Systematic review
Impact of comorbidity on treatment outcome in head and neck squamous cell carcinoma – A systematic review
Charlotte Rotbøl Bøje
Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark

ABSTRACT
The significant association with tobacco and alcohol combined with advanced age at time of diagnosis predispose head and neck squamous cell carcinoma (HNSCC) patients to increased risk of comorbidities. The presence of comorbidity affects treatment, treatment selection and subsequent outcome. Multiple studies have demonstrated comorbidity to be a strong prognostic factor for survival, and therefore comorbidity can be a major confounder in clinical trials. This review provides a summary of the current literature on comorbidity in head and neck cancer, measurements of comorbidity, the impact of comorbidity on treatment, treatment selection, and survival. A systematic search was performed in six electronic databases. In all, 31 papers were selected for this review. A meta-analysis on the prognostic impact of comorbidity was performed including 10 studies. Furthermore, 21 studies concerning comorbidity were reviewed. Several valid indices to classify comorbidity were described in the literature, none proven to be superior over the other. The prevalence of comorbidity increased with age and the presence of comorbidity influenced treatment and treatment selection. Furthermore, comorbidity was associated with lower socio economic status and increased the risk of early retirement after treatment. The meta-analysis on comorbidity as a prognostic factor, including 22,932 patients, showed that overall survival was significantly worsened among patients with comorbidity (HR = 1.38 (1.32–1.43)). Increasing comorbidity-score was associated with increased risk of death. Comorbidity is important in HNSCC and significantly impacts on overall survival. Trials concerning HNSCC should always include information on comorbidity and randomized trials should stratify patients according to comorbidity in order to avoid bias in the study.

© 2013 Elsevier Ireland Ltd. All rights reserved. Radiotherapy and Oncology 110 (2014) 81–90

Head and neck cancer accounts for more than 650,000 new cases annually worldwide representing an estimated 6% of all cancers [1]. Head and neck cancer includes malignancies arising in the pharynx, larynx, oral cavity, the thyroid gland, paranasal sinuses, nasal cavity, and lip. The most common histological type is squamous cell carcinomas (HNSCC) occurring in the larynx, pharynx and oral cavity. Tumours in nasopharynx, nose and paranasal sinuses constitute a separate group with respect to epidemiology, histology, growth and prognosis.

The strongest etiological factors for HNSCC are long-term abuse of tobacco and alcohol which accounts for approximately 75% of all head and neck cancer. There is 5–25 fold increased risk of head and neck cancer in heavy smokers compared to non-smokers. Alcohol consumption significantly increases the risk of cancer, especially in the upper aerodigestive tract, and a synergistic effect of smoking and high alcohol consumption is evident [2]. Other etiological factors include the Human Papilloma Virus (HPV) which is a major cause of oropharyngeal cancer. A meta-analysis confirmed that the proportion of oropharyngeal carcinoma caused by HPV has increased significantly worldwide from 40% in studies recruiting patients before 2000 to 72% in studies recruiting patients after 2005 [3]. Head and neck cancers due to HPV have important clinical and prognostic differences compared with those typically associated with tobacco and alcohol use [4]. Epstein Barr Virus (EBV) is a strong etiologic agent in the pathogenesis of nasopharyngeal carcinoma [5]. The worldwide distribution of nasopharyngeal carcinoma shows remarkable geographical and ethnic variation, with very low incidence rates in most populations, but high rates in areas of southern China, southeast Asia, north Africa, and in the Inuit population in the Arctic [5].

The incidence of head and neck cancer increases with age, and in Europe, 98% and 50% of patients diagnosed are over 40 and 60 years of age, respectively [1]. The percentage of elderly patients with head and neck cancer is rising due to an overall increase in life
expectancy. The incidence of HPV-induced HNSCC is steadily increasing whereas the tobacco induced HNSCC is decreasing due to smoking cessation.

Comorbidity in HNSCC is common, both due to the etiology of the disease, and also due to the fact that it is a disease of the elderly [6–14] and as the world demographic is changing more elderly HNSCC patients will be diagnosed and comorbidity will be of increasing importance. Multiple studies have demonstrated comorbidity to be a strong prognostic factor for survival, and it could therefore be a major confounder in clinical trials. In the past older patients that were often excluded from clinical trials or comorbidity were considered to be an exclusion criteria and as a result the generalizability of these studies was limited to younger and more fit patients. However, if a substantial proportion of deaths among HNSCC patients is caused by comorbidity, we need to focus on comorbidity, and this knowledge can help to improve treatment planning and prognostications for HNSCC patients.

The aim of this paper was to review the current literature on comorbidity in HNSCC patients, the methods used to measure and quantify comorbidity in head and neck cancer, and the impact of comorbidity on treatment, treatment selection and prognosis.

**Methods**

A systematic search was done in the six electronic databases from their inception until November 2012: Medline/PubMed, Embase, The Cochrane library, bibliotek.dk (Danish database), Sve-Med+, and Cinalh. Search terms were compiled from the medical subject headings (MeSH) “head and neck neoplasm”, “comorbidity”, “aged”, and “radiotherapy”. A secondary citation search of included studies was also undertaken and no language restrictions were imposed. In all, 279 original papers were identified. After screening of the papers, 31 articles published from 1997 to 2013 were included for this review (Fig. 1). The reasons for exclusions of papers were mainly due to low quality of comorbidity information, comorbidity not being the primary focus of interest and therefore only used as a confounding factor without any further specifications, and a general lack of information needed to be included in this review.

**Measuring comorbidity**

Comorbidity is a multidimensional variable and several scoring indices have been developed to measure comorbidity. A comorbidity index stratifies patients into groups with a similar risk of comorbidity-induced short term mortality, making it possible to use it during the sampling and randomization process. To enhance the generalizability and to improve the comparability of studies, validated indices should be used. Moreover, if the same indices are used, studies can be compared, meta-analyses can be performed, and comorbidity can be assessed uniformly in prospective clinical trials.

Comorbidity indices can be classified into two groups, depending on the origin of the data. The first group is based on indices that rely on primary data and data are collected from physicians or nurses or through chart reviews. The second group of indices is based on secondary data and these data are derived from administrative health care databases [8].

A variety of comorbidity indices have been used in HNSCC [13–20] (Table 1).

Charlson Comorbidity Index [21] is the most widely used index in cancer. It was published in 1987 by Charlson et al., who evaluated and recorded all comorbid conditions on admission in all patients admitted to medical service in the Cornell Medical Centre in a one month period (N = 607). One year follow up was obtained and the prognostic impact of comorbid diseases was evaluated. Afterward, it was tested on a cohort of 685 women with breast cancer and a weighted index was created. The weighting is based on severity. It includes 19 comorbid conditions and predicts 1 and 10 year survival of hospitalized patients based on numbers and seriousness of comorbid conditions. It has been validated for head and neck cancer patients by Singh et al. [19], who concluded that the CCI was a valid prognostic indicator in HNSCC patients, and furthermore, that it was easy to use, readily applied and suitable for retrospective studies. However, since the development of this index, the prognostic impact of the diseases within the CCI may have changed.

The Adult Comorbidity Evaluation-27 (ACE-27) index, developed specifically for cancer patients, is another index commonly used in HNSCC patients. ACE-27 was derived from the original Kaplan-Feinstein Index. This index was modified and validated by Piccirillo et al. [10] and now includes 27 different comorbidity ailments from different organ systems. It classifies comorbidity separately as mild, moderate, and severe according to the degree of organ decompensation and prognostic impact [22], and an overall comorbidity score (none, mild, moderate, or severe) is assigned based on the highest ranked single ailment. In the cases in which two or more moderate ailments occur in different organ systems or disease groupings, the overall comorbidity score is designated as severe. The ACE-27 is frequently used in HNSCC and its ability to predict survival is good. However, the index has some drawbacks since it is very difficult to use retrospectively because some of the ailments need invasive confirmation or specialist evaluation and thereby there is a risk that data will be wrongly graded [10,23].

The Washington University Head and Neck Comorbidity Index (WUHNCI) was developed by Piccirillo et al. [18] who studied...
Table 1
Summary of comorbidity indices used to describe comorbidity in head and neck patients.

<table>
<thead>
<tr>
<th>Comorbidity Index</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlson Comorbidity Index (CCI) [21]</td>
<td>Includes 19 weighted conditions. Developed from a study of 1-year mortality of 559 patients and validated in breast cancer patients. Validated in HNSCC.</td>
</tr>
<tr>
<td>Adult Comorbidity Index-27 (ACE-27) [10]</td>
<td>Includes 27 conditions from different organ systems each graded according to severity. Developed for cancer patients, validated for HNSCC patients.</td>
</tr>
<tr>
<td>Washington University Head and Neck Index (WUHNCI) [18]</td>
<td>Includes conditions from different organ systems each graded according to severity. Developed specifically for HNSCC patients.</td>
</tr>
<tr>
<td>Kaplan-Feinstein Index (KFI) [71]</td>
<td>Includes conditions from different organ systems each graded according to severity. Developed for diabetes patients in 1973.</td>
</tr>
<tr>
<td>Klabunde Index [72]</td>
<td>Includes conditions from different organ systems each graded according to severity. Uses the comorbid conditions in the CCI but incorporates the diagnostic and procedure data contained in both Medicare hospital claims and Medicare physician claims.</td>
</tr>
<tr>
<td>National Cancer Institute Comorbidity Index [73]</td>
<td>Includes 27 comorbidities. Validated in colon cancer patients.</td>
</tr>
<tr>
<td>Head and Neck Cancer (HNCA) index [14]</td>
<td>Includes 7 weighted conditions. Consists of 8 weighted conditions. Based on the prevalence of diseases in HNC population.</td>
</tr>
</tbody>
</table>

1153 patients with HNSCC. Seven comorbid conditions were significantly related to survival and these conditions were weighted according to the prognostic importance and then combined to create the WUHNCI. The conditions identified were pulmonary disease, other cancer controlled, peripheral vascular disease, cardiac arrhythmia, congestive heart failure, other cancer uncontrolled, and renal disease. Sanabria et al. [17] later did a study to validate the WUHNCI, but it did not prove better than the ACE-27.

A revision of the CCI was performed by Bøje et al. and a revised head and neck CCI-index (HN-CCI) was proposed for RT-treated HNSCC patients. It was developed and validated in a large retrospective analysis of 9388 Danish HNSCC patients treated with radiotherapy (RT) [15] from 1992 to 2008. The individual prognostic impact of the 19 medical conditions within the CCI was evaluated and only six of the conditions had an impact on overall survival. The index consisted of six conditions; congestive heart failure, cerebrovascular diseases, chronic pulmonary diseases, ulcer diseases, diabetes, and liver diseases. By assigning those conditions one point each a comorbidity score was calculated, and the index was able to stratify patients in prognostic groups. The index is very simple to use and is made specifically for HNSCC patients treated with RT.

Several comparison studies have been performed to investigate which index should be used for HNSCC (Table 2). The results have been diverging and no index has proven to be superior over the other. The CCI is easy-to-use and suitable for retrospective register-based comorbidity assessment. However, the index does not take into account the severity of the conditions, but merely the presence or absence. The ACE-27 may be more sensitive but it is time consuming and cannot per se be calculated solely from administrative data. The HN-CCI has been developed specifically for RT-treated HNSCC patients and can be used both retrospectively and prospectively. The comorbidities present in the CCI but not in the HN-CCI did not have any prognostic impact and therefore the simplified HN-CCI will be better to use in HNSCC patients.

Other indices used are the Kaplan-Feinstein Classification (KFC), the Klabunde index, Cumulative Illness Rating Chronic disease Scale (CIRS), The Index of Co-existent Disease (ICED), and the National Cancer Institute comorbidity Index (Table 1).

Prevalence of comorbidity and the association to age

Aging is a highly individualized process. Most HNSCC patients are diagnosed in their fifth to seventh decade, an age at which many will have comorbidities [24]. However, the number, degree, and combinations of comorbidities greatly vary from one patient to another.

The prevalence of comorbidity among patients with HNSCC has been investigated in several studies (Table 3). Due to the etiology of the disease, the prevalence of comorbidity among HNSCC patients is generally high when compared to other cancer sites [25]. In a large retrospective population-based cohort study on 12,623 patients [24], comorbidity was present in 36% of the patients and the most common diseases were cardiovascular and pulmonary diseases. Increasing age was associated with increasing level of comorbidity which peaked around the age of 70 years after which it declined. In the group of patients between 60 and 69 years of age, 52% had comorbidity, whereas 35% of patients below 50 years had comorbidity. The disease pattern differed among the age groups. In the younger age groups liver diseases and diabetes were relatively more frequent whereas patients in the older age groups had relatively more cerebrovascular and cardiovascular diseases. Piccirillo et al. [26] also investigated the prevalence of comorbidities across the age spectrum, and also found increasing age to be associated with increasing number and severity of comorbidity. Moreover, some comorbid diseases were found to be more frequently present in younger patients such as obesity, drug abuse and liver diseases. Similar results were demonstrated in other studies [25–28] all demonstrating that comorbidity increased with age but was also present in younger patients.

In the past, age and the presence of comorbidity were exclusion criteria in many randomised clinical trials. Nowadays, more elderly patients are enrolled into clinical trials since no age-limits exist and this will help to increase the knowledge concerning treatment of elderly patients. Data confirms that elderly patients benefit from treatment and chronological age should not exclude patients from receiving aggressive treatment.

Effect of comorbidity and age on treatment selection

The presence of comorbidity and older age has a direct impact on treatment decision in daily clinical practice. A few studies investigated the influence of comorbidity on treatment selection; Bøje et al. [24] found that elderly patients received palliative treatment more often than younger patients whereas the presence of comorbidity did not influence the treatment received. Sanabria et al. [29] found that the selection of substandard treatment decreased overall and cancer-specific survival (Table 4). If the substandard treatment was based on low performance status, or severe comorbidity, this option was reasonable. However, selecting substandard treatment based on chronological age or mild comorbidity worsened the prognosis of the patients. Similar results from Derks et al. [30] who found that the presence of comorbidity was associ-
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Period</th>
<th>Tumor site</th>
<th>Comorbidity Index</th>
<th>Aim</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piccirillo et al. [20]</td>
<td>7131</td>
<td>NR, from SEER database</td>
<td>HNSCC all sites</td>
<td>CCI Klabunde Index WUNCHI HNCA-index</td>
<td>Comparison of two general comorbidity indices (CCI and Klabunde) with 2 disease specific indices (WUNCHI and HNCA index)</td>
<td>Both general and disease specific indices provided important prognostic information. No index proved to be superior over the other</td>
</tr>
<tr>
<td>Rogers et al. [13]</td>
<td>157</td>
<td>1992–1993</td>
<td>HNSCC all sites</td>
<td>ACE-27 CCI WUNCHI</td>
<td>Comparison of indices: ACE-27 CCI WUNCHI</td>
<td>Many pts had comorbidity in ACE-27 but not in CCI or WUNCHI – the converse did not apply. ACE-27 is difficult to use retrospectively. ACE-27 more sensitive in identifying comorbidity</td>
</tr>
<tr>
<td>Piccirillo et al. [18]:</td>
<td>1153</td>
<td>1980–1991</td>
<td>Oral cavity, oropharynx larynx</td>
<td>WUNCHI</td>
<td>Development of new comorbidity index: WUNCHI</td>
<td>WUNCHI consists of seven comorbid conditions. WUNCHI can be used both prospectively and retrospectively</td>
</tr>
<tr>
<td>Sanabria et al. [17]:</td>
<td>321</td>
<td>Validation of WUNCHI</td>
<td>HNSCC all sites</td>
<td>WUNCHI</td>
<td>Validation of WUNCHI: 74% WUNCHI: 39%</td>
<td>WUNCHI does not offer predictive ability similar to that of ACE-27</td>
</tr>
<tr>
<td>Reid BC [14]</td>
<td>9386</td>
<td>1985–1993</td>
<td>HNSCC all sites</td>
<td>CCI HNCA-index*</td>
<td>Comparison of the prognostic ability of HNCA-index, CCI and ATC-index*</td>
<td>All indices displayed strong associations with survival</td>
</tr>
<tr>
<td>Hall FS [16]:</td>
<td>379</td>
<td>1990–1996</td>
<td>HNSCC all sites</td>
<td>CIRS KFI CCI ICED Chronic disease scale</td>
<td>Comparison of indices</td>
<td>All but the chronic disease scale were successful in stratifying patients on survival</td>
</tr>
<tr>
<td>Singh et al. [19]:</td>
<td>88</td>
<td>1983–1994</td>
<td>HNSCC all sites</td>
<td>KFI CCI</td>
<td>Validation of CCI</td>
<td>Establishes the validity of CCI to be used to measure comorbidity in HNSCC patients</td>
</tr>
</tbody>
</table>

HNSCC: Head And Neck Squamous Cell Carcinoma; ACE-27: Adult Comorbidity Index-27; CCI: Charlson Comorbidity Index; KFI: Kaplan-Feinstein Index; WUNCHI: Washington University Head and Neck Cancer Index; HNCA-index: Head and Neck cancer index; CIRS: Cumulative Illness Rating Scale; ICED: The Index of Co-existent Disease, ATC-index: Alcohol–Tobacco-Related Comorbidity.

* ATC-index and HNCA-index developed specifically for this study.
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Period</th>
<th>Tumor site</th>
<th>Comorbidity Index</th>
<th>Treatment</th>
<th>Prevalence of comorbidity</th>
<th>Outcome</th>
<th>Not included in meta-analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanabria et al. [27]</td>
<td>310</td>
<td>1990–2003</td>
<td>HNSCC all sites</td>
<td>ACE-27</td>
<td>RT: 43% Surgery ± RT: 57%</td>
<td>75% had at least one comorbidity</td>
<td>OS: HR = 1.72 for ACE-27 = 1: HR = 1.83 (1.24–2.71) ACE-27 = 2: HR = 1.97 (1.42–2.71) ACE-27 = 3+: HR = 2.08 (1.38–3.11) DSS:ACE-27 = 1: HR = 1.52 (0.95–2.42) ACE-27 = 2: HR = 1.71 (1.15–2.56) ACE-27 = 3+: HR = 1.55 (0.91–2.62)</td>
<td></td>
</tr>
<tr>
<td>Alho et al. [55]</td>
<td>221</td>
<td>1986–1996</td>
<td>HNSCC all sites</td>
<td>CCI</td>
<td>RT: 37% Surgery ± RT: 63%</td>
<td>49% had at least one comorbidity</td>
<td>OS:CCI = 1–2: HR = 1.2 (0.8–1.8)CCI &gt; 2: HR 2.1 (1.2–3.7)DSS: NR</td>
<td></td>
</tr>
<tr>
<td>Hall et al. [57]</td>
<td>595</td>
<td>1990–1999</td>
<td>Hypopha-rynx</td>
<td>ACE-27</td>
<td>RT: 63% Surgery ± RT: 20% Palliative: 6%</td>
<td>64% had at least one comorbidity</td>
<td>OS:ACE-27 &gt; 0: HR = 1.16 (1.05–1.27)DSS: ACE-27 &gt; 0: HR = 1.09 (0.97–1.27)</td>
<td></td>
</tr>
<tr>
<td>Bøje et al. [24]</td>
<td>12,623</td>
<td>1992–2008</td>
<td>HNSCC all sites</td>
<td>CCI</td>
<td>RT: 65% No treatment: 9%</td>
<td>36% had at least one comorbidity</td>
<td>OS:</td>
<td></td>
</tr>
<tr>
<td>Bøje et al. [15]</td>
<td>9388</td>
<td>1992–2008</td>
<td>HNSCC all sites</td>
<td>HN-CCI</td>
<td>RT: 94% Surgery ± RT: 6%</td>
<td>36% had at least one comorbidity</td>
<td>OS:</td>
<td></td>
</tr>
<tr>
<td>Liu et al. [31]</td>
<td>214</td>
<td>2000–2003</td>
<td>HNSCC all sites</td>
<td>CCI</td>
<td>RT: 47%RT + CT: 53%</td>
<td>33% had at least one comorbidity</td>
<td>OS:</td>
<td></td>
</tr>
<tr>
<td>Datema et al. [7]</td>
<td>1371</td>
<td>1981–1998</td>
<td>HNSCC all sites</td>
<td>ACE-27</td>
<td>RT: 58% Surgery ± RT: 42%</td>
<td>36% had at least one comorbidity</td>
<td>OS:</td>
<td></td>
</tr>
<tr>
<td>Piccirillo et al. [22]</td>
<td>1086</td>
<td>1995–2001</td>
<td>HNSCC all sites</td>
<td>ACE-27</td>
<td>NR</td>
<td>54% had at least one comorbidity</td>
<td>OS:</td>
<td></td>
</tr>
<tr>
<td>Reid BC et al. [56]</td>
<td>9386</td>
<td>1985–1993</td>
<td>HNSCC all sites</td>
<td>CCI</td>
<td>NR</td>
<td>12 % (only comorbidity registered 1 year prior to diagnosis)</td>
<td>OS:</td>
<td></td>
</tr>
<tr>
<td>Gimeno-hernandez et al. [50]</td>
<td>231</td>
<td>1995–2002</td>
<td>Larynx</td>
<td>CCI</td>
<td>Surgery</td>
<td>94% had at least one comorbidity</td>
<td>OS:</td>
<td></td>
</tr>
<tr>
<td>Homma et al. [51]</td>
<td>156</td>
<td>1995–2005</td>
<td>Hypopharynx</td>
<td>ACE-27</td>
<td>RT:65%Surgery:33%</td>
<td>65%, also specified the type of comorbidity</td>
<td>OS: Moderate/severe vs. non/mild: HR = 1.80 (1.21–2.68)DSS: NR</td>
<td></td>
</tr>
<tr>
<td>Chen et al. [35]</td>
<td>182</td>
<td>1990–1995</td>
<td>Larynx</td>
<td>Modified medical comorbidity index</td>
<td>RT: 50%Surgery: 50%</td>
<td>64% had at least one comorbidity</td>
<td>OS: none vs. severe: HR = 2.3 (1.4–3.6)DSS: No comparison to no comorbidity</td>
<td></td>
</tr>
</tbody>
</table>
Comorbidity in head and neck cancer

Many studies have investigated the effect of comorbidity on treatment decisions in head and neck cancer patients. When comparing patients older than 70 years of age to patients younger than 70 years of age, but with the same comorbidity score, the older patients received standard treatment less often. Within the elderly patient group, comorbidity, advanced tumor stage, marital status, pain, functional status, and opinions about the length of life were all determinants for non-standard treatment. A study by Liu et al. [31] investigating the impact of comorbidity on survival for HNSCC patients treated by RT or chemoradiation (CRT), CRT was used less if the patients were old or had comorbidity. Similar results were found by Sarini et al. [32] investigating the outcome of 4610 HNSCC-patients. In all, 273 patients were 75 years of age and older and when compared with the rest of the patients, chemotherapy was administered less often in the elderly cohort and surgery was performed in a smaller proportion of older patients. On the contrary, there was no difference in radio-therapeutic treatments. Tolerance to treatment was similar and there was no difference in treatment-related deaths. Gourin et al. [33] did not find comorbidity to affect whether surgical versus non-surgical treatment was selected. Schofield et al. [34] concluded that "chronological age is not a reliable indicator of frailty, does not necessarily reflect biological age and cannot be used as a measure to select an appropriate therapeutic strategy for the elderly". In conclusion, most studies found that comorbidity affects the treatment-decision process, but age was the most important factor for treatment selection.

Comorbidity and surgery

The presence of comorbidity in surgery-treated HNSCC patients may modify the long term prognosis. This is due to postoperative complications and the comorbid patients may undergo conservative and less radical procedures [10,30,35]. Nao et al. [36] performed a study on 418 patients surgically treated with free-flap procedure after extensive surgery for head and neck cancer. Ninety-five of the patients were aged 70 years of age or above. Compared to younger patients, the elderly patients had more comorbidity. Having comorbidity was associated with higher rates of postoperative complications and also higher free-flap failure (defined as total necrosis of the free flap). In contrast, older age did not increase the risk of free-flap necrosis, thus patients selected for this procedure should be based on comorbidity, rather than the chronological age. Ferrier et al. [37] undertook a study to identify risk factors for mortality and complications in head and neck cancer surgery. In all, 120 patients were enrolled and comorbidity was assessed using the ACE-27 comorbidity index and the American Society of Anesthesiologist index. Comorbidity and duration of anesthesia were associated with increased risks of complications. Furthermore, no association between age and the risk of complications was found. The same results were found by Borggreven et al. [38], Gleich et al. [39] prospectively reviewed a head and neck cancer database from the University of Cincinnati, Ohio, and investigated the difference between patients treated with surgery and RT. Patients with comorbidity were more prone to receive RT whereas patients in the surgery group were generally more fit.

Selection of patients eligible to undergo surgery is an important factor, and a multidisciplinary assessment of the patients prior to and after surgery is crucial for a successful outcome. Moreover, age by itself should never be a factor responsible to choose a less radical treatment. When patients are not suitable for surgery, RT may be a good alternative for curative treatment.

Comorbidity and radiation therapy

RT is generally well tolerated in the elderly patients [40] whereas the influence of comorbidity has received less attention. Until recently, clinical randomized trials prescribed an upper age

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Period</th>
<th>Tumor site</th>
<th>Comorbidity Index</th>
<th>Treatment</th>
<th>Prevalence of comorbidity</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paleri V [49]</td>
<td>188</td>
<td>1995–1999</td>
<td>Larynx</td>
<td>ACE-27</td>
<td>RT, surgery.</td>
<td>19% had at least one comorbidity</td>
<td>OS: ACE-27 = 1 vs. 0: HR = 1.97 (0.74–5.22)ACE-27 = 2 vs. 0: HR = 4.36 (1.69–11.26)ACE-27 = 3 vs. 0: HR = 6.62 (2.34–18.87)DSS: NR</td>
</tr>
</tbody>
</table>

HNSCC: Head and Neck Squamous Cell Carcinoma; ACE-27: Adult Comorbidity Index-27; CCI: Charlson Comorbidity Index; KFI: Kaplan Fenstein Index; HR: Hazard Ratio; NR: Not reported; OS: Overall Survival; DSS: Disease Specific Survival.
limit for enrollment, often 70 years of age. In 1996, Pignon et al. [41] reported on 1589 patients enrolled in EORTC trials who were followed for toxicity and survival. Among those, 20% were above 65 years of age. No difference in survival was found with increasing age, and there was no difference in acute mucosal toxicity or weight loss. In contrast, more elderly patients had more severe functional acute toxicity. The probabilities of late effects were not different in the different age groups. Based on these findings, recommendations were made to delete the age limit for future EORTC protocols of RT in HNSCC patients. Horiot [42] later performed a review on all EORTC trials since this recommendation was made. Nine EORTC protocols including 574 HNSCC patients were reviewed, and despite encouraging compliance to the recommendations by the protocol-writers, only 15% of these patients were older than 65 years of age and only one patient was older than 75 years of age. The proposed explanation for this low recruitment of elderly patients included resistance to change, insufficient information of doctors and patients, and need for specific protocol design for elderly head and neck cancer patients. As per se, no prospective randomized trials concerning RT have been designed specifically for the elderly patients and patients with comorbidities. Furthermore, the assessment of comorbidity has not been performed in most earlier randomized trials, and even though the trials did not have an upper age limit, stratification according to comorbidity was not performed. As a result, most of the knowledge gained on the tolerability of RT in elderly HNSCC patients and patients with comorbidity comes from retrospective analyses.

Bøje et al. [15] performed a retrospective population based study on the impact of comorbidity on outcome in 9388 patients treated with curatively intended RT. The study was based on all Danish HNCC patients treated in the period from 1992 to 2008 and comorbidity information was available for all patients from 10 years prior to the time of diagnosis. Comorbidity was associated with poorer overall survival, whereas cancer specific survival was not affected. Moreover, increasing age did not impact cancer specific death. In another study by the same group [24] compliance according to comorbidity level was investigated and it was concluded that the presence of comorbidity was not associated with poor compliance. Similar results have been reported from other studies [34,40,41]; A large meta-analyses by the MARCH Collaborative Group [43] found no benefit of altered fractionation in the elderly patients and patients with poor performance status. Information on comorbidity was not available. Bøje et al. [15] found significant benefit from altered fractionation, also among patients with comorbidity or of older age.

In conclusion, comorbidity does not impact the effectiveness of RT. RT can be given to all patients despite them having comorbidities, but supportive care of the patients and a multidisciplinary approach are crucial in order to treat both cancer and comorbidities.

Comorbidity and combined modality treatment

The altered functional reserve of elderly patients can change the pharmacokinetics of cytotoxic drugs and may result in enhanced toxicity. Moreover, poly-pharmacy, typical of the older age can
### Studies concerning the association between comorbidity and treatment selection, treatment decision-making, complications after treatment, and social inequality.

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>Tumor site</th>
<th>Comorbidity Index</th>
<th>Treatment</th>
<th>Aim</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baijal et al. [74]</td>
<td>2006–2010</td>
<td>HNSCC</td>
<td>ACE-27</td>
<td>CRT: 29%</td>
<td>The impact of comorbidity on decision making: Strong correlation between ACE-27 and change in therapeutic decision-making</td>
<td>The impact of comorbidity on decision making</td>
</tr>
<tr>
<td>Gourin et al. [33]</td>
<td>2003–2004</td>
<td>HNSCC</td>
<td>Modified medical comorbidity index</td>
<td>Association of comorbidity and complications after surgery</td>
<td>The impact of comorbidity on complications after surgery</td>
<td>The impact of comorbidity on complications after surgery</td>
</tr>
<tr>
<td>Borggreven et al. [38]</td>
<td>1995–1998</td>
<td>Oral and oropharyngeal carcinoma</td>
<td>KFI</td>
<td>Surgery ± RT: 57%</td>
<td>The impact of social inequality in cancer treatment: Increase in incidence rate of HNSCC with decreasing social status</td>
<td>The impact of social inequality in cancer treatment</td>
</tr>
</tbody>
</table>

**Notes:** NR: Not reported; OS: Overall survival; DSS: disease specific survival; RT: radiotherapy; CRT: chemo-radiation; ACE-27: Adult Comorbidity Index-27; CCI: Charlson Comorbidity Index; KFI: Kaplan Feinstein Index; HR: Hazard Ratio.

Comorbidity as a prognostic factor

The impact of comorbidity on prognosis is well documented, especially in RT treated HNSCC. Table 3 summarizes the current studies investigating the impact of comorbidity on prognosis, and the hazard ratios describing the association between comorbidity and survival [7,10,15,22,24,27,28,31,49–57]. All studies proved comorbidity to be a strong predictor of overall survival (Fig. 2). In all, 10 studies including 22,932 patients were included in the meta-analyses. Different indices to classify comorbidity were used and all studies comparing comorbidity to no comorbidity were included in the meta-analyses. The presence of comorbidity increased the risk of death significantly, with an overall HR = 1.38 (95% CI: 1.32–1.43). Increasing comorbidity score was associated with increasing risk of overall death when compared to patients without comorbidity. The largest study including 9388 HNSCC patients treated with curative intended RT found that the increasing level of comorbidity increased the risk of death significantly [15]. Comorbidity did not have an impact on cancer specific survival, neither did increasing age. When exploring which diseases were associated with survival, only congestive heart failure, chronic pulmonary diseases, cerebrovascular diseases, liver disease, diabetes, and peptic ulcer disease had an impact on survival and based on this the revised HN-CCI was developed. Only few studies investi-
gated the impact of comorbidity on cancer specific survival and the results have been diverging (Table 2). In RT treated patients, comorbidity did not impact on cancer specific survival. In patients treated with surgery alone, however, the cancer specific survival was affected, presumably because the surgery performed was less extensive and less aggressive. Among patients treated with CRT, survival rate was high if given to patients with preserved organ function and only mild comorbidity. Cancer specific survival was not affected in patients treated with RT [27,35] whereas diverging results were found in patients treated with CRT and surgery [28,31,35]. The presence of comorbidity influenced treatment strategy and less radical procedures were used if the patients had comorbidity, leading to poorer cancer specific survival (Table 4).

In conclusion, comorbidity is a strong prognostic factor for overall survival in HNSCC carcinoma. When designing randomized trials comorbidity should be taken into account to avoid bias in the study, and patients should be stratified according to comorbidity as well as other well established prognostic factors.

Comorbidity in HPV-positive HNSCC

The prevalence of HPV induced HNSCC has been strikingly increasing in the past three decades. Patients with HPV positive tumors are different from the classical HNSCC patients, as they are generally younger, more fit and a larger proportion of these patients are non-smokers [4,58–61]. Furthermore, the outcome after treatment has been thoroughly investigated [60,62,63] proving that HPV/p16 positive tumors respond better to RT and OS, DSS and DFS are superior in HPV positive patients compared to HPV negative patients. The p16-positive tumors are now considered as a different disease and studies are being done on whether or not to de-intensify treatment in this patient group. However, cigarette-smoking has proven to have a negative impact on the outcome of therapy in HPV/p16-positive HNSCC patients [59,60,64] and the favorable outcome after therapy is obscured if the patients smoke. Only one study investigated comorbidity patterns in HPV positive patients and the association to smoking [65]. The p16 positive patients were significantly younger, smoked less and had less comorbidity compared to the p16 negative patients. Both smoking and comorbidity had a significant impact on survival. The p16-positive patients had a favorable outcome even when adjusting for stage, smoking and comorbidity. Nevertheless, since they are not dying from their cancer, all efforts should be made for them not to die from other diseases and/or smoking.

Comorbidity and the association to patient characteristics

Apart from being old and having comorbidity, HNSCC patients are often vulnerable in other aspects of life. A large Danish study investigating social inequality in cancer patients [66,67] found a clear pattern of social inequality in HNSCC patients with an increase in incidence rates with decreasing social position (disposable income and level of education). Also, having comorbidity was associated with an increased incidence rate ratio of HNSCC. Furthermore, survival was significantly lower among patients with comorbidity as well as in patients with lower socio economic status. A study by Kjaer et al. [68] on 2436 RT treated HNSCC patients showed that comorbidity, short education and low income were associated with increased risk of early retirement and unemployment after treatment for HNSCC whereas disease related factors (stage, site) were not. Intensive social support or targeted rehabilitation programs aiming to improve or maintain the work market affiliation in this patient group was recommended.

Conclusions and future perspectives

Multiple studies have demonstrated that comorbidity in HNSCC is common and the presence of comorbidity has a direct impact on treatment decision in daily clinical practice. Furthermore, we conducted a large meta-analysis including 22,932 patients and showed that comorbidity is important in HNSCC patients and negatively impacts on prognosis. In elderly patients, the physiological decrements, chronic diseases, and other health related problems will accumulate and complicate the patients’ health status and quality of life [69,70]. However, age is a highly individualized process and chronological age does not necessarily reflect biological age. Most literature suggests that elderly fit patients have similar benefit from aggressive treatment as younger patients. In contrast, comorbidity affects overall survival, and since comorbidity is relevant to the prognosis of HNSCC treatment, it is crucial to assess and to measure the comorbidity burden of a patient. There is currently no standardized method for the inclusion of comorbidity assessment in daily clinical routine, but several valid tools/indices exist, e.g. the CCI, ACE-27 and the new HN-CCI especially suitable for prognostic staging of RT-treated HNSCC. Comorbidities are often included in the exclusion criteria when designing trials to avoid the confounding influence on the outcome. Inclusion of patients with significant comorbidity can reduce the effectiveness of the treatment, making the interpretation of any benefit or harm difficult. However, this limits the applicability of the findings to the entire patient cohort, and studies designed specifically for the frail patients are warranted. Future trials should secure enrollment of the elderly HNSCC patients into clinical trials as well as the young and fit patients. Moreover, patients with comorbidities should have optimal supportive care in order to secure optimal cancer treatment. This will demand a change in the health care system and necessitate a multidisciplinary approach to patients.

Acknowledgements

This work was supported by grants from the Danish Cancer Society, CIRRO – The Lundbeck Foundation Centre for Interventional Research in Radiation Oncology, The Faculty of Health, Aarhus University, “Fondet til fremme af dansk radiologi”, and the Danish Head and Neck Cancer Group (DAHANCA).

References

Comorbidity in head and neck cancer


