Management of Thyroid nodules and Well-Differentiated Thyroid Cancer

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Disclosures

☐ None
Educational goals

- To learn about the current guidelines in the medical workup and management of thyroid nodules and well-differentiated thyroid cancer
- To learn about the surgical management of well differentiated thyroid cancer
Prevalence of Thyroid Nodules

Adapted from Mazzaferri M. New England Journal Medicine 1993; 328:553 Figure 1
Thyroid Nodule Guidelines

- Nonpalpable nodules only >1cm should be evaluated
- Unless:
  - suspicious US findings
  - associated lymphadenopathy
  - history of H&N radiation
  - history of thyroid cancer in 1\textsuperscript{st} degree relative

- FDG avid thyroid nodules
  - 33\% risk of Ca, unless diffuse (thyroiditis)
Workup of thyroid nodule

- **History:**
  - History of H&N radiation
  - total body irradiation for BMT
  - family history of thyroid CA, or thyroid cancer syndrome (Cowden’s, familial polyposis, Carney complex, MEN 2, Werner syndrome)
  - rapid growth of nodule and hoarseness

- **PE:**
  - vocal cord paralysis
  - neck adenopathy
  - fixation of nodule
Lab tests/imaging if >1cm nodule

- Serum TSH
  - If low, then radionuclide thyroid scan to see if cold (likely Ca) or hot (less likely Ca) nodule
  - Higher TSH (or +TPO) = higher risk of Ca

- Thyroid ultrasound (for everybody)
  - Size and character of nodule
  - Cervical adenopathy
  - Cystic, posterior in gland, US features.

- Do **not** need serum Tg

- Equivocal need for Calcitonin screen
Approach to the Patient with Thyroid Nodules

Low TSH

Nuclear imaging

History

Physical TSH

Normal/high TSH

Molecular Testing?

Diagnostic US

Nodule(s) on US

FNA not indicated

Does not meet criteria for FNA

Meets FNA criteria

FNA

Indeterminate

Consider Nuclear Imaging

Consider Surgery

Molecular Testing?

Benign

Monitor

Malignant

Preop US

Surgery

Nondiagnostic

Repeat US-guided FNA

Role for FNA biopsy

- If nodule is predominantly cystic or posterior, recommend US guided FNA.

  - **Suspicious US Features:**
    - Hypoechogenicity
    - increased vascularity
    - irregular infiltrative margins
    - Microcalcifications
    - absent halo

- **Benign US Features:** Purely cystic, spongiform

- Routine FNA if <1cm not recommended unless:
  - Lateral and central nodes identified, family history, history of radiation, prior hemithyroidectomy & discovery of thyroid CA, and PET avid thyroid nodule
US features - Benign

Pseudonodules

Benign

Colloid nodules

Spongiform (‘leave me alone lesion’)

Images courtesy of B. Haugen, MD: used with permission
US features - Indeterminate

Hypoechoic
Sharp margins

Isoechoic
Internal vascularity

Mixed echogenicity
Taller than wide

Images courtesy of B. Haugen, MD: used with permission
US features - Malignant

Irreg margins
Internal echoes

Marked hypoechoic
Irregular margins

Abnormal LN

Marked hypoechoic
Irregular margins
Taller-than-wide

Images courtesy of B. Haugen, MD: used with permission
## What to biopsy?

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (≥ 5mm)</td>
<td>High risk (FH, radiation)</td>
</tr>
<tr>
<td></td>
<td>Abnormal LN (Bx LN)</td>
</tr>
<tr>
<td>≥ 1 cm</td>
<td>Microcalcifications</td>
</tr>
<tr>
<td></td>
<td>Solid nodule (esp hypoechoic)</td>
</tr>
<tr>
<td>≥ 1.5 cm</td>
<td>Solid (iso or hyperechoic)</td>
</tr>
<tr>
<td></td>
<td>Mixed cystic solid (suspicous features)</td>
</tr>
<tr>
<td>≥ 2 cm</td>
<td>Mixed (no suspicious features)</td>
</tr>
<tr>
<td></td>
<td>Spongiform</td>
</tr>
<tr>
<td>No biopsy (r/o malignancy)</td>
<td>Pure cyst</td>
</tr>
<tr>
<td></td>
<td>Spongiform?</td>
</tr>
</tbody>
</table>

| Table 1 |
The Bethesda System for Reporting Thyroid Cytopathology: Recommended Diagnostic Categories |

I. Nondiagnostic or Unsatisfactory
- Cyst fluid only
- Virtually acellular specimen
- Other (obscuring blood, clotting artifact, etc)

II. Benign
- Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc)
- Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context
- Consistent with granulomatous (subacute) thyroiditis
- Other

III. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance

IV. Follicular Neoplasm or Suspicious for a Follicular Neoplasm
- Specify if Hurthle cell (oncocytic) type

V. Suspicious for Malignancy
- Suspicious for papillary carcinoma
- Suspicious for medullary carcinoma
- Suspicious for metastatic carcinoma
- Suspicious for lymphoma
- Other

VI. Malignant
- Papillary thyroid carcinoma
- Poorly differentiated carcinoma
- Medullary thyroid carcinoma
- Undifferentiated (anaplastic) carcinoma
- Squamous cell carcinoma
- Carcinoma with mixed features (specify)
- Metastatic carcinoma
- Non-Hodgkin lymphoma
- Other

*Adapted with permission from Ali and Cibas.*
## Bethesda Classifications

### Table 2

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Risk of Malignancy (%)</th>
<th>Usual Management†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic or Unsatisfactory</td>
<td>1-4</td>
<td>Repeat FNA with ultrasound guidance</td>
</tr>
<tr>
<td>Benign</td>
<td>0-2</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance</td>
<td>~5-15†</td>
<td>Repeat FNA</td>
</tr>
<tr>
<td>Follicular Neoplasm or Suspicious for a Follicular Neoplasm</td>
<td>15-30</td>
<td>Surgical lobectomy</td>
</tr>
<tr>
<td>Suspicious for Malignancy</td>
<td>60-75</td>
<td>Near-total thyroidecтомy or surgical lobectomy§</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99</td>
<td>Near-total thyroidecтомy§</td>
</tr>
</tbody>
</table>

FNA, fine-needle aspiration.

* Adapted with permission from Ali and Cibas.³

† Actual management may depend on other factors (eg, clinical, sonographic) besides the FNA interpretation.

‡ Estimate extrapolated from histopathologic data from patients with “repeated atypicals.”

§ In the case of “Suspicious for metastatic tumor” or a “Malignant” interpretation indicating metastatic tumor rather than a primary thyroid malignancy, surgery may not be indicated.
Indeterminate cytology

- “Atypia” or “Follicular lesion of undetermined significance” (Class III)
  - 5-10% risk of malignancy
- “Follicular neoplasm” or “Hurthle cell neoplasm” (Class IV)
  - up to 15-30% of FNA specimens
  - 20-30% chance of malignancy
- Higher risk: >4cm, Male gender, older patients
- Molecular markers: Veracyte
**Indeterminate cytology**

- If follicular neoplasm:
  - Consider $^{123}$I scan, esp if serum TSH in low-normal range to evaluate for a hot nodule (more likely to be benign)

- If suspicious for PTC or Hurthle cell neoplasm:
  - Scan not needed
Afirma Veracyte

- 167 gene expression in indeterminate nodules >1cm
  - Identifies benign, rather than malignant nodules by focusing on benign gene expression
- 92% sensitivity with 52% specificity
- Negative predictive value 85-95%
- Helpful in patients wary of surgery

Implementing Afiroma Thyroid FNA Analysis into Practice
(A Representative Schematic)

Physician Performs FNA → Cytopathology

- Benign
  - Follow with Ultrasound

- Indeterminate
  - Gene Expression Classifier
    - BENIGN (94% NPV)
    - SUSPICIOUS

- Suspicious / Malignant
  - Surgical Consult
Follow up of thyroid nodules

- If benign, need follow up
  - Up to 5% false negative rate
- Serial US 6-18 months after initial FNA.
  - If no growth, then may extend to 3-5 year repeat US
- Repeat biopsy if:
  - 20% increase in diameter with 2mm growth in 2 dimensions
  - 50% volume increase
- If benign <2cm, rate of growth did not distinguish between malignant and non-malignant nodules
Follow up of benign nodules

- Recurrent cystic thyroid nodules should be removed based on compressive symptoms or cosmetic reasons
- DO NOT give suppressive treatment with Levothyroxine.
Multinodular disease?

- Multiple thyroid nodules have same risk of malignancy as solitary
- Solitary nodule does have higher risk of malignancy than nonsolitary nodule
  - Risk of malignancy per patient was same and independent of number of nodules
- If multiple nodules >1cm, biopsy more suspicious appearing one on US
- If both normal on US, biopsy the larger one
Multinodular disease

- If low-normal serum TSH:
  - RAI scan may be used to differentiate the two
  - FNA iso- or non-functioning nodules (>1-1.5cm), along with US features
Measure TSH (A)

US (neck) in all patients with suspected nodule (A)

Consider surgery for non-diagnostic solid nodules (B)

Molecular markers may be considered (C)

Benign nodule: FU US 6-18 months (C)

Routine LT4 not recommended for benign nodules (F)

Children same approach as adults (A)

Pregnancy – biopsy nodules (A), defer surgery for PTC unless growing (C), consider LT4 (C)
Well differentiated thyroid cancer

- 85% are PTC, 10% FTC, 3% Hurthle cell
- PTC and FTC similar prognosis
- Some subsets have worse prognosis:
  - Tall cell, columnar cell, diffuse sclerosing
  - Extensive vascular invasion, invasion into extrathyroidal tissue, necrosis, mitoses
  - Trabecular, insular, solid
Goals of therapy

- Remove primary tumor
- Minimize treatment-related morbidity
- Permit accurate staging
- Postop treatment with RAI
- Permit long-term surveillance
  - WBS
  - Tg
- Minimize risk of disease recurrence and metastatic spread
Preoperative staging

- Neck ultrasound
  - 20-50% Ca pts have spread to cervical LN
  - Micrometastases can approach 90% in some studies
  - Can only identify ½ the LN due to overlying thyroid gland

- Confirm malignancy with FNA – may change surgical approach (20-31%)

- Routine U/S for contralateral lobe and cervical neck nodes important

- Routine use of CT, MRI, PET not recommended

- No need for preop serum Tg
What type of operation?

- Nondiagnostic, suspicious, or suggestive of follicular neoplasm:
  - Risk higher with >4cm tumor, atypical features, radiation exposure, and family history of cancer, then suggest total thyroidectomy

- If indeterminate, a lobectomy is reasonable

- If indeterminate with bilateral nodular disease, can undergo total thyroidectomy
If FNA = malignancy

- Near-total (leaving <1g of tissue near RLN insertion) or total thyroidectomy if:
  - >1cm
  - Contralateral thyroid nodules
  - Regional or distant mets present
  - History of radiation therapy
  - First degree relative with DTC
  - Older age (>45) maybe
Lymph node dissection

- If involved level VI, then would perform therapeutic central neck dissection
- Prophylactic central neck may be considered in patients with advanced PTC (T3 or T4)
- Small PTC (T1 or T2) clinically node negative or follicular cancers do not need central neck dissection
- Lateral neck dissection only in cases of biopsy proven metastatic disease
Completion thyroidectomy?

- Patients who would have been offered total thyroidectomy should receive completion thyroidectomy.
- Those with <1cm cancers, unifocal, intrathyroidal, node negative, low-risk tumors may not need completion.
- Unknown if RAI ablation of remaining side is equivalent – thus not recommended.
ATA 2009 Post Op Staging Guidelines

Low Risk Patients Have The Following Characteristics

- No local or distant metastases
- All macroscopic tumor has been resected
- There is no tumor invasion of locoregional tissues or structures
- The tumor does not have aggressive histology (e.g. tall cell, insular, columnar cell carcinoma) or vascular invasion
- And, if $^{131}$I is given, there is no $^{131}$I uptake outside the thyroid bed on the first post-treatment whole body radioiodine scan

Intermediate Risk Patients Have The Following Characteristics

- Microscopic invasion of tumor into perithyroidal soft tissues
- Cervical LN mets OR I-131 uptake outside the thyroid bed
- Aggressive histology or vascular invasion

High Risk Patients Have The Following Characteristics

- Macroscopic tumor invasion
- Incomplete tumor resection
- Distant metastases
- Elevated Tg out of proportion to what is seen in post treatment scan

# Thyroid Cancer Risk Stratification

<table>
<thead>
<tr>
<th>Feature</th>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>&lt;45 years</td>
<td></td>
<td>&gt;45 years</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Female</td>
<td></td>
<td>Male</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>&lt;2 cm</td>
<td></td>
<td>&gt;4 cm</td>
</tr>
<tr>
<td><strong>Extent</strong></td>
<td>Intraglandular</td>
<td></td>
<td>Extraglandular</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td>Low</td>
<td></td>
<td>High</td>
</tr>
<tr>
<td><strong>Distant Metastases</strong></td>
<td>Absent</td>
<td></td>
<td>Present</td>
</tr>
<tr>
<td><strong>Treated, %</strong></td>
<td>39</td>
<td>39</td>
<td>22</td>
</tr>
<tr>
<td><strong>Death Rate, %</strong></td>
<td>&lt;1</td>
<td>13</td>
<td>53</td>
</tr>
</tbody>
</table>


Standard Treatment of Thyroid Cancer

- Total Thyroidectomy
- RAI Ablation
- Suppression Therapy

RAI Ablation after 1 Year

Whole Body Scan Tg Assay

Standard Treatment of Thyroid Cancer

Phases of Follow-Up

**Phase 1**
- Determine extent of disease
- Treat detectable disease

**Initial surgery**
- RAI ablation

**Phase 2**
- No detectable disease
- At risk for recurrence

- Whole body scan
- Stimulated Tg

**Phase 3**
- Long-term disease-free
- Survivor. Low risk for recurrence

- Suppressed Tg assay
- TSH assay
- T4 assay
- Neck examination

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I-131 Therapy

- Adjuvant ablation of residual thyroid tissue and possible microscopic residual cancer
- Imaging for possible metastatic disease
- Treatment of known residual or metastatic disease
  - Uptake dependent upon adequate stimulation by TSH
    - Levothyroxine withdrawal
    - Thyrogen (recombinant TSH)
  - Effectiveness reduced by stable iodide excess
    - Recent CT scan with contrast
    - Exogenous iodine supplements
    - Amiodarone
Postoperative RAI

- FTC and Hurthle cell considered higher risk and RAI utilized.
- RAI not recommended for <1cm (unless high risk features)
- If multifocal all <1cm (in absence of other high risk features), suggest RAI is not beneficial
- RAI recommended for:
  - Known distant metastasis
  - Gross extrathyroidal extension
  - Size >4cm
  - Select patients 1-4cm: lymph node mets, age, size, extrathyroidal extension
## Major factors impacting decision making in RAIA: T factors

<table>
<thead>
<tr>
<th>Factors</th>
<th>Description</th>
<th>Decrease risk of death</th>
<th>Decrease risk of recurrence</th>
<th>Facilitate initial staging and f/u</th>
<th>RAI usually recommended</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>1cm or less or multifoc</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>1-2cm (IT)</td>
<td>No</td>
<td>??</td>
<td>Yes</td>
<td>Selective</td>
<td>I</td>
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<tr>
<td>T2</td>
<td>&gt;2-4cm (IT)</td>
<td>No</td>
<td>??</td>
<td>Yes</td>
<td>Selective</td>
<td>C</td>
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<tr>
<td>T3</td>
<td>&gt;4cm</td>
<td>No</td>
<td>??</td>
<td>Yes</td>
<td>Yes</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>&lt;45y</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>≥45y</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>B</td>
</tr>
<tr>
<td>Min ETI</td>
<td>No data</td>
<td>No data</td>
<td>Yes</td>
<td>Yes</td>
<td>Selective</td>
<td>I</td>
</tr>
<tr>
<td>T4</td>
<td>Gross ext</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>B</td>
</tr>
</tbody>
</table>

**Note:**
- **No** = not recommended
- **Yes** = recommended
- **Selective** = recommendation depends on additional factors

?? = either conflicting or inadequate data, cannot recommend either for or against

However, selected patients within this subgroup with higher risk features may benefit.
Major factors impacting decision making in RAIA: N/M factors

<table>
<thead>
<tr>
<th>Factors</th>
<th>Description</th>
<th>Decrease risk of death</th>
<th>Decrease risk of recurrence</th>
<th>Facilitate initial staging and f/u</th>
<th>RAI usually recommended</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx N0</td>
<td>No Documented Nodes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>I</td>
</tr>
<tr>
<td>N1</td>
<td>&lt;45y</td>
<td>No</td>
<td>???</td>
<td>Yes</td>
<td>Selective</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>≥45y</td>
<td>???</td>
<td>???</td>
<td>Yes</td>
<td>Selective</td>
<td>C</td>
</tr>
<tr>
<td>M1</td>
<td>Distant Mets</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>A</td>
</tr>
</tbody>
</table>

??? = either conflicting or inadequate data, cannot recommend either for or against
However, selected patients within this subgroup with higher risk features may benefit.
Delivery of RAI

How is it done?

Prepared for RAI?

- Low iodine (<50ug/d of dietary iodine) diet for 1-3 weeks
  - Effectiveness of RAI reduced by stable iodide excess
    - Recent CT scan with contrast
    - Exogenous iodine supplements
    - Amiodarone

- Requires TSH stimulation >30 for uptake in tumor
  - Thyroxine withdrawal for 3 weeks or
  - rhTSH (thyrogen) stimulation

- Pre-treatment RAI scan – useful for determining extent of thyroid remnant, or if dose of RAI or decision to treat is based on this
Scheduling of rhTSH Doses and Diagnostic Procedures

- Recommended dose: 0.9mg IM q24 hr x 2 doses
- Serum Tg protocol is identical for both Tg alone testing and when combined with WBS
- 4 mCi $^{131}\text{I}$ should be used for scans; which should be acquired for $\geq 30$ minutes and/or $\geq 140,000$ counts

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>rhTSH 0.9 mg</td>
<td>rhTSH 0.9mg</td>
<td>$^{131}\text{I}$ (if WBS is performed)</td>
<td></td>
<td>Serum Tg with or without WBS</td>
</tr>
<tr>
<td>Monday</td>
<td>Tuesday</td>
<td>Wednesday</td>
<td>Thursday</td>
<td>Friday</td>
</tr>
</tbody>
</table>

Please see Thyrogen safety information
Dosing of Initial RAI Ablation

- 30-200 mCi
  - Less if thyroid hormone withdrawal
  - More if rTSH (thyrogen)
    - 30-50 mCi for lower risk (<45yo or <2cm)
    - 75-100 mCi for intermediate risk
    - 150-200 mCi for high risk (distant mets, macroscopic disease)

- Post therapy scan is recommended 2-10 days after therapeutic dose given
  - Pick up new abnormal uptake/distant mets
Complications of RAI therapy

- Transient loss of taste and sialadenitis
- Salivary gland damage, dental caries, secondary malignancies, nasolacrimal alteration
- Secondary malignancies: bone and soft tissue (breast, colorectal, kidney, salivary, myeloma, leukemia)
  - Dose related, particularly >500-600 mCi cumulative exposure
- Should not be given to pregnant or nursing women, renal insufficiency
- Should avoid pregnancy for 6-12 months
TSH suppression

- DTC expresses TSH receptor and responds to TSH stimulation by increasing cell growth
- Attempt to reduce risk of recurrence with supraphysiologic doses of LT4
- TSH Targets
  - <0.1 mU/L Good for high-intermediate risk thyroid cancer pts
  - 0.1-0.5mU/L appropriate for low-risk patients
  - 0.3-2 in low risk (disease free, or microPTC)
- Adverse effects and considerations:
  - Angina in known CAD, Afib, osteoporosis
# Target TSH Suppression in Patients With Thyroid Cancer

<table>
<thead>
<tr>
<th>TSH, mIU/L</th>
<th>Low to Undetectable</th>
<th>Suppressed but Detectable</th>
<th>Low Normal</th>
</tr>
</thead>
</table>
| <0.1       | • Persistent or recurrent disease  
            • High-risk patients | • Most patients with no evidence of disease | • Very low-risk patients  
            • Long-term survivors |


Braverman LE, Utiger RD, eds. *Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text.*  
Other adjuvant therapy

- External beam irradiation
  - Consider for primary tumor age > 45, gross extrathyroidal extension, or in whom further surgery or RAI would likely be ineffective

- No current role for chemotherapy
WDTC long term management: 1\textsuperscript{st} 6-12 months post ablation

- Periodic neck US should occur at 6, 12 mos
- Serum Tg q6-12months with Tg antibodies assessed
  - Stimulated Tg> 2 ng/mL sensitive for persistent tumor
  - +Tg Ab (25% of pts) falsely lowers serum Tg
    - Persistently +Tg Ab usually indicates +thyroid tissue
  - In low risk pts Tg measured after thyroxine withdrawal or rhTSH stimulation yearly

- WBS
  - Do not necessarily need whole body radionuclide scanning for low risk.
  - If med-high risk, q1 year x 2
    - +WBS: retreat with RAI 100-150 mci
WDTC long term management: >1 year ablation

- Yearly TSH, FT4, Tg
  - ↑Tg = TUS & bx, WBS, CT, PET
- Negative RAIU and scan x 2 = no need for further WBS unless ↑Tg
  - Consider more RAI if +WBS
- Neck US q1-2 year, eventually q3-5 years
Ultrasound

- Central and lateral neck node US done at 6-12 months, and then periodically (q1-3 yrs) depending on risk and Tg status
- If positive result changes management, suspicious 5-8mm lymph nodes should be biopsied with Tg measurement in needle washout fluid
Conclusions

- Management of WDTC is a multi-disciplinary approach
- There are numerous subtleties to its management which are not always data driven
- Must consider the disease and the patient when making management decisions
Head and Neck Tumor Board

5/3/2013
Axial CT Images showing multiple sites of adenopathy in the right neck
Axial CT showing adenopathy more inferiorly and right thyroid mass
Coronal and Sagittal Images showing extent of adenopathy