Anaplastic and other locally advanced thyroid carcinoma

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Thyroid carcinoma
Types and locally invasion

- Well-differentiated
  - papillary
  - follicular
- Poorly differentiated (insular)
- Undifferentiated (anaplastic)
- Medullary
- Others: thyroid lymphoma, squamous cell carcinoma, etc.
Anaplastic carcinoma

Introduction

- 2-10% of all primary thyroid cancer
- Peak incidence: 6th and 7th decade
- One of the most lethal tumour
- ½ of thyroid cancer death
- Decreasing in incidence:
  - refined and accurate diagnosis
  - early resection for differentiated thyroid cancer
  - iodine prophylaxis
  - improvement in socioeconomic status
Anaplastic carcinoma

Clinical features

• History of long-standing goitre
• Rapidly enlarging neck mass
• Pain and compressive symptoms
• Invasion of contiguous structures (70%):
  – trachea, larynx, oesophagus, carotid vessels and skin
  – hoarseness of voice due to RLN palsy
• Cervical nodal metastases (40%)
• Distant metastases (50%)
  – lung, bone, liver, brain and adrenal glands
  – 25% during course of disease
Anaplastic carcinoma

Pathology

- Spindle, polygonal and giant cells
- Epithelial neoplastic structures
- Sarcomatous differentiation components
- Concomitant WDTC: 24-89%
  - WDTC to insular to undifferentiated
  - accumulation of allelic loss
  - dedifferentiation/ transformation: <1%
Anaplastic carcinoma

**Diagnosis**

- Clinical suspicion
- FNAC: immunotyping and markers
- DDx: MTC, insular carcinoma, lymphoma, SCC
- Open/core biopsy
- Biopsy of LN or metastases
- WDTC or recurrence with anaplastic transformation
Anaplastic carcinoma

Investigations

- Blood tests
- Laryngoscopy
- CXR
- USG/CT/MRI
- Bone scintigraphy
- PET scan
Anaplastic carcinoma

Treatment dilemma

- Surgical emergency
- Delayed presentation
- Advanced disease
- Elderly with poor co-morbid state
- Aggressive and rapidly growing
- Frequent distant metastases
- Lack of effective treatment
- Invariably palliative and fatal
Anaplastic carcinoma
Options

• Surgery
• Chemotherapy
• Radiotherapy
• Combined multimodal therapy
• New targeted therapies
Anaplastic carcinoma

Surgical options

• Resection: complete/debulking
  – for selected patients
  – potential curative
  – facilitate postoperative therapy
  – possibly palliative
  – avoid tracheostomy
  – pre-requisite
    • preserve vital structures
    • without inducing morbidity
Anaplastic carcinoma

Surgical options

- Radical resection
  - inducing morbidity
  - low chance of cure
  - poor form of palliation

- Tracheostomy
  - palliating airway obstruction
  - not performed prophylactically
Anaplastic carcinoma

Treatment options

• Radiotherapy
  – combined with surgery or chemotherapy
  – postoperative radiation
  – hyperfractionated radiotherapy + chemotherapy
  – surgery for residual disease in responders
  – can be primary treatment option for all patients

• Chemotherapy
  – combined with surgery and radiotherapy
  – doxorubicin as monotherapy
    • poor response rate
    • as radiosensitizer
  – cyclophosphamide, bleomycin, 5-FU
  – taxol or taxotere
Management strategies
Management strategies
## Treatment outcome of anaplastic carcinoma

<table>
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<tr>
<th>Author (Yr)</th>
<th>No.</th>
<th>Rx</th>
<th>Median (mean) survival (mths)</th>
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Anaplastic carcinoma

Novel therapies

• Target therapy:
  – EGFR and VEGF inhibitors
  – sodium iodide symporter re-differentiation therapy
  – bovine seminal ribonuclease
  – vascular targeting therapy: combretastatin A4
  – Gene therapy: p53 and others (bcl-2, cyclin D1, β-catenin, Met, c-myc, Nm23 and ras)
  – combined with chemotherapy

• Evidence:
  – inhibit cellular proliferation and induce apoptosis in cell lines
  – control tumour growth in nude mice xenograft
Anaplastic thyroid carcinoma

Summary

• Anaplastic thyroid carcinoma commonly presents as locally advanced disease associated with distant metastases in elderly patients

• It is an invariably lethal disease associated with dismal prognosis because of the lack of effective therapies

• Treatment aims at effective palliation in particular to airway obstruction

• The development of new target therapies is essential and promising
Locally advanced thyroid carcinoma

Well-differentiated thyroid carcinoma (WDTC)

- an adequate resection feasible
- potentially cure after radical resection
- availability of adjuvant therapies
- associated with long-term survival
Well differentiated thyroid carcinoma
Treatment and controversies

• Primary treatment
  – thyroidectomy
    • extent and radicality
  – neck dissection for nodal metastases
    • nature and type

• Adjuvant therapies
  – administration of $^{131}$I ablation
  – indication of external radiation therapy
  – need of $T_4$ suppressive therapy
Well differentiated thyroid carcinoma

Summary of treatment and outcome

- 80%: do well with lobectomy or more aggressive treatment
- 5%: do poorly despite aggressive treatment
- 15%: benefit from total thyroidectomy/aggressive resection followed by I^{131} ablation and TSH suppressive therapy

<table>
<thead>
<tr>
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<th>Low risk</th>
<th>High risk</th>
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<tr>
<td>% of patients</td>
<td>85-90</td>
<td>10-15</td>
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<tr>
<td>Mortality (10-20 yrs)</td>
<td>2-5 %</td>
<td>40-50 %</td>
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<tr>
<td>Recurrence rate</td>
<td>10 %</td>
<td>45 %</td>
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Well differentiated thyroid carcinoma

Risk group stratification

• AGES (Age, Grade, Extent, Size)
• AMES (Age, distant Metastasis, Extrathyroidal Invasion, Size)
• Degroot (Intrathyroidal, Lymph nodes, Extrathyroidal invasion, Metastasis)
• UICC/AJCC pTNM classification
• MACIS (Distant Metastasis, Age, Completeness of resection, Invasiveness, Size)
Locally advanced WDTC
Management and considerations

• High-risk patients
  – invasion/pT4/extrathyroidal extension
  – incomplete resection

• Management
  – extent of surgical resection
    • total thyroidectomy
    • complete/radical resection
  – postoperative adjuvant therapies
    • I$^{131}$: improve survival and decrease recurrence
    • external RT: facilitate locoregional control
Locally advanced WDTC

Value of external beam irradiation (EBRT)

- High-risk disease: pathological stage pT4 or N1

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Local recurrence rate at 10-yr (%)</th>
<th>Surgery+\textsuperscript{I\textsubscript{131}}</th>
<th>Surgery+EBR+\textsuperscript{I\textsubscript{131}}</th>
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Locally advanced WDTC
Types of adjacent structures invasion

- strap muscles
- perithyroidal soft-tissue
- recurrent laryngeal nerve
- upper aerodigestive tract
  - trachea
  - larynx
  - oesophagus
- vascular structures
- bony structures: manubrium
Locally advanced/invasive WDTC
Definition and incidence

• Extrathyroidal extension ≠ pT4 tumours
  – pT3: sternohyoid muscle, perithyroid tissue
  – pT4a: larynx, tracheal, oesophagus, recurrent nerve
  – pT4b: prevertebral fascia, mediastinal/carotid vessels
• Significance of aerodigestive tract invasion:
  – up to 20% overall incidence
  – up to 50% disease-related death
    • asphyxia
    • hemoptysis
Locally advanced/invasive WDTC
Therapeutic challenge and controversy

• Surgical options:
  – radical resection (pT3 and pT4a)
  – conservative shaving procedure
    • residual microscopic tumour (pT4a)
    • gross residual tumour (pT4a and pT4b)

• Outcome considerations:
  – oncological principle
  – functional preservation
  – medical evaluation/physical conditions
  – availability of adjuvant therapy
WDTC with trachea invasion

**Shaving procedure**

- 28 of 47 patients with larynx or trachea invasion
- Curative resections
- Without laryngectomy or tracheal resection
- Outcome:
  - 10-yr overall survival rate: 62%
  - 10-yr disease-free survival rate: 50%
- Recommendation:
  - surgical removal of all gross disease
  - preservation of function if possible

WDTC with trachea invasion

Shaving procedure

• 1979-1988:
  – 16 of 432 patients
  – 14 PTC and 2 FTC

• Treatment:
  – cartilage-shaving with gross tumour removal
  – postoperative I$^{131}$ (n=11) and/or EBR (n=5)

• Mean follow-up: 70.7 (36-122) months
  – 7 died (22-82 months)
  – 5 persistent/recurrent disease (43-122 months)
  – 4 disease free (49-112 months)

• Recommended for more extensive resection

Park CS, et al Head Neck 1993
Locally advanced PTC
Types of invasion and resection

• 1940-1990: n=262
• Extrathyroidal invasion
• 63% 10-yr overall survival
  – Types of invasion
  – Type of resection
    • I: complete resection
    • II: shave resection
    • III : gross tumour left

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<th>Factor</th>
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<td>0.10</td>
<td>1.42</td>
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## Different surgical strategies

### Long-term survival

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<tr>
<th>Author(yr)</th>
<th>S (No.)</th>
<th>C (No.)</th>
<th>In (No.)</th>
<th>Mean FU (yr)</th>
<th>S Vs C</th>
<th>C Vs In</th>
<th>S Vs In</th>
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S=shaving; C=complete resection; In=incomplete resection; *=statistically significant
+ve: better survival; -ve: worse survival; ND: no difference; -: not available
WDTC with invasion of larynx and trachea

Staging system

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<th>Stage</th>
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<td>I</td>
<td>Extends through the capsule of the thyroid gland and abuts the external perichondrium</td>
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<td>II</td>
<td>Invades between the rings of cartilage or destroys cartilage</td>
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<tr>
<td>III</td>
<td>Extends through the cartilage or between the cartilaginous plates into the lamina propria of the tracheal mucosa</td>
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<tr>
<td>IV</td>
<td>Extends through the entire thickness of, and expands the trachea mucosa, and is visible through a bronchoscope</td>
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Shin MH et al Hum Pathol 1993
WDTC with aerodigestive tract invasion

Types of resection and reconstruction

WDTC with aerodigestive tract invasion

Frequency of resection types

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<td><strong>Total</strong></td>
<td><strong>284</strong></td>
<td><strong>17 (6%)</strong></td>
<td><strong>24 (8%)</strong></td>
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Surgical strategies

Lymph nodes

Recurrent nerve

Internal jugular vein

Strap muscle
Surgical strategies
Shaving resection
Circumferential tracheal resection
Preservation of recurrent laryngeal nerve
Laryngotracheal resection
Locally advanced WDTC

Summary (1)

- Management of locally advanced WDTC depends on the extent and site of invasion

- Complete resection should be attempted without inducing significant morbidity

- Shaving with possibly incomplete resection should be considered for functional preservation aiming at macroscopic clearance
Locally advanced WDTC

Summary (2)

• Laryngotracheal resection and reconstruction is indicated for selected patients to achieve macroscopic clearance

• Postoperative therapies are effective in improving survival and controlling local recurrence for patients with incomplete excision

• Surgical decision should be individualized because of the variable tumour behaviour, functional disability of radical resection and the availability of postoperative adjuvant therapies