CHAPTER 8

IMPACT OF TRIMODALITY TREATMENT ON QUALITY OF LIFE AND ARM AND SHOULDER FUNCTION FOR SUPERIOR SULCUS TUMORS

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ABSTRACT

Purpose
Trimodality treatment lead to improved survival for superior sulcus tumor (SST) patients. Not much is known about the impact of this treatment on arm function and quality of life. We analyzed arm function and quality of life in SST patients undergoing trimodality treatment.

Methods
Prospective cohort study including consecutive SST patients treated with trimodality treatment. The SF-36 and disability of the arm and shoulder (DASH) questionnaires were used to assess quality of life and subjective arm function at 0 (preoperative day), 3 and 12 months after trimodality treatment.

Results
Between April 2010 and October 2012, for 20 out of 22 eligible patients informed consent was obtained. DASH scores were significantly lower at 3 (P = 0.024) and 12 months (P = 0.011) when compared to preoperatively. Significantly lower scores were reported for the SF-36 domain physical functioning at 12 months (P = 0.020), physical role functioning at 3 months (P = 0.041) and significantly more pain was reported at 3 (P = 0.006) and 12 months (P = 0.019). Patients undergoing T1 nerve root resection had lower scores for the SF-36 domain health change at 3 months (P = 0.037) compared to those in whom the T1 root was spared. For all other domains no differences were found.

Conclusion
Subjective arm function and quality of life is reduced following trimodality treatment. Resection of the T1 nerve root has no significant long-term effect on the subjective arm function and quality of life.
INTRODUCTION

Standard treatment for superior sulcus tumors (SST) is induction chemoradiotherapy followed by surgery.\(^1\) This trimodality treatment lead to improved survival in these patients but is associated with considerable morbidity.\(^2\)

SST typically invade the chest wall and possibly the brachial plexus, subclavian vessels and/or spine.\(^2\) Impaired arm and shoulder function can be caused by direct invasion or compression of the brachial plexus or blood vessels by the tumor. Another cause is the local detrimental effect of radiotherapy and surgery in this region rich of vital structures. Additionally, systemic chemotherapy can lead to neuropathy, which could further increase arm and shoulder disability. On the other hand, trimodality treatment could also reduce impairment by reducing invasion or compression.

While not much is known about the exact impact of trimodality treatment on arm function and quality of life\(^3\), this knowledge could identify factors that could help optimize perioperative supportive care (for example intensified physiotherapy for specific functions). Moreover, this improved knowledge could aid pre-operative counseling. Therefore, we prospectively analyzed both arm and shoulder function-related and overall quality of life in a cohort of SST patients before and after trimodality treatment.

MATERIALS AND METHODS

Patient selection

After approval of the VU University Medical Center Medical Ethics Board and written informed consent was obtained, all consecutive SST patients between April 2010 and October 2012 were included. SST were defined as non-small cell lung cancers (NSCLC) located at the superior sulcus with involvement of structures of the apical chest wall above the second rib.\(^2,4\) Eligibility for trimodality treatment was discussed in a multidisciplinary thoracic oncology meeting for all patients. Patients with pre-existing impaired function of the upper extremity due to causes not related to trimodality treatment (i.e. cerebrovascular accident, trauma, brain metastasis) were excluded.

Trimodality treatment

All patients received trimodality treatment as published before.\(^3,5\) In short, treatment consisted of concurrent chemoradiotherapy followed by surgery. Chemotherapy consisted
of 1 cycle cisplatin 80 mg/m² on day 1 and either gemcitabine 1250 mg/m² on day 1 and 8 for squamous histologies and of pemetrexed 500 mg/m² on day 1, and 2 cycles of cisplatin 80 mg/m² on day 1 and etoposide 100 mg/m² days 1 - 3 for 3 weeks for non-squamous histologies. Involved field radiotherapy (46 - 66 Gy in fractions of 2 Gy) was administered, starting on day 2 of the second cycle of chemotherapy.

When no progression and no distant metastasis occurred, patients were operated approximately 6 weeks after completion of induction therapy. All patients received physiotherapy for breathing and coughing without any focus on arm function. An upper lobe resection with en-bloc resection of the involved chest wall and whenever necessary the C8 or T1 root of the brachial plexus was performed. Hilar and mediastinal lymph node dissection and covering of the bronchial stump with a vascularized intercostal muscle flap was routinely performed. Generally, tumors were approached through a Shaw-Paulson incision, although anteriorly located tumors were resected through a hemi-clamshell incision. 

**Assessment of arm and shoulder disability and quality of life**

The overall quality of life was assessed using the SF-36 questionnaire. The Dutch language version of the SF-36 questionnaire is validated for general population surveys as well as for patients with cancer. The SF-36 questionnaire evaluates the following domains: physical functioning, social role functioning, physical role functioning, emotional role functioning, mental health, vitality, pain, general health perception, health change. Higher scores (maximum 100) implicate a better quality of life and lower scores implicate impairments of daily functioning. The disability of the arm and shoulder (DASH) questionnaire was used to assess the subjective disability of arm and shoulder function. The DASH questionnaire is frequently used in functional studies after limb surgery. A higher score (maximum 100) implies a higher subjective disability of arm and shoulder function. Both questionnaires were assessed at 0 (i.e. after completion of induction chemoradiotherapy on the day before the operation), 3 and 12 months postoperatively.

**Data collection**

In the prospectively maintained thoracic surgery database patients age, sex, treatment details, dominant side, staging characteristics (cTNM, ypTNM 7th edition), pathology results, surgical details, complications and follow-up data were stored and collected for the analysis.
Statistical analysis
All statistical analyses were performed using the statistical software package SPSS, version 17.0 (SPSS Inc., Chicago, IL, USA). The scores of the DASH and SF-36 questionnaires assessed on the three different time points (preoperatively, 3 and 12 months postoperatively) were compared using the Wilcoxon signed rank test. Additionally, a comparison was made between the scores of patients treated on their dominant side and of those treated on their non-dominant side. A third analysis was performed, comparing scores of patients in whom T1 nerve root was resected to those in whom the T1 nerve root could be spared. For statistical evaluation of the latter two comparisons the Mann-Whitney U test was used. Correlations were investigated using the Spearman's correlation coefficient. Missing data were left out of the analysis. Statistical significance was defined as $P < 0.05$.

RESULTS

Patient characteristics
Between April 2010 and October 2012, 22 patients received trimodality treatment for a SST in our center. Informed consent was obtained from 20 patients to participate in the study. Patient characteristics are displayed in Table 1. Four patients did not return the preoperative questionnaires completely and one patient did not respond at the measurement point at 3 months after the operation. During the follow-up period 2 patients died within three months leaving 18 patients that could be analyzed.

Arm and shoulder disability and quality of life
Patients experienced a significantly higher subjective disability in arm and shoulder function at both 3 months ($P = 0.024$) and 12 months ($P = 0.011$) of follow-up when compared to the pre-operative measurement. Patients reported significantly lower scores for the SF-36 domain physical functioning at 12 months ($P = 0.020$) but not at 3 months. Scores for physical role functioning significantly deteriorated at 3 months ($P = 0.041$), but at 12 months scores improved and the difference compared to 0 months was not statistically significant anymore. Patients reported significantly more pain at 3 months ($P = 0.006$) and although pain scores improved they still were significantly lower at 12 months ($P = 0.019$) when compared to 0 months. For the remaining domains (social functioning, emotional role functioning, mental health, vitality, general health perception and health change) no statistically significant differences were found at the different time points. The results from...
the SF-36 and DASH questionnaires measured at 0, 3 and 12 months are displayed in Table 2.

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients included</td>
<td>20 (100%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>median (range) 54 (32 - 71)</td>
</tr>
<tr>
<td>Radiation dose (Gy)</td>
<td>median (range) 50 (45 - 66)</td>
</tr>
<tr>
<td>T1 nerve root resection</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (65%)</td>
</tr>
<tr>
<td>No</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Dominant side</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Right</td>
<td>17 (85%)</td>
</tr>
<tr>
<td>Operated on dominant side?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14 (70%)</td>
</tr>
<tr>
<td>No</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>Approach operative technique</td>
<td></td>
</tr>
<tr>
<td>Shaw-Paulson</td>
<td>18 (90%)</td>
</tr>
<tr>
<td>Hemi-clamshell</td>
<td>2 (10%)</td>
</tr>
</tbody>
</table>

**Table 2. DASH & SF-36 scores at 0, 3 and 12 months**

<table>
<thead>
<tr>
<th>Item</th>
<th>0 months</th>
<th>3 months</th>
<th>P-value(^a)</th>
<th>12 months</th>
<th>P-value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DASH</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>N = 16</td>
<td>N = 17</td>
<td></td>
<td></td>
<td>N = 18</td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>21 ± 16</td>
<td>39 ± 18</td>
<td>0.024</td>
<td>37 ± 18</td>
<td>0.011</td>
</tr>
<tr>
<td>Social functioning</td>
<td>71 ± 21</td>
<td>61 ± 15</td>
<td>ns</td>
<td>55 ± 20</td>
<td>0.020</td>
</tr>
<tr>
<td>Physical role functioning</td>
<td>63 ± 29</td>
<td>65 ± 33</td>
<td>ns</td>
<td>65 ± 29</td>
<td>ns</td>
</tr>
<tr>
<td>Emotional role functioning</td>
<td>34 ± 43</td>
<td>1 ± 6</td>
<td>0.041</td>
<td>21 ± 29</td>
<td>ns</td>
</tr>
<tr>
<td>Mental health</td>
<td>58 ± 46</td>
<td>63 ± 45</td>
<td>ns</td>
<td>56 ± 44</td>
<td>ns</td>
</tr>
<tr>
<td>Vitality</td>
<td>67 ± 23</td>
<td>68 ± 24</td>
<td>ns</td>
<td>71 ± 20</td>
<td>ns</td>
</tr>
<tr>
<td>Pain</td>
<td>61 ± 20</td>
<td>50 ± 19</td>
<td>ns</td>
<td>57 ± 17</td>
<td>ns</td>
</tr>
<tr>
<td>General health perception</td>
<td>69 ± 16</td>
<td>44 ± 22</td>
<td>0.006</td>
<td>54 ± 20</td>
<td>0.019</td>
</tr>
<tr>
<td>Health change</td>
<td>50 ± 16</td>
<td>54 ± 20</td>
<td>ns</td>
<td>48 ± 24</td>
<td>ns</td>
</tr>
</tbody>
</table>

\(^a\) comparison 3 months versus 0 months; \(^b\) comparison 12 months versus 0 months; ns - not significant; Wilcoxon signed rank test
Subgroup analyses

Subgroup analysis of DASH and SF-36 scores for patients with and without T1 nerve root resection failed to detect any significant difference except for the SF-36 domain health change at 3 months, where patients in whom the T1 nerve root was resected had significantly lower scores (P = 0.037). After 1 year this difference disappeared. No statistically significant differences were found for both the DASH scores and scores on all SF-36 domains between patients that were operated on their dominant side and those that were treated on their non-dominant side. There were no correlations between the quality of life scores (SF-36 and DASH) and the dose of radiation, sex, age at the time of diagnosis and the operative approach.

DISCUSSION

Arm and shoulder function and quality of life are negatively influenced by trimodality treatment for superior sulcus tumors. Patients reported increased subjective arm and shoulder function disability after 3 and 12 months. The experienced physical functioning 1 year after resection was also worse. However, while the physical role functioning is significantly decreased 3 months postoperatively, it returns to baseline (i.e. the first, preoperative, measurement) functioning after 1 year of follow-up. Patients reported significantly more pain 3 months postoperatively and although pain scores improved thereafter there was still significantly more pain reported compared to baseline. Possibly pain scores could further improve with longer follow-up, but at this moment this remains unclear.

The influence of resection of the T1 nerve root seems to be mild. Although patients initially reported a greater deterioration in their general health compared to those in whom the T1 nerve root could be spared, these differences disappeared after 1 year. 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 might already be lost preoperatively due to compression or invasion by the tumor; (3) due to the subjective nature of the questionnaires people might consider their function rather satisfying when taking into account the fact that they are surviving a possibly lethal disease.

No correlations were found between the subjective arm and shoulder function and reported quality of life and treatment on the dominant side, radiotherapy dose, operative approach,
age and sex. These findings are in accordance with the results of our previous report where we investigated arm and shoulder function and quality of live in a retrospective cohort of patients.\(^3\)

In SST patients, arm and shoulder function might be at risk due to several causes. Compression or invasion of vital structures by these tumors located in the cervico-thoracic junction and detrimental effects of radiotherapy, systemic chemotherapy (neuropathy) and surgery can all damage the nerves, vessels, muscles and other structures vital for arm and shoulder function. On the other hand, trimodality treatment can improve arm function, and for example pain, by alleviating compression due to shrinkage or resection of the tumor.\(^12\) Our study investigated the results of all these factors together.

Previous studies mentioned that resection of the T1 nerve root is generally well tolerated but resection of C8 leads to loss of function, although objective measurements were not reported.\(^13-15\) Davis et al report that resection of the T1 nerve root (with or without the C8 nerve root) causes significant loss of function and investigated sparing of the T1 nerve root in only 5 patients with promising results, but they did not compare these results to patients in whom the T1 nerve root was resected.\(^16\) Shahian et al scored the functional outcome of long-term survivors after resection of pancoast tumors as excellent, good, fair or poor, without further defining these groups.\(^17\) They reported that shoulder function is generally excellent, but dependent on aggressive physical therapy following resection or radiotherapy.\(^17\)

The present study is the largest reported study focusing on arm and shoulder function and quality of life in superior sulcus tumor patients. However, we do recognize some limitations of the presented study. We did not formally test the actual arm and shoulder function but assessed it using validated questionnaires. Therefore this study only reports the subjective arm and shoulder function. In addition, the numbers of patients investigated were small, warranting a careful interpretation of our findings due to the risk of bias. For example survivorship bias (patients who have died might have had worse outcomes) and non-response bias (patients with worse outcomes might more likely refuse participation) cannot be ruled out. The risk of bias is even higher when subgroup analyses are performed. Investigating correlations and searching for prognostic factors is limited by the small dataset and the risk for confounders. Moreover, the collected dataset was too small to perform a multivariate analysis to identify prognostic factors for arm and shoulder function and quality of life. Therefore we failed to identify factors that could be influenced to improve function
and quality of life in these patients. However, the currently available literature on this topic is scarce, and the presented data could aid to inform superior sulcus tumors patients.

CONCLUSION

Subjective arm function and quality of life is reduced following trimodality treatment. Resection of the T1 nerve root has no significant long-term effect on the subjective arm function and quality of life.
REFERENCES


