

# IL CARCINOMA DIFFERENZIATO DELLA TIROIDE: DALLA DIAGNOSI AL FOLLOW-UP

LA QUESTIONE DELL'N: IL  
PUNTO DI VISTA  
DELL'ENDOCRINOLOGO

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21 MARZO 2009

# TNM STAGING SYSTEM

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IL “TNM STAGING SYSTEM”, SVILUPPATO NEL 1940 DA PIERRE DENOIX , E’ STATO ADOTTATO E PUBBLICATO PER LA PRIMA VOLTA NEL 1968.

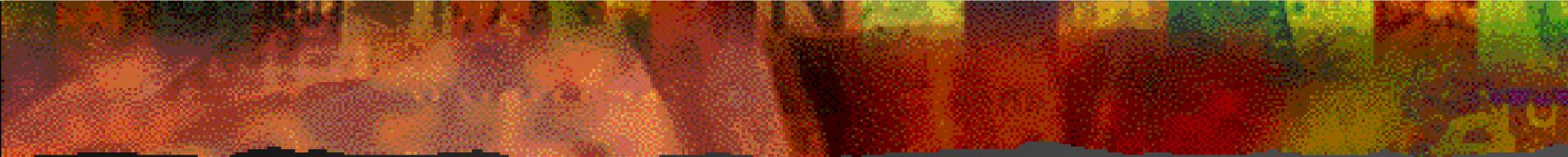
T: tumor

N: node

M: metastasis

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- Per definire e comunicare il rischio di mortalità tumore specifica da Carcinoma tiroideo differenziato viene consigliata la stadiazione TMN:
  - lo scopo è di dividere i pz entro classi di rischio che indirizzino prognosi e modalità di trattamento
  - il suo utilizzo a livello internazionale aiuta il confronto dei dati raccolti nelle diverse parti del mondo



LA REVISIONE PIU' RECENTE DEL  
SISTEMA DI STADIAZIONE TMN PER IL  
CARCINOMA TIROIDEO E' STATA  
PUBBLICATA NEL 2002 E SI BASA SU  
EVIDENZE DI LIVELLO III



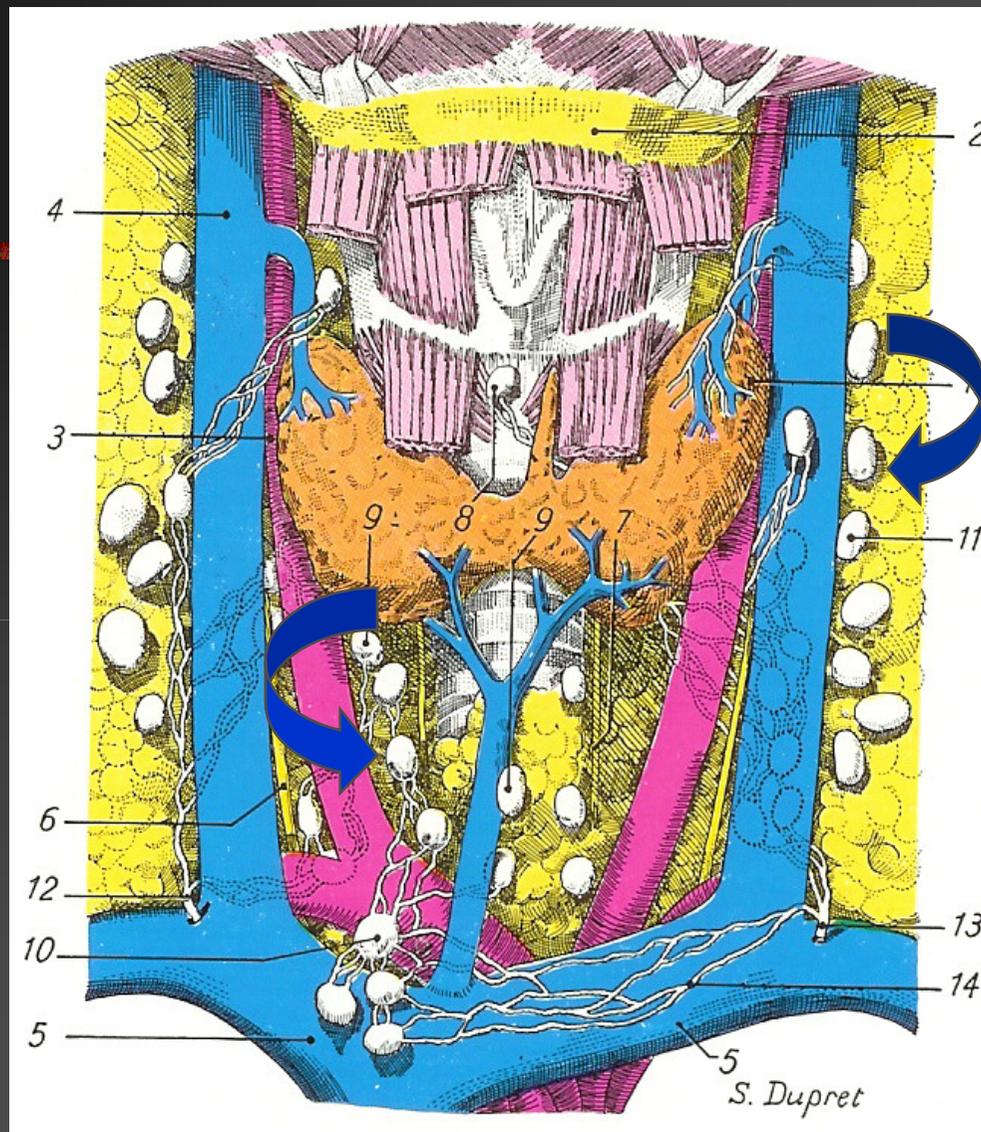
PER QUANTO ATTIENE IL CARCINOMA TIROIDEO, I DATI  
PROVENGONO PRINCIPALMENTE DA STUDI  
RETROSPETTIVI POICHE' NON SONO DISPONIBILI STUDI  
PROSPETTICI RANDOMIZZATI CONTROLLATI

## Stadiazione TNM 6a edizione (2002) del Ca differenziato della tiroide

	Linfonodi Regionali
Nx	Linfonodi regionali non valutabili
N0	Assenza di metastasi linfonodali
N1	Metastasi nei linfonodi regionali
N1a	Metastasi a livello VI
N1b	Metastasi omolaterali, controlaterali, bilaterali ai linfonodi cervicali o mediastinici superiori

La distinzione in N1a ed N1b non si riferisce piu' alla lateralita'

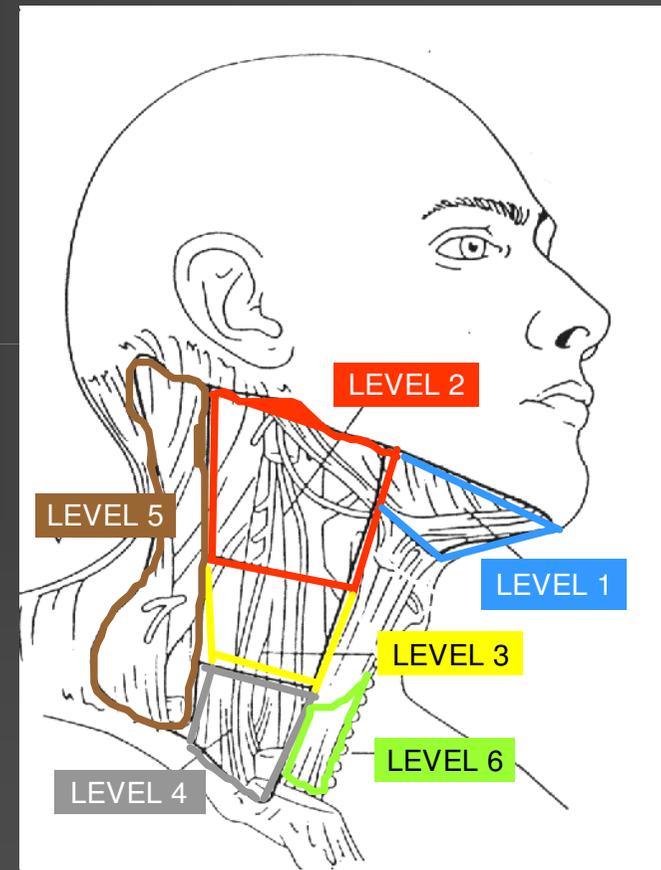
N1a



N1b

La diffusione delle cellule tumorali avviene generalmente dalla ghiandola tiroidea, ai linfonodi del comparto centrale (livello VI), ai linfonodi latero-cervicali omolaterali, poi ai controlaterali, poi ai linfonodi mediastici (VII° livello).

Sono stati riportati casi di “skip metastasis” ai linfonodi latero-cervicali senza coinvolgimento del comparto centrale.



# PERCENTUALE DI INTERESSAMANTO LINFONODALE

- CARCINOMA PAPILLARE:
  - Metastasi linfonodali sono presenti in percentuale variabile fra il 35% ed il 65% dei casi, valore che può arrivare all'80% in età pediatrica
- CARCINOMA FOLLICOLARE:
  - Metastasi linfonodali meno frequenti, riportate in meno del 20% dei casi

Schlumberger M et al, 2003

Nel carcinoma papillare si possono frequentemente riscontrare micrometastasi, fino al 90% dei linfonodi esaminati in un lavoro pubblicato sul JCEM nel 1997 (Arturi F. et al., 1997: 82, 1638)

## Stadi TNM 6a edizione (2002) Carcinoma papillare e follicolare della tiroide

	Età < 45aa			Età ≥ 45aa		
STADIO	T	N	M	T	N	M
I	Ogni T	ogni N	M0	T1	N0	M0
II	Ogni T	ogni N	M1	T2	N0	M0
III				T3	N0	M0
				T1-T3	N1a	M0
IVA				T4a	N0	M0
				T4a	N1a	M0
				T1-T4a	N1b	M0
IVB				T4b	ogni N	M0
IVC				Ogni T	ogni N	M1

# CLASSI DI RISCHIO

- La conoscenza dei principali fattori prognostici ha condotto alla formulazione di **Sistemi di classificazione di rischio** che consentono di identificare pz con:

- **Alto rischio**
- **Medio rischio**
- **Basso rischio**

**Di mortalità tumore specifica**

**Per quanto attiene il rischio di recidiva, nei soggetti di età inferiore a 45aa, la suddivisione in due sole classi non fornisce uno strumento adeguato alla sua identificazione**

**La stadiazione non descrive inoltre adeguatamente, per gli stessi soggetti, la mortalità tumore specifica, in presenza di metastasi a distanza o di fattori di rischio non considerati nel TMN (es presenza di varianti istologiche più aggressive)**

# MEMORIAL SLOAN KATTERING CANCER CENTER RISK GROUP DEFINITIONS

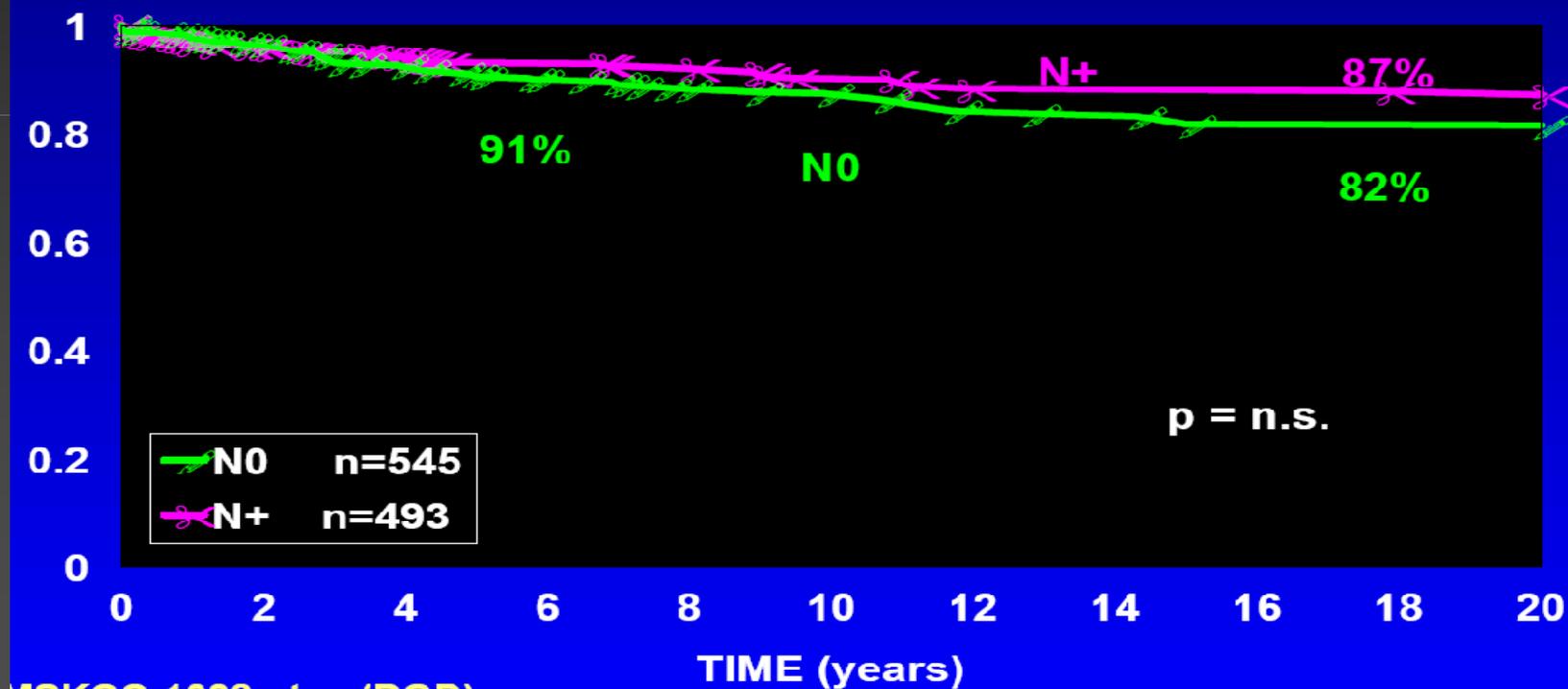
## Differentiated Cancer of the Thyroid Risk Group Definitions

	Low Risk	Intermediate Risk	High Risk	
<b>Age (years)</b>	<45	<45	>45	<=45
<b>Distant mets</b>	M0	M+	M0	M+
<b>Tumor size</b>	T1/T2 (<4cm)	T3/T4 (>4cm)	T1/T2 (<4cm)	T3/T4 (>4cm)
<b>Histology &amp; Grade</b>	Papillary	Follicular &/or high grade	Papillary	Follicular &/or high grade

# MEMORIAL SLOAN KATTERING CANCER CENTER

## Differentiated Thyroid Cancer 1930-1985

### SURVIVAL: Nodal Status



# Clinically Significant Prognostic Factors for Differentiated Thyroid Carcinoma

*A Population-Based, Nested Case-Control Study*

528 CANCER February 1, 2006 / Volume 106 / Number 3

TABLE 3

Occurrence of Lymph Node and Distant Metastases in Patients with Differentiated Thyroid Carcinoma, Demonstrating Univariate and Multivariate ORs of Dying from Thyroid Carcinoma with 95% CIs

Metastases	Cases		Controls		Univariate analysis <sup>a</sup>		Multivariate analysis <sup>b</sup>		Multivariate analysis <sup>c</sup>	
	Total	%	Total	%	OR	95% CI	OR	95% CI	OR	95% CI
Lymph node metastases <sup>d</sup>	196	33	127	21	2.5	1.6-4.1	3.2	1.7-6.0	1.9	1.1-3.6
No lymph node metastases <sup>d</sup>	116	19	179	30	1.0	Reference	1.0	Reference	1.0	Reference
Initial distant metastases <sup>e</sup>	146	25	29	5	6.8	4.1-10.5	5.0	2.9-8.5	2.9	1.3-7.4
No initial distant metastases	427	72	547	92	1.0	Reference	1.0	Reference	1.0	Reference
Late distant metastases <sup>f</sup>	394	66	93	16	15.3	9.0-24.0	14.9	8.5-25.6	14.7	9.0-24.0
No late distant metastases	122	21	456	77	1.0	Reference	1.0	Reference	1.0	Reference

OR: odds ratio; 95% CI: 95% confidence interval.

The percentages were calculated from the total number of cases and controls, including those with incomplete information.

<sup>a</sup>Adjusted for matching variables (age, gender, and calendar period).

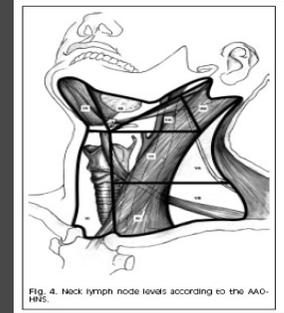
<sup>b</sup>Adjusted for histopathologic subgroup (follicular thyroid carcinoma and papillary thyroid carcinoma) and tumor differentiation.

<sup>c</sup>Adjusted for TNM stage.

<sup>d</sup>Included only those patients in whom lymph node surgery was performed; 672 patients lacked information regarding lymph node status or surgery.

<sup>e</sup>A total of 41 patients lacked information regarding distant metastases at the time of diagnosis.

<sup>f</sup>A total of 125 patients lacked information regarding late distant metastases (i.e., > 3 months after diagnosis and no initial distant metastases were detected in the same location).



- Le metastasi linfonodali loco-regionali sembrano non avere un importante impatto prognostico nei pz con carcinoma tiroideo differenziato, per lo meno per quanto attiene la mortalità tumore specifica.
- E' comunque piu' elevato nei pz di eta' piu' avanzata, eta' nella quale tuttavia è meno frequente l'interessamento linfonodale.



Quale impatto dell'interessamento  
linfonodale sul rischio di recidiva  
loco-regionale?

# CLASSI DI RISCHIO

- L'indicazione al trattamento con  $^{131}\text{I}$  dovrebbe essere data sulla base dei fattori prognostici:
  - Soggetti a “basso rischio”: neoplasia di dimensioni inferiori al centimetro (pT1aN0M0) → non indicazione
  - Soggetti a “medio-alto rischio”: neoplasie con stadiazione superiore a pT1aN0M0, carcinomi follicolari, varianti aggressive del carcinoma papillare → indicazione

## CONSENSUS STATEMENT

**European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium**

Furio Pacini, Martin Schlumberger<sup>3</sup>, Henning Dralle<sup>2</sup>, Rossella Elisei<sup>3</sup>, Johannes W A Smit<sup>4</sup>, Wilmar Wiersinga<sup>5</sup> and the European Thyroid Cancer Taskforce

*Section of Endocrinology and Metabolism, University of Siena, Via Bracci, 5 3100 Siena, Italy, <sup>1</sup>Service de Médecine Nucléaire, Institut Gustave Roussy, Villejuif, France, <sup>2</sup>Department of General, Visceral and Vascular Surgery, University of Halle, Germany, <sup>3</sup>Department of Endocrinology, University of Pisa, Italy, <sup>4</sup>Department of Endocrinology and Metabolic Disease, Leiden University Medical Center, The Netherlands and <sup>5</sup>Department of Endocrinology and Metabolism, University of Amsterdam, The Netherlands*

**Table 1** Indications for postsurgical thyroid ablation (risk stratification).

No indication (low risk of relapse or cancer-specific mortality)	Definite indication (use high activity ( $\geq 3.7$ GBq (100 mCi)) after thyroid hormone withdrawal)	Probable indication (use high or low activity (3.7 or 1.1 GBq (100 or 30 mCi)))
Complete surgery Favorable histology Unifocal T $\leq 1$ cm, N0, M0 No extrathyroidal extension	Distant metastases or Incomplete tumor resection or Complete tumor resection but high risk for recurrence or mortality: tumor extension beyond the thyroid capsule (T3 or T4) or lymph node involvement	Less than total thyroidectomy or No lymph node dissection or Age <18 years or T1 > 1 cm and T2, N0 M0  Or unfavorable histology: Papillary: tall-cell, columnar-cell, diffuse sclerosing Follicular: widely invasive or poorly differentiated

	<p>American Association of Clinical Endocrinologists</p>	<p><b>AAACE/AAES MEDICAL/SURGICAL GUIDELINES FOR CLINICAL PRACTICE: MANAGEMENT OF THYROID CARCINOMA</b></p>	<p>2001</p>
	<p>British Thyroid Association</p>	<p>Guidelines for the management of thyroid cancer in adults</p>	<p>2002 2007</p>
    	<p>Società Italiana di Endocrinologia           Associazione Italiana di Medicina Nucleare           Associazione Italiana di Fisica in Medicina</p>	<p><b>CARCINOMA DIFFERENZIATO DELLA TIROIDE          LINEE GUIDA SIE-AIMN-AIFM          PER IL TRATTAMENTO ED IL FOLLOW-UP</b></p>	<p>2004</p> <p>36</p>

	National Comprehensive Cancer Network	<div style="background-color: #cccccc; padding: 10px; display: inline-block;"> <b>Thyroid Carcinoma</b> </div>	2006
	European Thyroid Association	European consensus for the management of patients with <i>differentiated thyroid carcinoma of the follicular epithelium</i>	2006
	American Thyroid Association	Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer	2006
	CNR MIUR	<b>TIROIDE</b>	2006
			37

# Thyroid Cancer Treatment Guidelines: 2001-2006

## AACE/AAES

*Endocr Pract.* 2001;7:202-208.

## British Thyroid Association

*www.british-thyroid-association.org*,  
2002.

## European Thyroid Association

*Eur J Endo.* 2006;154:787-803.

## American Thyroid Association

*Thyroid.* 2006;16(2):109-142.

## National Comprehensive Cancer Network

*www.nccn.org*, 2007.

## **Papillary Thyroid Cancer: Monitoring and Therapy**

*RM Tuttle, R Leboeuf, A Martorella*

*Endocrinology and Metabolism Clinics of North America*

*Edited by Ken Burman, Summer 2007*

AACE/AAES MEDICAL/SURGICAL GUIDELINES  
FOR CLINICAL PRACTICE:  
MANAGEMENT OF THYROID CARCINOMA

Lymph node metastatic lesions are present in about 40% of adult patients with PTC; complete lymphadenectomy of involved nodes is recommended (6). In children and young adults, clinical node involvement is more common. Nodal metastatic lesions increase the risk for subsequent nodal recurrences but have little effect on survival.

AACE/AAES MEDICAL/SURGICAL GUIDELINES  
FOR CLINICAL PRACTICE:  
MANAGEMENT OF THYROID CARCINOMA

Ipsilateral lymph node metastatic lesions occur in only about 10% of patients with follicular thyroid cancer (FTC) and in about 25% of patients with Hurthle cell cancer(22). When lymphadenopathy is extensive in a patient with a follicular neoplasm as determined by FNA cytology, the tumor is usually a follicular variant of PTC. Enlarged lymph nodes in the central neck area should be removed.

# Guidelines for the management of thyroid cancer

British Thyroid Association

Royal College of Physicians

2007

## Surgery for papillary thyroid carcinoma

In patients with clinically uninvolved nodes but who are deemed high risk (ie they have any of the following features: male sex, age >45 years, tumours greater than 4 cm in diameter, extracapsular or extrathyroidal disease), total thyroidectomy *and* level VI node dissection should be performed.

Palpable disease in level VI nodes discovered at surgery is treated by a level VI node dissection.

# Guidelines for the management of thyroid cancer

British Thyroid Association

Royal College of Physicians

2007

## Surgery for follicular thyroid carcinoma

“Palpable/suspicious cervical lymph nodes are dealt with in a similar manner to papillary carcinoma”

Non vi è specifica menzione al VI° livello

Linee Guida SIE-AIMN-AIFM per il  
Trattamento e Follow-up del  
Carcinoma Differenziato della Tiroide

2004

*B.2. Chirurgia delle metastasi linfonodali*

➔ *Lo svuotamento del compartimento centrale del collo dovrebbe essere eseguito in tutti i casi.*

La linfadenectomia "di principio" delle altre catene cervicali, eseguita a scopo profilattico, non è invece la terapia di scelta nel carcinoma tiroideo differenziato.

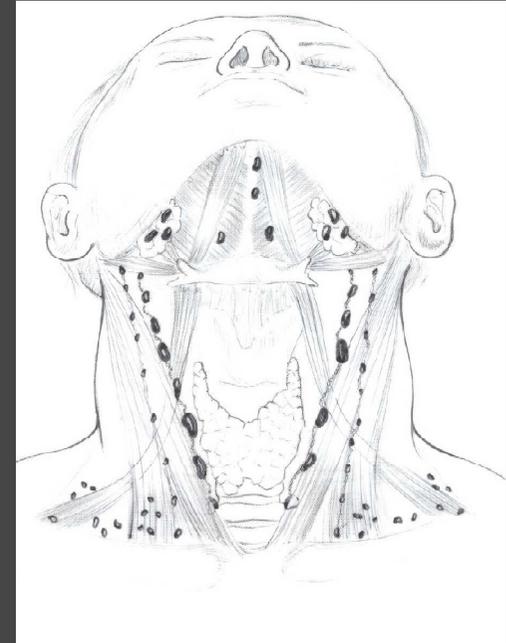
➔ *La linfadenectomia omolaterale deve essere eseguita solo in caso di metastasi linfonodali documentate ecograficamente e/o con esame citologico e/o con dosaggio della Tg sul liquido di lavaggio dell'ago utilizzato per eseguire la agospirazione o in caso di secondarietà linfonodali dimostrate dalla esplorazione chirurgica.*

CONSENSUS STATEMENT

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Furio Pacini, Martin Schlumberger<sup>1</sup>, Henning Dralle<sup>2</sup>, Rossella Elisel<sup>3</sup>, Johannes W A Smit<sup>4</sup>, Wilmar Wiersinga<sup>5</sup> and the European Thyroid Cancer Taskforce

*Section of Endocrinology and Metabolism, University of Siena, Via Bucci, 53100 Siena, Italy. <sup>1</sup>Service de Médecine Nucléaire, Institut Gustave Roussy, Villejuif, France. <sup>2</sup>Department of General, Vascular and Vascular Surgery, University of Halle, Germany. <sup>3</sup>Department of Endocrinology, University of Pisa, Italy. <sup>4</sup>Department of Endocrinology and Metabolic Disease, Leiden University Medical Center, The Netherlands and <sup>5</sup>Department of Endocrinology and Metabolism, University of Amsterdam, The Netherlands*



“The benefit of profilactic “en bloc” central node dissection in the absence of pre- or intraoperative evidence for nodal disease is controversial. There is no evidence that improves recurrence or mortality rate, but it permits an accurate staging of the disease that may guide subsequent treatment or follow-up”

## Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association Guidelines Taskforce\*

Members: David S. Cooper,<sup>1</sup> (Chair), Gerard M. Doherty,<sup>2</sup> Bryan R. Haugen,<sup>3</sup> Richard T. Kloos,<sup>4</sup> Stephanie L. Lee,<sup>5</sup> Susan J. Mandel,<sup>6</sup> Ernest L. Mazzaferri,<sup>7</sup> Bryan McIVER,<sup>8</sup> Steven I. Sherman,<sup>9</sup> and R. Michael Tuttle<sup>10</sup>

Regional lymphonode metastases are present at the time of diagnosis in 20%–90% of patients with papillary carcinoma and a lesser proportion of patients with other histotypes. In many cases, these lymphnodes do not appear abnormal to inspection. Bilateral central (compartment VI) node dissection may improve survival (compared to historic controls) and reduce the risk for nodal recurrence (76,103). This central compartment dissection can be achieved with low morbidity in experienced hands (104–107).

Routine central-compartment (level VI) neck dissection should be considered for patients with papillary thyroid carcinoma and suspected Hürthle carcinoma.

Near-total or total thyroidectomy without central node dissection may be appropriate for follicular cancer, and when followed by radioactiveiodine therapy, may provide an alternative approach for papillary and Hürthle cell cancers.

L'esecuzione di una dissezione profilattica del VI livello ("compartimento centrale") in corso di tiroidectomia totale è argomento ancora controverso, dal momento che essa determina un significativo aumento della morbidità chirurgica. Lo svuotamento del compartimento centrale può essere evitato in caso di CDT a basso rischio, mentre nei pazienti ad alto rischio trova indicazione soprattutto perché permette di effettuare una corretta stadiazione del parametro N, nel caso vengano asportati e tipizzati istologicamente almeno sei linfonodi (11). Se eseguito da chirurghi esperti, lo svuotamento del compartimento centrale non aumenta il rischio di danni del nervo laringeo inferiore, ma viene riportato un tasso di ipoparatiroidismo transitorio e definitivo significativamente aumentato.



### PREOPERATIVE OR INTRAOPERATIVE DECISION-MAKING CRITERIA

Indications for total thyroidectomy:  
(any present)

- Age < 15 y or > 45 y
- Radiation history
- Known distant metastases
- Bilateral nodularity
- Extrathyroidal extension
- Tumor > 4 cm in diameter
- Cervical lymph node metastases
- Aggressive variant



### PRIMARY TREATMENT

Total thyroidectomy  
If lymph node(s) palpable or biopsy positive:

- Central neck dissection (level VI)
- Lateral neck dissection (levels II-V, sparing spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle)

Consider preservation of the cervical sensory nerves, when feasible



See  
Postsurgical  
Evaluation  
(PAP-3)



La versione 2008 di NCCN Guidelines dà indicazione alla dissezione profilattica del VI° livello solo per il Carcinoma a cellule di Hurthle, in considerazione della maggior frequenza di metastasi locoregionali e della minor frequenza con cui le metastasi di tale istotipo neoplastico captano lo iodio 131.

**Table 2.**  
Prognostic factors in papillary thyroid cancer (PTC)

Level of evidence	Reference	Total patients	Total CLND	Factors predictive of recurrence	P	Survival factors	P
III	28 Göteborg, 1996	195	195 <sup>a</sup>	Not reported	NA	CLND compared with contemporaneous series, distant metastases, age	Not reported
IV	14 Hannover, 1994	342	60 <sup>a</sup>	Increased with node metastases, decreased with compartment-oriented dissection	All < 0.005	Node metastases, distant metastases, age, tumor invasion, compartment-oriented dissection	All < 0.001
IV	29 Toronto, 2003	103	27 <sup>a</sup>	No correlation with dissected compartment, no increase in unoperated central compartment with microscopically positive nodes	All > 0.20	No analysis; only 1 death	NA
IV	30 Berlin, 2000	139	53 <sup>b</sup>	Not reported	NA	Distant metastases, age, extrathyroidal growth, cervical lymphadenectomy	All ≤ 0.04
IV	31 Osaka, 1998	2,966	2391 <sup>a</sup>	Not reported	NA	Node metastases, sex, age, tumor size, extrathyroidal invasion; effect of CLND alone not reported	All < 0.04
IV	37 Sydney, 2006	447	56	Thyroglobulin level decreased with CLND, more patients athyroglobulinemic with CLND	P = 0.02 P < 0.001	No disease-specific deaths	NA
V	11 Barcelona, 2005	43	43 <sup>a</sup>	Increased in lateral compartments with more positive central nodes; decreased with CLND	0.003 Not reported	No deaths	NA
V	13 Tokyo, 2003	414	259 <sup>a</sup>	Palpable nodes	<0.0005	No deaths	NA
V	32 Düsseldorf, 1996	252 <sup>b</sup>	252 <sup>a</sup>	Increased with greater tumor size; decreased with central neck dissection	All < 0.0001	Not reported	NA
V	33 Paris, 2005	148	148 <sup>a</sup>	Increased with more node metastases and elevated postoperative thyroglobulin	All ≤ 0.03	Not reported	NA
V	34 Paris, 1998	281	63	Extent of thyroidectomy and number of tumor foci	All < 0.01	Not reported	NA
V	35 Niigata, 1998	139 <sup>b</sup>	139 <sup>a</sup>	Not reported	NA	Distant metastases, age, and TNM stage	All ≤ 0.012
V	36 Kobe, 2006	759	759 <sup>a</sup>	Increased with positive central nodes, age, and extrathyroidal extension	All ≤ 0.0259	Not reported	NA

CLND: central lymph node dissection.

<sup>a</sup>Additional lateral compartments were dissected.

<sup>b</sup>Minority had follicular thyroid cancer (FTC) instead of PTC.

**Grazie per l'attenzione**

