SUMMARY & GENERAL DISCUSSION

Nowadays, superior sulcus non-small cell lung cancer is no longer uniformly fatal and the number of long-term survivors is increasing, with 5-year survival rates for patients with operable tumors just above 50%.1-8 This thesis is concerned with trying to improve the outcome of patients with operable superior sulcus tumors and is divided into 4 parts. In the first part an introduction to superior sulcus tumors is provided and the current state of the art management of these tumors is discussed. The second part is concerned with response evaluation and prognosis prediction using the end-point of pathological response.2-5,9-12 Research on arm function and quality of life in patients who received trimodality treatment is lacking - this topic is investigated in the third part of this thesis. In the fourth part two cases highlighting complex multidisciplinary surgery and its challenges are presented. In the following paragraphs the chapters of this thesis will be summarized and discussed. At the end of this chapter the main conclusions of this thesis are presented and future perspectives are discussed.

PART I: Introduction

The present state of the art management of superior sulcus tumors, based on the currently available literature, is discussed in Chapter 2. The history, diagnostic approach, staging, treatment and prognosis are described. Superior sulcus tumors are distinguished from other non-small-cell lung cancers (NSCLC) by their location in the lung apex and their tendency to invade surrounding structures. Superior sulcus tumors are rarely detected at an early stage, due to the low incidence and the late occurrence of symptoms.10,13 Shoulder pain, often radiating to the ipsilateral arm or hand, and Horner’s syndrome are often the first symptoms.10,14 Due to their peripheral location, pulmonary symptoms, such as cough, dyspnea or post-obstructive pneumonia, are rare.8,10 In many centers, standard treatment for patients with operable tumors is induction chemoradiotherapy followed by surgery, leading to 5-year survival rates of over 50%.1-3,8,10,13 The tendency to invade surrounding structures can cause severe pain that can be hard to palliate, and further justifies an aggressive approach to local treatment in this disease.13 Therefore, local invasion, mediastinal lymph node metastasis and, in selected patients, distant metastasis, are not necessarily contraindications for surgery. Treatment should take place in a multidisciplinary environment, preferably in a specialized center.13 A complete resection and a complete pathological response are associated with significantly higher survival rates.1-3,10
Between different centers in the world, considerable variation exists with regards to patient selection, staging and induction therapy schemes. The VU University Medical Center is a tertiary referral center for superior sulcus tumors. To standardize treatment, a regional clinical protocol was developed. We retrospectively evaluated the results of this protocol and identified prognostic factors that influence survival in a cohort of 54 superior sulcus tumor patients treated between January 2003 and December 2009 (Chapter 3). All patients received induction chemotherapy and concurrent radiotherapy, followed by en-bloc resection of the tumor and involved structures. In our cohort, patients with suspected or proven N2 stage were included, while in some previously reported larger studies these patients were excluded. Overall 2-year survival was 50% (95%CI: 36.7 - 63.3). For patients with a complete pathological response 2-year survival was 81% (95%CI: 62.1 - 100.0), while it was 37% (95%CI: 21.5 - 52.1) in patients with remaining vital tumor in their resection specimens (P < 0.003). Logistic regression identified complete pathological response as a significant predictor of survival. A complete pathological response was obtained in approximately 30% of patients. These findings are in accordance with the current available literature and confirm complete pathological response as an important prognostic factor.

PART II: Response evaluation in superior sulcus tumors
The assessment of clinical response to induction treatment is currently based on the Response Evaluation Criteria in Solid Tumors (RECIST), where one-dimensional measurements (i.e. the longest diameter) are used. It has been postulated that the change in tumor volume might be a more sensitive measure of response. However, studies evaluating the relationship of volume change with pathological response and survival in NSCLC patients have shown conflicting results. If the pathological response could reliably be determined prior to surgery, response-directed therapy studies could become feasible. Examples include studies evaluating whether patients with an insufficient response to treatment might benefit from intensified induction therapy, or whether patients with a complete pathological response still require resection. In Chapter 4, we reported a retrospective study investigating the use of volume change for response evaluation in a cohort of 30 superior sulcus tumor patients, treated with trimodality treatment between January 2002 and December 2011. Volume change was measured using CT-scans performed before and after induction and was correlated with pathological complete response and survival. Because volume measurements are time consuming and subject to inter-observer variation, we additionally evaluated a semi-automatic method for volume measurement using deformable image registration (DIR) for contour propagation between the radiotherapy planning CT scan and the post-
induction CT scan. Tumor volumes derived using DIR alone were similar to those obtained after manual editing of the contours ($R^2 = 0.99$, $P < 0.01$), indicating that on the whole, DIR performed well. We were not able to demonstrate a relationship between volume change and pathological complete response or survival. This contrasts with a number of studies in other types of cancer that have identified volume change as a predictor for either pathological response or survival. This suggests that volume change might have different implications depending on the type of cancer and type of therapy administered.

Patients with large primary tumors are at risk of being considered to have incurable disease and might be excluded from radical treatment. We investigated whether tumor size could predict pathological complete response and whether even large tumors could be sterilized with modest doses of radiotherapy (Chapter 5). In this retrospective study, all superior sulcus tumor patients treated with 45-50 Gy between 2002 and 2011 were included ($n = 36$). Using correlation coefficients and ROC-curve analysis, no relationships could be demonstrated between baseline maximum axial diameter, cranio-caudal diameter or tumor volume, all measured on CT-scans, and pathological response. When the population was divided into two groups with size values above and below the median (i.e. large and small tumors), there was no significant difference in the occurrence of pathological complete response. Consistent with other data, this suggests that patients with a large primary tumor should not automatically be excluded from radical treatment. The results of the studies described in Chapter 4 and Chapter 5 demonstrate the need for more robust biomarkers for determining pathological response.

Nowadays, FDG-PET/CT-scanning is widely used for the initial staging of NSCLC patients. However, the exact role of FDG-PET/CT-scanning for pathological response evaluation after induction chemoradiotherapy has not yet been established. In Chapter 6, it was investigated whether changes in metabolic activity, measured by FDG-PET/CT-scanning, could predict pathological response. Maximum and mean standardized uptake values ($SUV_{\text{max}}$ and $SUV_{\text{mean}}$), a 1 ml sphere around the pixel with the highest standard uptake value ($SUV_{\text{peak}}$) and tumor-to-liver ratios ($SUV_{\text{TTL}}$) were the metabolic parameters studied. Also, imaging parameters and histopathological findings were correlated. Changes in all metabolic parameters were correlated with a pathological response with 10% or less remaining vital tumor cells. The strongest predictor was a 55% decrease in $SUV_{\text{max}}$, which could predict 10% or less remaining vital tumor cells with a sensitivity and specificity of 85 and 100%, respectively (ROC-curve analysis, area under the curve (AUC): 0.962; $P < 0.002$). However, changes in $SUV_{\text{max}}$ could
not predict a complete pathological response (ROC-curve analysis, AUC: 0.782; P = 0.054). Only changes in tumor to liver ratios ($\text{SUV}_{\text{TTL}}$ and $\text{SUV}_{\text{peak-to-liver}}$) were predictive for a complete pathological response. In patients with remaining vital tumor cells, the location of these cells corresponded to the post-induction $\text{SUV}_{\text{peak}}$ area in all but one patient (93%). In contrast to previous studies\textsuperscript{33,34}, no correlation was found between post-induction $\text{SUV}_{\text{peak}}$ areas and the presence of macrophages, neutrophils or lymphocytes.

Since $\text{SUV}_{\text{max}}$ is a parameter commonly used in clinical practice, it might be a suitable candidate biomarker for pathological response. Although tumor-to-liver ratios are not typically available they merit further investigation in larger, prospective, studies for predicting a complete pathological response. An advantage of this parameter is that knowledge of patient’s weight and injected dose of FDG is not needed, and the ratio calculation compensates for variations in scanner calibration settings. However, the liver $\text{SUV}_{\text{mean}}$ should be stable within patients\textsuperscript{35,36} and the use of tumor-to-liver ratios does not correct for variations in PET acquisition, correction and reconstruction settings.

**PART III: Arm function and quality of life**

Following the improvements in treatment described in chapter 2, survival rates have increased, and as a consequence, the number of long-term survivors has increased as well. Not much is known about the quality of life of these patients and in addition, chemoradiotherapy and surgery might all contribute to impairment in arm function. At present, there are no studies investigating quality of life in patients with superior sulcus tumors and only a few reports mention arm function without formally investigating this\textsuperscript{37,38}

More detailed knowledge about arm function and quality of life could aid in pre-treatment counseling. In addition, factors that can be addressed, for example with physical therapy, to improve functional outcome might be identified.

To obtain this knowledge, we first performed a retrospective study in patients that had been treated with trimodality treatment for a superior sulcus tumor (**Chapter 7**). Three hypotheses were formulated: (1) arm function on the ipsilateral side is worse than that on the untreated side; (2) patients treated on their dominant side will report worse quality of life compared to those treated on the non-dominant side; (3) resection of the T1 nerve root leads to greater impairment in arm function and worse quality of life when compared to patients in whom the T1 nerve root could be spared. Survivors received validated quality of life questionnaires (SF-36\textsuperscript{39} and Disability of the arm and shoulder (DASH)\textsuperscript{40-42}) and arm function was objectively measured with range of motion\textsuperscript{43}, nine-hole peg test\textsuperscript{44,45} and the action-research-arm test.\textsuperscript{46}
Unfortunately, of the 39 survivors we contacted, only 19 returned the questionnaires and only 15 consented to the arm function testing. When arm function between the treated and untreated side was compared, no significant differences were found in any of the tests described above. Also, no differences in quality of life were found between patients treated on their dominant side and patients treated on their non-dominant side, with the exception that patients treated on their non-dominant side reported more pain. No differences were found in the arm function tests between patients undergoing resection and sparing of the T1 nerve root, respectively, which is in contradiction to previous reports. However, the results confirmed the previous reports which suggested that resection of the T1 nerve root is usually well tolerated. In the quality of life questionnaires a significant difference was only found for the SF-36 domain mental health in favor of patients in whom the T1 nerve root could be spared. Important limitations of this study were the low number of patients that agreed to participate and the fact that no comparison could be made with the preoperative situation.

A prospective analysis of subjective arm function and quality of life was therefore conducted (Chapter 8), in consecutive patients that underwent resection between April 2010 and October 2012 (n = 20). All patients were requested to fill out the SF-36 and DASH questionnaires before the operation and at 3 and 12 months after the operation. In comparison to the pre-operative scores, patients reported significantly more subjective impairment of arm function at both 3 (P = 0.024) and 12 months (P = 0.011) postoperatively. Significantly lower scores were reported for the SF-36 domain physical functioning at 12 months (P = 0.020). Scores for the domain physical role functioning initially deteriorated and were significantly lower at 3 months (P = 0.041), however with further follow-up scores improved and at 12 months they were comparable to baseline values. Patients reported significantly more pain at 3 months (P = 0.006) and although pain scores improved, patients still reported significantly more pain at 12 months (P = 0.019). Subgroup analysis of patients with and without T1 nerve root resection only demonstrated significantly lower scores for the domain health change at 3 months for patients in whom the T1 nerve root was resected. However, at 12 months, this difference disappeared. Furthermore, no differences were found between patients treated on either their dominant or non-dominant side and no correlations were found between quality of life and radiation dose, sex, age or operative approach. These findings again suggest that resection of the T1 nerve root is well tolerated. Possible explanations include: (1) chemoradiotherapy might have a larger impact on arm function compared to surgery; (2) most of the function of the T1 branch
PART IV: Complex surgery and the challenge of extensive resections

In this supplementary part two interesting cases were described. The first case, presented in Chapter 9, concerned a patient who underwent an extensive resection of the tumor, involved chest wall and 3 vertebrae. This case illustrated that complete resections can be achieved and long-term survival is possible despite extensive invasion of surrounding structures. Chapter 10 demonstrated an example of technical failure after a partial resection of the first and second thoracic vertebrae. The patient developed progressive kyphosis and scoliosis resulting in symptomatic spinal cord compression. Reduction under traction and, in a second operation, a dorsal laminectomy and anterior and posterior spondylodesis were performed and the neurological deficit resolved. The case illustrates that early stabilization is warranted when any angulation or dislocation is seen after (partial) resection of a vertebra.

CONCLUSIONS

Superior sulcus tumors are a subtype of NSCLC with distinguishing features as a result of their location in the pulmonary apex where they are surrounded by important vital structures. Although local control and survival improved over the years, distant metastases remain a major problem. In addition to other factors, such as tumor stage and complete resection, pathological response is an important prognostic factor with superior survival rates for those patients in whom a complete pathological response can be obtained. Tumor
size and volume, measured by CT-scans, are not sensitive enough to predict complete pathological response. Additionally, a large tumor size does not preclude achieving a complete pathological response and should not be used as an argument to exclude patients from radical treatment.

Metabolic activity, measured by FDG-PET/CT-scanning, seems to be more sensitive when compared to size and volume measurements and can predict pathological response. Finally, arm function and quality of life are reduced following trimodality treatment, even though the influence of chemoradiotherapy was not formally investigated. Resection of the T1 nerve root is well tolerated and does not lead to significantly reduced arm function or quality of life.

**FUTURE PERSPECTIVES**

Developments over the past few decades have improved overall survival rates for superior sulcus tumors, with 5-year survival rates exceeding 50%. Nonetheless, distant metastases remain a major problem. Although metastases and their management are not investigated in this thesis, it is an important issue to address with future research on more effective treatment modalities. An example of efforts in this area are the recent trials on prophylactic cranial irradiation for the prevention of brain metastases.\(^49,50\) Long-term results are needed to proof any survival benefits. The search for more effective chemotherapeutic agents, biologicals and radiotherapy schemes also continues.\(^51-54\) Furthermore, ways to influence the immune system to increase its ability to kill cancer cells are currently under investigation.\(^55\) The optimal combination of chemotherapeutic agents and most effective radiotherapy dose still needs to be established. In a study by Kappers et al, higher radiation doses (66 Gy) resulted in higher pathological complete response rates (62%), although 5-year survival was only 37%.\(^7\) Similar pathological complete response rates were found in a larger study by Rusch et al, where radiotherapy doses of 45 Gy were administered, with a 5-year survival rate of 54%.\(^3\) Moreover, Maas et al. found a pathological complete response rate of only 17%, but the 5-year survival rate was 30%.\(^56\) The majority of patients (30/42) in the latter study received 45 Gy. When searching for the optimal treatment scheme, the question seems more complex than just considering the radiotherapy dose. The combination and type of chemotherapeutic agents, techniques of delivering radiotherapy, tumor characteristics and patient selection are probably important factors that contribute to the difference in results described above.
Finally, centralization of treatment in specialized centers might also contribute to improved outcome, through hospital volume and surgeon specialization. However, evidence based minimum volume-standards for surgical resection are lacking.\(^{57}\)

Anatomical features, such as tumor size and volume, are probably not sensitive enough for response evaluation and cannot predict the occurrence of a complete pathological response. Metabolic activity, measured with FDG-PET/CT-scanning, is more promising, but larger studies with standardized protocols for PET acquisition and timing are needed to establish its use for response evaluation in clinical practice. When the reliability of metabolic activity for the preoperative prediction of pathological response is confirmed, studies evaluating response directed treatment strategies may become feasible. Examples of these strategies include: intensified induction schedules in case of no or insufficient response on the follow-up FDG-PET/CT-scan, or possibly performing no resection in case of a predicted complete pathological response. Future studies might justify performing a follow-up FDG-PET/CT-scan early during induction treatment to evaluate if there is a response, and if not, the induction treatment (type, dosage or modality) can be adjusted.

The metabolic activity measured by FDG-PET/CT-scanning is based on the uptake of FDG by metabolically active cells and is visualized as hotspots, because uptake of FDG is higher in these cells than that of background tissue.\(^{58,59}\) A disadvantage of this technique is that it is non-specific.\(^{58}\) Non-malignant conditions, such as infection, auto-immune diseases, surgical procedures and radiotherapy can induce increased FDG uptake, mainly by inflammatory cells.\(^{58,59}\) Additionally, in some malignant tumors, uptake of FDG is similar to that of surrounding tissues and these tumors are not visualized on FDG-PET/CT-scanning.\(^{59}\) Therefore, development of new radiopharmaceuticals that specifically bind to tumor cells, or maybe even specifically to cells of the tumor in an individual patient, could lead to more specific imaging which could improve the reliability of response evaluation.

Other biomarkers that could identify patients that respond well to therapy are under investigation.\(^{55,60}\) Examples include the high-mobility group box 1 (HMGB1) protein, which is released by dying tumor cells and stimulates anti-tumor immune activity. Studies demonstrated increased levels of HMGB1 in patients treated with chemoradiotherapy and higher serum levels correlated with improved survival. Therefore, the hypothesis that HMGB1 expression could indicate response to treatment has been proposed.\(^{55}\) Paradoxically, HMGB1 has also been found to promote invasive behavior and metastasis. Therefore, the true value of this biomarker still needs to be elucidated. Another example of a biomarker
that could predict response to induction treatment is the enzyme aldehyde dehydrogenase-1 (ALDH-1).\textsuperscript{60} Increased expression of ALDH-1 was found in tumors more resistant to induction chemoradiotherapy for several types of cancer, including NSCLC. Moreover, low expression of ALDH-1 could predict pathological complete response. Identification of these and other biomarkers could result in more robust methods to predict response to treatment and outcome.

Our studies on arm function and quality of life, described in chapter 7 and 8, demonstrate some deterioration in subjective arm function and quality of life following surgery in superior sulcus tumor patients treated with trimodality treatment. However, overall quality of life is not significantly worse after surgery. Ideally our study would be repeated in a larger prospective population and measurements would start at the time of diagnoses and be repeated before, during and after induction treatment and before and after surgery. Such a study could also include objective testing of arm function.

Patient reported outcomes are becoming more and more important in both cancer research and clinical practice.\textsuperscript{61} The growing and aging population with increasing complex medical histories, the increased number of treatment options with several effects and side-effects, the increasing healthcare costs and required cost-effectiveness all lead to increased interest in these patient reported outcomes and quality of life.\textsuperscript{61} However, there is currently a lack of standardized and validated instruments to investigate patient reported outcomes, which hampers comparison of findings of different studies and informed decision-making.\textsuperscript{61} Standardization of research methods and reporting of patient reported outcomes could improve comparability and interpretation of studies and help improve informed decision-making for individual patients.\textsuperscript{61}
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CHAPTER 11  SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES


