5.1 Background

Thyroid cancer can be divided into three main groups: tumors with follicle cell differentiation (differentiated thyroid cancer), tumors with C-cell differentiation (medullary thyroid cancer), and anaplastic carcinomas. The insular carcinoma takes an intermediate place between differentiated and anaplastic cancer. Within the category of differentiated cancers, a distinction is made between papillary and follicular tumors. Papillary tumors are found most frequently and several subtypes are defined referring to tumor capsule invasion, the extent of invasion, the presence of sclerosis and oncocytic or oxyphil cells. The last subtype is also called Hürthle-cell carcinoma and is of critical importance because iodine uptake is often low or completely missing. C-cell cancer can develop spontaneously or be genetically determined as familial medullary cancer or in a multiple endocrine neoplasia (MEN-2a/MEN-2b).

Differentiated thyroid cancer (DTC) occurs in three to five per 100,000 inhabitants and represents about 1% of all malignant tumors [33]. Incidence increases with age, as shown in autopsy studies, with rates of occult thyroid cancer in up to 35% of cases. This might be explained by the biological behavior of DTC known to be a very slowly growing tumor entity. An absolute increase of DTC is observed after ionizing radiation of the thyroid during childhood. Whether an increased iodine supply leads to a higher rate of DTC is not clear. However, there is a relative shift in histological findings from follicular to more frequent papillary cancers after better iodine supply.

Important prognostic factors are age, tumor stage, and histopathological grading. The TNM classification according to the recommendations of the International Union Against Cancer/Union Internationale Contre le Cancer (UICC) [32] is given in Table 5.1. Histopathological grading is based on the evaluation of nuclear atypia, the extent of necrosis, and vascular invasion [1]. Follicular carcinomas generally exhibit more frequent distant metastases in the lungs and bones than papillary cancers. These tend to spread in the cervical and mediastinal regional lymph nodes, a stage that most authors, in contrast to other tumors, consider not to be associated with a poorer prognosis for the group of differentiated tumors. In most cases, prognosis is favorable [10]. However, there are marked differences depending on the tumor type. It has been shown that the 10-year survival rate for papillary, follicular, insular and anaplastic thyroid cancer is 89%, 68%, 20%, and 2%, respectively. The 10-year survival rate for non-hereditary medullary cancer lies between 50% and 70%. These survival rates demonstrate the prognostic value of the histologic diagnosis.

For clinical purposes, different staging systems have been developed to divide patients into low- and high-risk cases. For differentiated (papillary and follicular) thyroid cancer,
a widely accepted system is the already men-
tioned TNM-based concept of the UICC that is
shown in Table 5.2. It was demonstrated that
age is one of the most important prognostic fac-
tors. Therefore, in this staging system, patients
are grouped in a section with either below or
equal/over 45 years. Surprisingly, patients un-
der 45 years of age enjoy the favorable status
of stage II even when distant metastases are
present. This results from the experience that
pulmonary metastatic disease is curable by
high-dose iodine therapy in younger patients.
Especially in younger patients with diffuse

Table 5.2. TNM stage classification for differentiated
thyroid cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>&lt; 45 years</th>
<th>DTC &gt; 45 years or medullary cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Any T, any N, M0</td>
<td>T1 N0 M0</td>
</tr>
<tr>
<td>II</td>
<td>Any T, any N, M1</td>
<td>T2 N0 M0</td>
</tr>
<tr>
<td>III</td>
<td>–</td>
<td>T3 N0 M0 or T1–3 N1a M0</td>
</tr>
<tr>
<td>IV</td>
<td>–</td>
<td>T1–3 N1b M0 or T4 any N M0 or any T any N M1</td>
</tr>
</tbody>
</table>

pulmonary spread which can be visualized by
scintigraphy but not by radiography or CT of
the chest [19], prognosis is still good when suf-
ficient iodine uptake is present. The 10-year
survival for stage II patients is estimated at a
level of 87%. However, it must be mentioned
that some of these patients might demonstrate
recurrent pulmonary disease even after a time
interval of 20 years. Furthermore, patients
with bone metastases cannot be cured but sta-
obilized over a long period. Bone metastases are
a rare finding in differentiated thyroid cancer
and are more frequently found in less differen-
tiated cancers.

The prognostic relevance of lymph node me-
tastases is an issue of discussion because some
studies have shown a prognostic relevance of
lymph nodes but others have not. However, it
seems to be generally accepted that lymphatic
disease is of low prognostic impact at least in
patients with differentiated thyroid cancer
aged under 45 years. In patients over 45 years,
the presence of pre- and peritracheal (cervico-
central, N1a) and cervicomedial or medias-
tinal (N1b) lymph node metastases is grouped
as stage III and stage IVA in the UICC system,
indicating a higher risk. This is especially true