Towards a more personalized approach in the treatment of esophageal cancer focusing on predictive factors in response to chemoradiation

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CHAPTER 1

General introduction

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Introduction

Esophageal cancer (EC) is one of the most aggressive gastrointestinal malignancies worldwide. It usually appears in the fifth or sixth decade of life. Patients commonly present with progressive dysphagia and weight loss. Generally, there is a relative 'silent' early development of the disease, which becomes rapidly symptomatic when the tumor involves more than half of the esophageal circumference. At the time of diagnosis the disease is locally advanced or even presents with metastatic spread in approximately half of the patients [1,2]. There are two main histological types; the esophageal adenocarcinoma (EAC) that arises from the glandular tissues and the esophageal squamous cell carcinoma (ESCC) that derives from the epithelium layer. The incidence of EAC has increased rapidly over the last two decades overruling ESCC as the most common form of EC in the western world. On the other hand, ESCC still dominates in the Asian world [3]. EC is currently staged according to the 7th TNM edition of the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) Cancer Staging Manual for tumors of the esophagus and gastroesophageal junction (Table 1) [4].

Table 1: TNM 7th edition of the AJCC Cancer Staging Manual: esophagus and esophagogastric junction tumors.

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as the aorta, vertebral body, and trachea
Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Early staged T1/N0 ECs are generally treated endoscopically with a mucosal resection (EMR) or a submucosal dissection (ESD). Potentially resectable locally advanced EC (clinical TNM classification cT2-4/N0-3 without signs of metastatic spread, M0) is commonly treated using neoadjuvant chemotherapy. The CROSS regimen (5 weekly treatments of carboplatin AUC=2 and paclitaxel 50mg/m2) with concurrent radiotherapy (total dose of 41.4 Gy in daily fractions of 1.8 Gy five times a week) followed by a surgical resection with curative intent (R0 resection) is commonly used in The Netherlands and many western countries [5]. The implementation of this multimodality treatment has improved the 5-year survival rate significantly to 47%, from 33% with surgery alone with a medium survival gain of 24.6 months (48.6 months multimodality treatment compared to 24 months surgery alone) [6]. Although, this regimen is of great clinical relevance, only 29% of all patients eligible for neoadjuvant treatment will reach pathologic complete response (pCR) [5]. In other words, the majority of the EC patients will

only benefit partially (53%) and others not at all (18%) from this intensive treatment. Therefore, further research is demanding in order to decrease treatment resistance and to develop more specific targeted therapies. One way to approach this is to focus on cancer stem cells (CSCs) as this population is thought to be resistant to conventional anti-cancer therapies. CSCs are able to self-renew (symmetrical division) and to give rise to cells with less tumorigenic potential (asymmetrical division), hereby ultimately able to generate a new tumor [7,8] (Figure 1). Although, they might be few in numbers and dormant for most of the time, their existence should not be underestimated. Once the environment becomes favorable, they will re-enter the cell cycle and proliferate, which potentially leads to the formation of a new tumor or metastasis. Therefore, CSCs might be appealing as a potential target for future cancer therapy. Besides developing new targeted therapies, it is also essential to better predict treatment response to the current regimen (CROSS) in order to withhold treatment for those with no clinical benefit (the non-responders). Patient and tumor characteristics as well as current functional imaging features based on positron emission and computed tomography (PET-CT), could be valuable in predicting treatment response. By predicting non-responders up-front will prevent them from undergoing useless chemoradiation while predicting the proportion of patients with a complete pathological response might omit surgery in the near future.

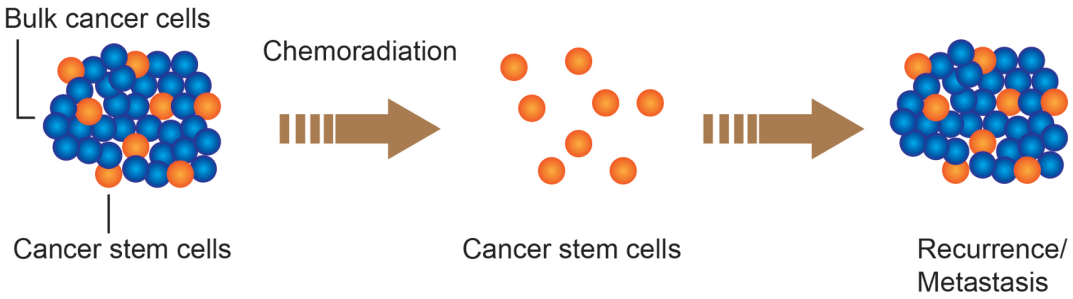

Figure 1: Schematic representation of CSCs escaping chemoradiation to ultimately form a new tumor or metastasis.

Rationale

Despite modern advances in esophageal cancer treatment, the prognosis remains poor. This is mainly due to the general presentation of patients with locally advanced or metastatic disease at the time of diagnosis. The treatment of choice is neoadjuvant chemoradiation (nCRT) followed by surgery (CROSS regimen) [9]. However, over 50% of these tumors do not respond adequately and 18% will not respond at all to the given nCRT [5]. In addition, most of the patients will develop recurrences or distant me-

tastases in a short period of time [5]. Therefore, it is critical to look into potential factors, eg. CSCs, on the basis of tumor resistance providing new insights for future treatment leading to an enhanced tumor response. On the other side, there is a need to better predict response to the current treatment regimen in order to withhold patients from clinical irrelevant therapy. This thesis will therefore focus on CSCs as a potential target for future cancer therapy and on identifying potential predictive factors for therapy response to the current neoadjuvant regimen leading to more personalized medicine.

Thesis outline

Metastatic spread, both lymphatic or hematogenous, is a great problem in EC since the majority of patients present with involved lymph nodes at the time of diagnosis. Nodal metastases (pN) and pathologic complete response (pCR) are strong prognostic factors in determining recurrent disease. Interestingly, early metastases may develop even in patients who have had a pCR to nCRT after an obviously microscopic radical (R0) resection suggesting an aggressive type of tumor. **Chapter 2** provides a comprehensive review on esophageal CSCs in general and will elucidate their role in the potential regulatory mechanisms in the formation of metastases. Moreover, it will give some insight in the future treatment options for individual patients. The subtypes in the so-called Tumor Cancer Genomic Atlas (TCGA) may aid in the search for new therapeutic targets. The role of CSC in these genomic subtypes is not yet clear, but as one of the hallmarks of CSCs is the generation of metastases, they could play a more active role in these subtypes.

The Hedgehog and the mTOR pathways are two of the regulatory pathways implicated in cancer stemness. Modulating these pathways could potentially lead to a decrease or inactivation in cancer stemness which could be beneficial for patients' outcome. **Chapter 3 & 4** will highlight the potential role of the Hedgehog and the mTOR pathways in cancer stemness and the way we could potentially apply future targeted treatment. **Chapter 4** also provides a patient-derived organoid model as a novel way to study regulatory pathways in esophageal cancer and opens the door for other exciting possibilities in the field such as guiding future treatment of patients with EC individually.

Current standard therapy with curative intent for esophageal cancer patients, consisting of neoadjuvant chemoradiation followed by a surgical resection, leads to a pathologic complete response of 29%.

Prediction of therapy response would be of great progress in preventing patients from undergoing unnecessary therapy. In addition, the effect of surgery might be limited in patients who will have a complete response at pathological examination and therefore a 'wait-and-see policy' would have been more beneficial for them. Clinical tumor response can nowadays be evaluated more accurately by functional PET-CT scans, but clinical complete response can not be considered equivalent to pathologic response yet. Intratumoral heterogeneity based on FDG distribution is related to the degree of response to therapy. An useful tool to quantify this heterogeneity and therefore predicting pathological response is by the analysis of textural features. **Chapter 5** emphasizes the potentially additive value of CSC related proteins in the tumor as predictors of response combined with patient characteristics and PET-CT textural features.

It has been demonstrated that nCRT will induce an immune response causing a change in the levels of several cytokines which in turn might influence tumor response and tumor progression. In addition, patients with increased pro-inflammatory factors are more prone to postoperative complications. **Chapter 6** demonstrates the changes in inflammatory factors over the course of the multimodality CROSS regimen and includes a different approach in predicting pathological response and complications after surgery by measuring patients' immunologic response.

Locoregional lymph node metastases have a strong negative impact on survival. The survival becomes worse with increasing number of affected lymph nodes. The rationale behind the introduction of neoadjuvant chemoradiation includes the reduction or elimination of the number of nodal micrometastases (NMM). However, the degree of this reduction or elimination and its impact on survival and recurrences is not clear and will be discussed in **chapter 7**.

The summary and the clinical perspectives will be discussed in the final **chapter 8**.

References

[1] Lagergren J, Lagergren P. Oesophageal cancer. BMJ 2010 Nov 26;341:c6280.

[2] Lin SH, Chang JY. Esophageal cancer: diagnosis and management. Chin J Cancer 2010 Oct;29(10):843-854.

[3] Hongo M, Nagasaki Y, Shoji T. Epidemiology of esophageal cancer: Orient to Occident. Effects of chronology, geography and ethnicity. J Gastroenterol Hepatol 2009 May;24(5):729-735.

[4] Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC Cancer Staging Manual: esophagus and esophagogastric junction. Ann Surg Oncol 2010 Jul;17(7):1721-1724.

[5] van Hagen P P. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012-5-31;366(22):2074-84.

[6] Shapiro Joel J. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncology, The 2015-9;16(9):1090-8.

[7] Rich JN, Bao S. Chemotherapy and cancer stem cells. Cell Stem Cell 2007 Oct 11;1(4):353-355.

[8] Yu Z, Pestell TG, Lisanti MP, Pestell RG. Cancer stem cells. Int J Biochem Cell Biol 2012 Dec;44(12):2144-2151.

[9] Lordick F, Stein HJ, Peschel C, Siewert JR. Neoadjuvant therapy for oesophagogastric cancer. Br J Surg 2004 May;91(5):540-551.