Daily clinical practice and patterns of care in upper gastrointestinal cancer treatment

Toxicity, quality of life and survival

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Citation for published version (APA):
Chapter 11

General discussion and future perspectives
GENERAL DISCUSSION AND FUTURE PERSPECTIVES

In this thesis we focused on studying real-world toxicity, quality of life and survival in patients treated for upper gastrointestinal cancer. The ultimate goal of treating patients with upper gastrointestinal cancer is to improve both survival and quality of life. Although there has been some improvement in survival over the last decennium, overall prognosis of these patients remains poor and the effects on quality of life differ largely between treatments. Thus, when deciding on treatment options, the potential benefits and harms have to be balanced.

Treatment decisions are increasingly made by shared decision-making between doctor and patient. In partnership with their clinician, patients are encouraged to explore the treatment options. One key element of shared decision-making is the exchange of information on both the possible treatment options and the expected benefits (survival, improvement of quality of life) and harms (toxicity, deterioration of quality of life) of each option. Both the patient and the physician need accurate information in order to be able to construct a sound treatment plan, which can be mutually agreed upon. The results of this thesis contribute to the relevant information required to make a shared treatment plan for physicians and patients with upper gastrointestinal cancer in daily practice.

In this chapter the main results of this thesis are summarized in propositions and put into a (future) perspective in the context of shared decision-making.

POPULATION-BASED STUDIES ARE COMPLEMENTARY TO RESULTS OF RCTS TO TRANSLATE OUTCOMES TO THE GENERAL POPULATION

When informing patients on the benefits and harms of a treatment option, outcomes from randomized clinical trials (RCTs) are usually used, as RCTs are the gold standard for establishing efficacy of new therapies. However, the strict inclusion criteria for participation of patients in RCTs hampers the generalizability of the outcomes in routine practice. Outcomes from population-based studies may contribute to better generalizability, as all patients are included and treatment decisions are by definition based on clinical and patient preferences. Therefore, population-based studies provide information on therapy outcomes in daily clinical practice.

Real-world data from the Netherlands show that survival of patients with metastatic pancreatic cancer treated with palliative chemotherapy is poor with an overall survival of 25 weeks. Improvement of survival over time is not observed. This is probably caused by the absence of an effective chemotherapy regimen during the study period. Gemcitabine was registered on the basis of the primary outcome improved clinical benefit, which was a composite of measurements of pain (use of analgetics and pain intensity), Karnofsky performance status, and weight. Clinical benefit required a sustained (≤ 4 weeks) improvement in at least one parameter without worsening in any others. However, gemcitabine showed no significant improvement of survival compared
to 5-FU.\(^4\) Only recently two effective chemotherapy regimens have been established, FOLFIRINOX (combination chemotherapy consisting of oxaliplatin, irinotecan, leucovorin and fluorouracil) and gemcitabine combined with nab-paclitaxel.\(^{15, 6}\) In the study by Conroy et al. that investigated the efficacy of FOLFIRINOX versus gemcitabine, patients older than 75 years old were excluded.\(^{8}\) Physicians less experienced with the regimen and toxicity may be reluctant to start treatment in patients aged higher than 75 years old with a good performance score. In would be interesting to explore in future population-based studies the real-world applicability and efficacy of FOLFIRINOX or gemcitabine-nab-paclitaxel. This information can be used when informing a 76-year-old patient on the effect of survival of treatment with FOLFIRINOX during shared decision-making. We observed a difference in overall survival in patients with metastatic esophagogastric cancer treated with palliative chemotherapy in our population-based study (8 months) compared to the OS in RCTs (11 months).\(^{7}\) (chapter 9) This apparently small absolute difference is clinically relevant as survival gain from treatment of palliative chemotherapy is estimated in months.\(^{7, 8}\) These survival data describe the true efficacy of palliative chemotherapy in daily practice and can be directly used in the consultation room when informing on the efficacy of a treatment.

Population-based data provide information on (predictors for starting) treatment due to adequate sample sizes for proper regression analyses. Less than a third of the patients with metastatic upper gastrointestinal cancer in the Netherlands (chapter 7, 8, 9 and 10) was treated with palliative chemotherapy. Younger and male patients had higher odds for receiving palliative chemotherapy (chapter 8 and 9). These data demonstrate that a minority of the patients with metastatic upper gastrointestinal cancer is treated with palliative chemotherapy and confirms the lack of generalizability of RCTs in daily practice. Moreover, population based data can provide prognostic factors. Multivariate regression analysis in patients with metastatic pancreatic cancer that were treated with palliative chemotherapy showed that younger age and single site metastasis (chapter 10) were associated with improved survival. These prognostic data can be used to inform patients which factors are associated with improved survival and therefore which patients are most likely to benefit from a treatment.

In conclusion, with the information from chapter 7, 8, 9, and 10, patients can be informed on predictors for starting palliative treatment and (prognostic factors for) survival with real-world data and therefore provide input for shared decision making in daily clinical practice.

Population-based studies are able to show adverse events that are infrequent or occur in the period beyond average clinical trial duration. From our prospective study on heart volume of patients treated with neoadjuvant chemoradiotherapy (chapter 2), we observed a reduction in heart volume, consistent with volume depletion. No acute cardiac
toxicity was reported, however, the follow-up period with 1 week after finishing neoadjuvant chemoradiotherapy was short. Information on cardiotoxicity after years of completion of the chemoradiotherapy and in a larger number of patients is needed, as anti-cancer drug-related cardiotoxicity is the leading cause of treatment-associated mortality in cancer survivors.\textsuperscript{9}\textsuperscript{9} For radiotherapy, an analysis from the Surveillance, Epidemiology, and End-Results (SEER) database comparing patients with cancers from miscellaneous origins treated with or without definitive radiotherapy showed that treatment with radiotherapy was predictive of death from heart disease at long follow up (HR 1.62, 95% CI: 1.43-1.82).\textsuperscript{10}\textsuperscript{10} Therefore, information on long-term toxicity of chemoradiotherapy can be derived from population-based data when considering treatment options and select the treatment that matches with patients’ preferences and characteristics.

Observational data require critical interpretation. Population-based data are by definition observational in nature and present summary data on groups of patients rather than on patient level. Acknowledging the potential sources of bias such as selection bias and confounding by indication is essential. Confounding by indication arises from the fact that patients who are treated with a certain therapy may be inherently different from those who are not treated, as treatment choice is dependent on clinical features, and provider or patient preferences. Multivariable testing to adjust for established prognostic factors may reduce this bias, but it is possible that a factor is not included or that factors interact.\textsuperscript{11}\textsuperscript{11} Other methodological aspects as non-controlled conditions and no randomization of treatment are important limitations. Furthermore, only associations, not causations can be addressed. Finally, the quality and availability of the registered data remain a challenge. In chapter 9 and 10 these limitations are of vital importance for interpretation of the results. We found that patients with metastatic upper gastrointestinal cancer treated in high-volume surgical centers have an improved survival compared to patients treated in low-volume surgical centers. For example, patients in high-volume centers may be a selection of patients with good prognostic characteristics and probably a better survival. To a certain extent, it is possible to adjust for differences in age, and number of metastases between patients treated in high-volume centers and those treated elsewhere. However, in our study period registration of important variables as the specific type of chemotherapy, number of cycles of chemotherapy and performance status were lacking, therefore adjusting for case-mix was limited. Even if adjustment would be possible, presence of differences in case-mix cannot be ruled out. To illustrate, a 50-year-old patient that is documented as having peritoneal metastases from gastric cancer may have i) large peritoneal depositions visible on imaging or ii) found to be irresectable during laparoscopy because of the presence of a small peritoneal deposition. The prognosis in the second case is much better than in the first case, but in our analyses no distinction could be made.
**Future perspective:**
As patients consider quality of life as important or even more important as survival, real world data on quality of life are paramount in balancing risks and benefits in shared-decision making.\(^{[13]}\) As we illustrated in chapter 7 and 9, efficacy differs between RCTs and population-based studies, making it likely that quality of life outcomes might be different as well. The Dutch Cancer Registry, which is a population-based database that collects information on all patients newly diagnosed with a malignancy in the Netherlands, unfortunately lacks information on quality of life. However, the Dutch Cancer Registry serves a sampling frame. The prospective observational oesophageal cancer project (POCOP) and the prospective observational pancreatic cancer project (PACAP) are currently (starting Jan 2015) gathering data on quality of life, among other data. These registries not only provide clinical data on population-based treatment and survival outcomes, but also provide patient reported outcomes. POCOP and PACAP will be an excellent platform for measuring (cardio)toxicity, quality of life and survival in patients with upper gastrointestinal cancer. This database will enable to provide patients and clinicians with evidence-based tailored data to facilitate shared-decision making.

Furthermore, the extensive data from these registries can be used to create (shared) decision tools. For example, SOURCE is a Dutch Cancer Society funded project that uses population-based data in order to provide information on survival, treatment-related morbidity and quality of life on treatment for esophageal cancer. The doctor and the patient can use these tools to \(^{[13]}\) decide together on the most appropriate treatment regimen that matches with patient preferences and characteristics.

**CENTRALIZATION OF CARE TO HIGH-VOLUME HOSPITALS FOR PATIENTS WITH METASTATIC UPPER GASTROINTESTINAL CANCER MAY IMPROVE OUTCOMES**

The positive association between improved survival and performing high-complex surgery in high-volume centers is well established.\(^{[14-17]}\) As a consequence, to improve the quality of cancer care several countries have introduced volume quota for high-complex surgery.

In chapter 9 and 10 we show comparable associations for improved survival in patients with metastatic esophagogastric and pancreatic cancer treated with systemic palliative therapy; patients treated in high-volume hospitals have a better survival than patients treated in low-volume hospitals. Improved outcomes and high-volume hospitals were associated but are not per se causative. Therefore the key performance measures of a high-volume hospital should be unraveled. We found that especially treatment with palliative systemic therapy in high-volume hospitals that were based on the annual number of curative resections was associated with improved survival.
Birkmeyer et al. described the potential processes of care that may explain improved outcomes in high-volume hospitals for high complex surgery.\textsuperscript{[18]} Adequate resources imbedded in a multidisciplinary approach were one of the main attributes for improved outcomes. Although multidisciplinary approach in cancer treatment was not the focus of our investigations, and was not qualified as a factor of improved outcomes, it deserves further attention. Moreover, literature on the relevance of a multidisciplinary approach is growing. In esophageal and pancreatic cancer, review by a multidisciplinary tumor board leads to changes in therapeutic recommendations in close to one-quarter of patients.\textsuperscript{[19, 20]} In urologic cancer, the impact of multidisciplinary teams, defined as a major change in the management plan, has proven to be even higher in metastatic than in non-metastatic cancer in general.\textsuperscript{[21]}

Therefore, in many guidelines a multidisciplinary approach is advocated to arrange proper care by a range of professionals with different backgrounds.\textsuperscript{[22-24]} Patients with metastatic pancreatic cancer in general have a high symptom burden at the time of diagnosis and can present with symptoms as pain,\textsuperscript{[25]} fatigue, cholangitis,\textsuperscript{[26]} making multidisciplinary collaboration to formulate treatment important. The ASCO guidelines state: “Multidisciplinary collaboration to formulate treatment and care plans and disease management for patients with metastatic pancreatic cancer should be the standard of care. Ancillary care as stent placement in bile ducts and gastric outlet, enteral or percutaneous celiac blockade and palliative radiotherapy should be well equipped by a team of divergent specialists.”\textsuperscript{[27]}

The multi-disciplinary approach may not be the exclusive explanation for the improved outcomes as in the Netherlands in every hospital multidisciplinary meetings are advocated. Other factors described by Birkmeyer et al. were case-mix, the level of the personnel's expertise and skills.\textsuperscript{[18]} With the emerging complexity of tumor biology and expansion of treatment options in patients with metastatic upper gastrointestinal cancer identical explanations for improved outcomes in high-volume hospitals may exist. In metastatic esophagogastric cancer, palliative treatment options vary broadly from local treatment to systemic treatment.\textsuperscript{[28]} The optimal approach is not well defined, as the various modalities have not been compared head to head. Moreover, novel systemic therapeutic strategies have been evaluated and have introduced a new era in the treatment of advanced esophagogastric cancer.\textsuperscript{[29]} Many drugs target specific cell signaling pathways important in growth, progression and spread of cancer. An example is the adding of trastuzumab to chemotherapy in patients with HER2 amplification.\textsuperscript{[30]}

In metastatic pancreatic cancer new insights in cellular metabolism have emerged and lead to potential targets for therapeutic intervention.\textsuperscript{[31]} However, the clinical applicability of these findings is unknown to date. Prospective studies are ongoing but face the delay in reporting results for patients often in a poor condition.\textsuperscript{[32]}
In general, the evolving developments in the treatment of upper gastrointestinal cancer mandate the advice to centralize treatment to certain hospitals with expertise on this field. On the basis of our data, it is preliminary to state that all patient with metastatic upper gastrointestinal should be treated in high-volume hospitals. However, in shared decision-making our results should be discussed with patients explaining that there is an association with improved survival and high-volume hospitals.

**Future perspective:**

We observed center-specific variation in survival. Consequently efforts should be made on identifying and measuring factors for best practices. However, the search for determining the specific structural factors and processes that explain the improved outcomes is challenging in that the key performance measures may all be associated with each other. Which definition for high-volume should be used for future studies is not straightforward. In the surgical domain, there is no consensus about the minimum number of resections considered as a high-volume. The annual minimum volume standard of esophagectomies varies between countries from 13 to 60 per year.[33-35] For treatment of patients with metastatic cancer, it seems plausible to apply the surgical high-volume definition, as this definition may be the proxy for a well-developed infrastructure of a complete hospital.

Also the minimum or optimum number of pancreatic cancer procedures for optimal outcomes is still under debate. In three states of the United States mortality from pancreatectomy was lower in high-volume hospitals, but did not appear to be significantly different if a pancreatectomy was performed at medium (11-25 procedures annually), high (25-60 procedures annually) or very high (≥61 procedures annually) volume hospital. [34] In other words, there may be a plateau for the optimal hospital volume threshold.

A meaningful cut off point for the number of esophagectomies performed per year was analyzed by Henneman et al.[37]: increasing annual hospital volume was associated with a decrease in mortality up to 40-60 esophagectomies /per year.

Importantly, application of a volume per se is not the primary goal. Goodhart’s Law describes: “When a measure becomes a target, it ceases to be a good measure.”[38] For example: in December a hospital has performed 19 esophagectomies, but is supposed to perform 20 annually. The surgeon might operate the patient with comorbidity to achieve the threshold of 20 annually performed esophagectomies and the possibility to maintain the predicate high-volume hospital. Obviously, this illustration is not praiseworthy for good quality of care.

Whether a plateau exists for the optimum number of treating patients with metastatic upper gastrointestinal cancer as in esophagectomy should be the focus of future research.
To improve quality of care in cancer surgery in the Netherlands, initiatives have started to share data from surgical audits. These quality indicators, for example morbidity and mortality, are being used to compare surgical outcomes in order to define best practices. To improve quality of cancer care for patients with metastatic cancer, survival should not be the single appropriate quality indicator to be measured. However, how to precisely measure quality of life as a quality indicator is challenging as well.

**NEXT TO TOXICITY AND SURVIVAL, PATIENT-REPORTED OUTCOMES SHOULD BE FORMAL ENDPOINTS IN ALL RCTS EVALUATING TREATMENT OF PATIENTS WITH A POOR PROGNOSIS.**

Unfortunately, treatment for upper gastrointestinal cancer is not without side effects. Adverse drug events may lead to dose reduction or discontinuation of treatment. It is essential that these toxicities do not jeopardize the clinical benefit of the treatment by stopping the treatment. Therefore information on toxicity of the treatment is an important endpoint in clinical trials as underlined by the Consolidated Standards of Reporting Trials (CONSORT).

To illustrate, toxicity of definitive chemoradiation for irresectable esophageal cancer is substantial and well documented. Definitive chemoradiotherapy (dCRT) is offered to patients with esophageal cancer with medically inoperable or technically irresectable disease, for example due in growth in the trachea or vertebra (T4b). In trials conducted with dCRT both groups were represented. However, both indications have different patient and tumor characteristics. Because comparative information on toxicity was lacking, we performed a case-series and concluded that there is a clinically significant and relevant difference in the toxicity between these two groups of patients. (chapter 5)

Patients that are medically inoperable experience higher acute toxicity than patients with irresectable esophageal cancer. Compared to neoadjuvant chemoradiotherapy, toxicity of dCRT is worse, with 40% grade 3 or higher toxicity versus approximately 20% in neoadjuvant chemoradiotherapy, but comparable to 40% of the patients experiencing grade 3 or higher toxicity with palliative chemotherapy with capecitabine and oxaliplatin. This cross-sectional study adds valuable information for patients with inoperable esophageal cancer and their physicians that can be used for shared decision-making.

The balance between risk of treatment and potential benefit is particularly challenging when treating patients with palliative intent. In chapter 6 we found that “less is more” for combination chemotherapy in first line in patients with metastatic esophagogastric cancer in the absence of the need of a high response rate. More chemotherapy induces more toxicity but not a meaningful improvement in survival.

So far we have only discussed toxicity as endpoint, which is a physician centered measure. Physicians often under- or over-report the level of severity of symptoms compared
Quality of life is a patient reported outcome and defined as a measurement of any aspect of a patient’s health status that comes directly from the patient (i.e., without interpretation of the patient’s responses by a physician or anyone else). In a recently published review it was reported that agreement between CTCAE and patient-reported outcomes ratings was moderate at best. Interestingly, severity of toxicity is not always related to quality of life. For example, in the COUGAR trial, which showed superiority in terms of survival of second-line treatment versus placebo in patients with metastatic gastric cancer, chemotherapy use was associated with more toxicity. However, quality of life improved as well. Also, in patients with metastatic pancreatic cancer treated with the triplet chemotherapy FOLFIRINOX were reported having more grade 3-4 toxicity. However, quality of life in this group was higher than in the control group that was treated with less toxic gemcitabine monotherapy. Given the discordance between a clinician centered outcome and a patient centered outcome, acquiring information on patient-reported outcomes complementary to toxicity is of paramount importance. Especially in treating patients with upper gastrointestinal cancer, harboring a poor prognosis, patient-reported outcomes such as improvement in symptom control or quality of life should not be viewed as a surrogate endpoint, but regarded as an important option among the many endpoints that can be used. The Consolidated Standards of Reporting Trials (CONSORT) suggested recommendations for inclusion, analysis, implementation and reporting of quality of life in clinical trial design. Brundage and colleagues showed that only 25 percent of the RCTs report on quality of life as a primary outcome, thereby showing the shortcomings in reporting of patient-reported outcomes in clinical trials. Results for quality of life were not reported in most studies included in our meta-analysis (chapter 6).

Future perspective:
Systematic use of information of PROs in clinical studies and practice leads to better communication and decision-making between doctors and patients. Preferably, longitudinally measured patient-reported outcomes can be collected in a population-based cohort study as POCOP and PACAP and utilized for patients to make an informed decision combined with their own personal value set.
BURDEN OF SPOUSAL CAREGIVERS OF PATIENTS WITH ESOPHAGEAL CANCER TREATED WITH CURATIVE INTENT SHOULD BE ACKNOWLEDGED IN DAILY CLINICAL PRACTICE.

With cancer incidence rising, many patients diagnosed with cancer will require help from an informal caregiver. Caregivers of cancer patients were negatively affected by the caregiver role in the physical and psychological domain.\textsuperscript{[60]} The impact of the caregiver responsibilities on their emotional and physical well-being is documented by multiple studies.\textsuperscript{[61, 62]} In a meta-analysis of 84 studies on caregiver burden in various cancer types it was found that spousal caregivers were more distressed than other caregivers and that female caregivers were more distressed than males.\textsuperscript{[63]} This is a very relevant fact, as in esophageal cancer patients are predominantly male, and informal caregivers predominantly female.

Indeed, our findings from a tertiary referral center in spousal caregivers of patients with esophageal cancer indicate a great need for (psycho-oncological) support. (chapter 4) Especially fatigue of the patient and depression of the caregiver were associated with higher caregiver burden. Fatigue occurs in 30-40\% of cancer survivors.\textsuperscript{[64, 65]} Effective interventions for fatigue have been established.\textsuperscript{[66, 67]} The factors associated with higher caregiver burden, i.e. fatigue of the patient and depression of the caregiver were characteristics related to both the caregiver and the patient, highlighting the need to design interventions that target both of these groups.

To date, unfortunately very few interventions have been implemented in daily clinical practice to reduce caregiver burden. Australian researchers have made a first step in intervening in caregivers burden in patients with gastrointestinal cancers. They concluded that telephone-based interventions to improve caregivers well-being did not have any measurable impact on patient quality of life, level of unmet supportive care need, or psychological distress. The intervention comprised of 4 telephone calls to the caregiver in which caregivers’ needs were assessed. If necessary, strategies to assist caregivers to deal with the challenges were offered. Only unplanned emergency department visits were significantly fewer in the intervention group.\textsuperscript{[68]}

Future perspective:

Ideally, caregiver burden should be measured with a validated clinically relevant tool and on different time points. Burden may be different when the patient is first diagnosed with cancer in comparison to the moment of change from a curative intention to a palliative intention. Interventions may include information on the anticipated course of the disease, related symptoms, treatment and side effects and management of medical emergencies.\textsuperscript{[69]} Second, regularly measurements of patient-reported outcomes can also be used in best interest of the spousal caregiver. If the information on fatigue of the patient is ac-
cessible in daily practice, the caregiver could be better supported in referral to the social worker to examine the caregiver for presence of high burden. Third, depression of the caregiver should be scored and intervened.

Next to intervention, prevention is equally important. In order to better understand the caregivers needs Northouse et al.⁷⁰ state that first the vital role of caregivers has to be recognized. Second, the caregiver’s willingness and ability to provide care should be examined. Third, training programs to provide knowledge and skills to care for the patient should be developed. And last, compensation for the caregiver provided care should be given. If caregiver burden is associated with treatment decision should be subject of further research.

**CONCLUDING REMARKS**

In conclusion, toxicity, quality of life and survival of a treatment have to be balanced for both curative and palliative treatment of patients with upper gastrointestinal cancer. Not only the patient’s well-being, but also the spousal caregiver needs should be addressed in the consultation room.

In daily practice, there is profound variety of survival between hospitals. The exact underlying mechanism should be explored in order to achieve an optimal and equal quality of care for upper gastrointestinal cancer. The improved knowledge on patterns of care, toxicity, quality of life and survival serve as a source of information that is directly applicable to clinical daily practice and can serve as a basis for shared decision-making.
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