Prognostication in esophageal cancer
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Future perspectives
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In future, the care for patients with esophageal cancer will probably be increasingly individualized. In specialized centers, 5-year survival (without neoadjuvant chemoradiation) is around 40% for all stages\textsuperscript{1-4}. On the one hand, neoadjuvant treatment with radiotherapy and/or chemotherapy may lead to better survival figures\textsuperscript{5,6}; on the other hand better patient selection for esophageal surgery may lead to better survival (at least for operated patients). Furthermore, a better knowledge of the molecular bases of esophageal cancer might further individually tailor therapeutic strategies and lead to improvement of clinical outcome. This paragraph describes novel options that might, in future, be implemented in the management of esophageal cancer.

Neoadjuvant chemoradiation therapy

It is possible that a plateau in the effectiveness of surgical resection as primary therapy in esophageal cancer may well have been reached. Further improvement in survival from this single modality approach seems unlikely. Neoadjuvant treatment with radiotherapy and/or chemotherapy, might theoretically have an additional role, since it might eliminate micrometastases and improve primary tumor resectability. Many centers apply preoperative chemo- and/or radiotherapy (CRT) to improve local control and overall survival. However, evidence remains conflicting. Randomized trials published so far on the value of neoadjuvant CRT have shown equivocal results\textsuperscript{5,6}. The minority of patients develop a complete pathological response and have a better survival\textsuperscript{7,8}. However, the question remains, if these patients live longer because they achieved a complete pathological response or would they have done just as well if they had had no preoperative therapy? At present, considerable attempt is made to improve the efficacy of preoperative therapy by using new chemotherapeutic drugs, optimizing the dose of radiotherapy and adding hyperthermia. In the Netherlands a randomized multi-center trial in several high/mid volume centers is currently performed to evaluate the effect of neo-adjuvant chemoradiation therapy (41.4 Gy in 23 fractions of 1.8 Gy plus paclitaxel 50 mg/m\textsuperscript{2} and carboplatin AUC = 2 on days 1, 8, 15, 22, and 29) on survival compared to surgery alone.

In a large proportion of patients an insufficient objective response is achieved. These non-responding patients do not benefit from neoadjuvant therapy, but do suffer from toxic side effects. This negative impact on the general condition of the patient may lead to an increased peri-operative morbidity and protracted postoperative recovery. Moreover, prolonged but ineffective preoperative treatment will inevitably delay appropriate surgical therapy. The use of positron emission tomography using 18F-fluorodeoxyglucose (FDG-PET) is a promising tool for early response monitoring\textsuperscript{9}. The value of FDG-PET in early response-monitoring is currently analyzed in the neoadjuvant arm of the randomized trial mentioned above.
New developments in diagnostic modalities
Better patient selection for esophageal surgery may lead to better survival (at least for those patients, who are operated on). Recent research indicated that FDG-PET only had limited value after state-of-the-art diagnostic work-up\textsuperscript{10}. A relatively new medical imaging technique is combined PET-computed tomography (CT). This technique combines the cross-sectional anatomic information provided by CT and the metabolic information provided by PET\textsuperscript{11}. Hopefully, PET-CT is able to improve the selection of patients for potentially curative surgery. Also other targeted contrast agents may accomplish better site-directed imaging\textsuperscript{12}. The present thesis shows that it is feasible to give better prognostic estimates according to standard pathological postoperative parameters. However, clinical preoperative staging modalities for esophageal cancer are inaccurate at determining prognosis. Positron-emission tomography (PET) is able to quantify tissue metabolic activity generally expressed in the standard uptake value (SUV). It has been postulated that tumors which are metabolically very active might be more aggressive. Therefore, FDG-PET might have a role in predicting prognosis in esophageal cancer patients\textsuperscript{13}. This issue is currently investigated in the Netherlands.

The presence of extracapsular lymph node involvement is a sign of biological aggressiveness of the primary tumor. Prognosis is significantly worse in patients with extracapsular disease and surgery alone is not enough when cureation is aimed at. To facilitate a tailored approach in the neo-adjuvant setting it would be necessary to discriminate preoperatively between positive nodes with and without extracapsular lymph node involvement. In this respect, the diagnostic accuracy of endosonography, computer tomography and magnetic resonance imaging has only been tested in very small studies\textsuperscript{14-16}, and should be analyzed in larger series of patients in future.

Tailoring treatment strategies in patients with locally advanced esophageal carcinoma is of the utmost importance. Possibly, more reliable preoperative staging is possible by taking into account the number of malignant-appearing periesophageal lymph nodes as detected by endosonography. In squamous cell carcinoma, disease stratification seems valuable, especially in patients with eight or more malignant-appearing lymph nodes; these patients can not be cured with surgery alone. However, in patients with adenocarcinoma of the esophagus and gastroesophageal junction, the prognostic value of this parameter must still be proven.

Molecular biology of cancer recurrence
The completion of the sequencing of the human genome in 2003 marked the dawn of a new era of human biology and medicine\textsuperscript{17}. Although molecular research is still in its infancy, the ultimate goal is the individualization of treatment therapies according to the biological profile of the patient and the tumor\textsuperscript{18}. The field of molecular biological research is rapidly evolving and an astonishing number of biomarkers have already been described. But even in colorectal cancer, which is, in terms of genetics, one of the best understood of all malignant diseases, the significance of these factors in determining prognosis remains unclear\textsuperscript{19}. This may be caused by different laboratory techniques, statistical differences, and heterogeneity in study populations. Tests can only be used to tailor individual treatment options; if they
have a high sensitivity and high specificity. The results of the present study also indicate that
the original enthusiasm about the prognostic potential of microarray technology is further
silenced. One of the reasons could be that its bioinformatic analysis appears to be much
more complicated and demanding than originally thought. Another reason might be more
related to the cancer itself. For long cancer was seen as a more or less homogeneous mass of
cells which all possessed unlimited growth potential. This would imply that every cell within
a tumor is capable in metastasizing and forming a new tumor. However, recent research
suggests that the majority of tumor cells has lost its unlimited growth potential\textsuperscript{20,21}. Possibly,
only a small amount of tumor cells are responsible for this capacity. Cancer stem cells, which
normally have the function to maintain the integrity of tissues, have the ability to perpetuate
themselves through self-renewal and to generate mature cells of a particular tissue through
differentiation. Growing evidence suggests that pathways which regulate self-renewal are
deregulated in these cancer stem cells. This results in the continuous expansion of self-
renewing cancer cells and thus cancer formation. Currently, research is addressing the role of
stem cells in adenocarcinoma of the esophagus.

Molecular biology of development of complications
This thesis shows that the severity of complications is difficult to predict with use of patient
related factors (medical history and physical condition). This may have a variety of reasons,
but recent research indicates that patient genetics are associated with increased susceptibility
to infectious and cardiac complications\textsuperscript{22-26}. Researchers are just beginning to unravel genetic
and molecular determinants, including polymorphisms, that predispose to increased risk for
postoperative complications. This new field, the so called peri-operative genomics aims to
apply functional genomics to uncover biological reasons why seemingly similar patients can
have dramatically different clinical outcomes after surgery\textsuperscript{23}. Future research is necessary to
analyze the influence of patient genomics on developing complications after esophagectomy
for cancer.

Tailored information giving
In the present thesis, data are presented indicating that after potentially curative esophagectomy
for cancer, the majority of patients wants detailed prognostic information and wants their
specialist to start the prognostic discussion. However, a substantial proportion of patients
wants a more delicate approach. In future, it is a challenge to tailor information supply to
the individual patient. Furthermore, the psychological impact and the impact on quality of
life, when discussing prognosis after curative treatment remain unknown. On the one hand
individualized prognostic information is desired by patients and may even help in coping with
threatening situations. On the other hand, realistic (negative) prognostic information may be
sometimes blunt and brutal and may have a negative effect on quality of life, anxiety levels
and fear of recurrence. Future research is necessary and only a trial randomizing between
the supply of general prognostic information versus individualized prognostic information may
answer this question.
References


