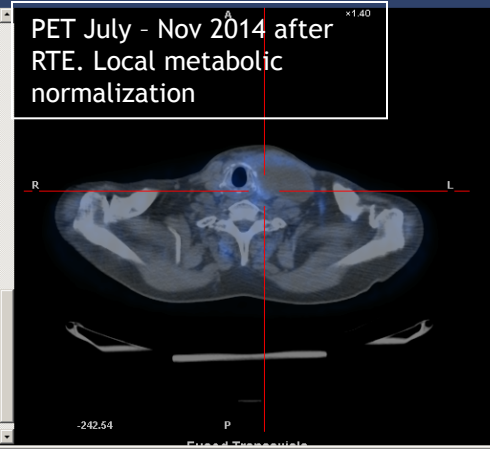


(2) Volumetrix for PET-CT

Tomoscintigrafia
27/Nov/14

Az. Osp. Univ. Bologna
Centro PET Medicina Nucleare

PET July - Nov 2014 after
RTE. Local metabolic
normalization

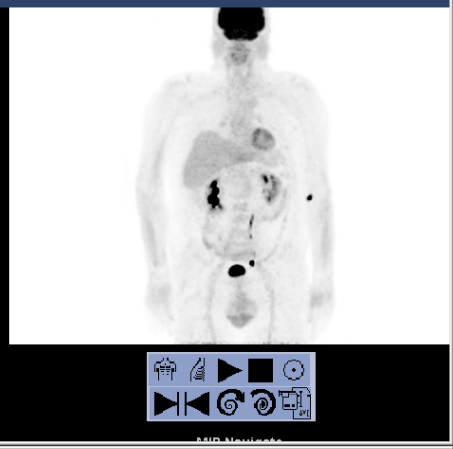
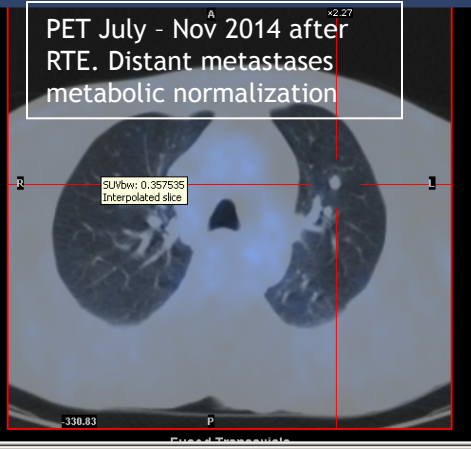


(2) Volumetrix for PET-CT

Tomoscintigrafia
27/Nov/14

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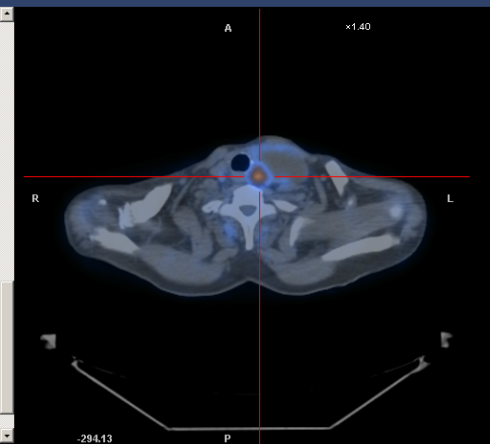
PET July - Nov 2014 after
RTE. Distant metastases
metabolic normalization



(1) Volumetrix for PET-CT

Tomoscintigrafia
30/Jul/14

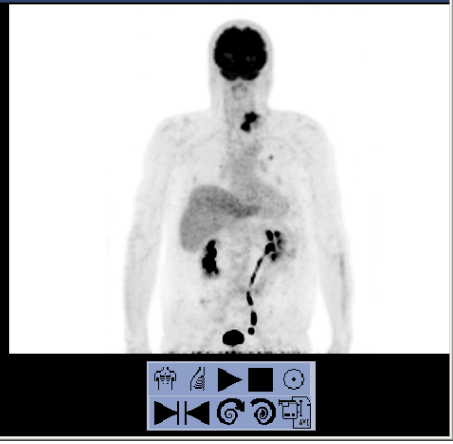
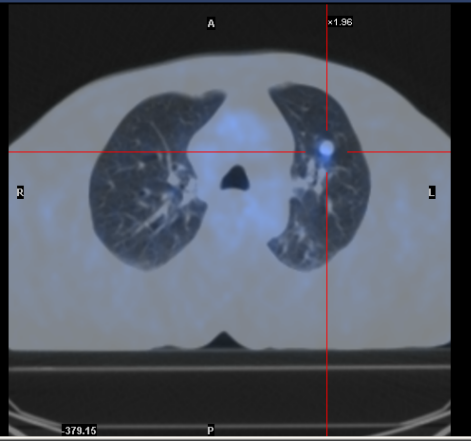
Az. Osp. Univ. Bologna
Centro PET Medicina Nucleare



(1) Volumetrix for PET-CT

Tomoscintigrafia
30/Jul/14

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Centro PET Medicina Nucleare





Roma, 9-12 novembre 2017

NATURE - multicentric prospective study of radiotherapy



ITALIAN CHAPTER



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*NeoAdjuvant Radiation Therapy for UnREsectable
locally Advanced Anaplastic Thyroid Cancer: a
multicentric prospective study of radiotherapy*



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Obiettivi dello studio:

- **Primario:** definire l'incidenza dei pazienti afferenti ai centri partecipanti affetti da carcinoma anaplastico in stadio localmente avanzato, inoperabili o borderline resectable, aventi indicazione a terapia radiante sulla lesione primitiva
- **Secondari:**
 - definire la percentuale di pazienti che dopo CRT/RTE neoadiuvante sono candidabili a intervento chirurgico radicale;
 - Ddefinire il tasso di risposta in termini di resecabilità con margini R0, R1 o R2 in pazienti giudicati operabili dopo RTE neoadiuvante;
 - definire il tasso di risposta patologica completa o parziale in termini di assenza di malattia macro o microscopica rilevabile all'esame istologico in pazienti giudicati operabili dopo RTE neoadiuvante;
 - definire il controllo locale di malattia;
 - definire la tossicità acuta e cronica correlata alla RTE;
 - definire la sopravvivenza globale e libera da progressione di malattia;
 - valutare la qualità della vita.



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- **Criteri di inclusione:**

- Diagnosi citologica FNAB o istologica di carcinoma anaplastico della tiroide in stadio localmente avanzato;
- Indicazione al trattamento radioterapico
- Età > 18 anni
- ECOG 0-2
- Non gravidanza o allattamento
- Sufficiente funzionalità midollare, renale ed epatica.

- **Criteri di esclusione:**

- Presenza di patologie internistiche che controindichino RTE;
- Comorbilità che possano costituire un rischio per la partecipazione allo studio;
- Mancata disponibilità al follow-up clinico e strumentale;
- Precedente radioterapia a livello del distretto testa-collo.

- Non vi sono restrizioni all'utilizzo di farmaci prima e/o in concomitanza e/o dopo il trattamento radiante. Altre terapie (chemioterapia) saranno permesse a discrezione dell'indicazione data dai Medici Oncologi secondo le linee guida.

- Es trattamento combinato sec. Schema 1-2 cicli CT con taxani e CDDP pre-RTE seguita da 2 cicli CT con taxani e CDDP concomitanti alla radioterapia ed infine 2-3 cicli di CT con taxani e CDDP post-RTE.



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- Trattamento radiante eseguito una volta al giorno per 5 giorni consecutivi con **TECNICA IMRT-SIB**.
- **66 Gy** in 30 frazioni al PTV 1, **60 Gy** in 30 frazioni al PTV 2, **54 Gy** in 30 frazioni al PTV 3. PTV = CTV + 1 cm.
 - CTV 1: GTV definito dalle immagini della TC di centratura e la ghiandola tiroide.
 - CTV 2: includerà il CTV 1 + linfonodi ad alto rischio (laterocervicali dal II al VI livello, omolaterali alla lesione).
 - CTV 3: includerà il CTV 2 + linfonodi a basso rischio (laterocervicali dal II al VI livello, controlaterali alla lesione).
- Maschera termoplastica a 5 punti.
- Pianificazione con TC con/senza mdc, intervallo tra scansioni non superiore ai 3 mm. Immagini di fusione per migliorare l'accuratezza del contouring targets.



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- Durante il corso del trattamento:
 - Visita il 1° giorno di RTE, una visita settimanale per tutta la durata del trattamento e una visita alla fine del trattamento radiante esterno.
- Al termine del trattamento:
 - A distanza di un mese rivalutazione clinica, rivalutazione strumentale con TC total body con mdc e ^{18}F -FDG-PET/TC e rivalutazione chirurgica.
- In caso di resecabilità: **chirurgia non prima delle 6 settimane dal termine della RTE.**
 - Successive visite a 1 mese dall'intervento e a seguire ogni 6 mesi.
- Per i pazienti non resecabili dopo RTE, visite ogni 6 mesi.
- La valutazione sarà composta da raccordo anamnestico, esame fisico e strumentale (eco collo ogni 6 mesi per i primi due anni, poi annualmente; TC collo e torace annualmente, ^{18}F -FDG-PET/TC annualmente).



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Take Home Messages



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- Anaplastic thyroid carcinoma is a rare cancer of the head and neck
- It represents an oncologic urgency and needs a quick approach.
- A **Multimodal Approach** could give the best outcome.
- It is auspicious to activate 1-2 dedicated tertiary level centers for each regional area.
- **Quality of the approach** can make the difference in Overall Survival and Toxicity.
- Need to use adjuvant or neoadjuvant RTE at high therapeutic dose (> 60 Gy).
- We should **combine Systemic Therapy** when it's possible .
- Most of the studies are retrospective; prospective randomized studies are needed.

The background of the slide is a vibrant sunset sky with a gradient from blue at the top to orange and yellow at the bottom. Numerous white, fluffy clouds are scattered across the sky, catching the low light of the sun. Several black silhouettes of hot air balloons are floating at various heights and positions. One large balloon is at the top center, another is on the left side, and several smaller ones are clustered in the bottom left corner. The overall mood is peaceful and hopeful.

**With a correct therapeutic approach
long-lived survivors may exist**

Thanks for the attention

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