Pattern of Failure after Adjuvant Radiotherapy Following Extrapleural Pneumonectomy of Pleural Mesothelioma in the SAKK 17/04 Trial

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Summary

Postoperative radiotherapy after extrapleural pneumonectomy of malignant pleural mesothelioma was investigated in the randomized phase II trial SAKK17/04. The relapse rate within the high and/or low-dose PTV without previous distant failure was 24%, the isolated in-field-relapse rate within the PTVs was 5% and the distant relapse rate outside of the PTVs was 81%. Clinical outcome was mainly determined by distant disease progression outside of the radiation field.

Key words: Mesothelioma; radiation therapy; radiotherapy; extrapleural pneumonectomy; adjuvant therapy; volumetric modulated arc therapy; intensity modulated radiotherapy; multimodal therapy.

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a rare cancer associated with exposure to asbestos. The concept of trimodal therapy including chemotherapy, extrapleural pneumonectomy (EPP) and postoperative radiotherapy (RT) has long been considered to be a promising treatment approach based on single arm studies and retrospective analyses reporting high local control rates and promising survival [1-3]. In order to improve the scientific evidence for the trimodal approach and on the basis of own multicenter clinical data [3], the Swiss group for Clinical Cancer Research (SAKK) launched a randomized trial addressing the question if postoperative RT after EPP would give an additional benefit to the patients. The SAKK 17/04 trial was designed as a two-part multicenter randomized phase II trial exploring the effect of high-dose hemithoracic RT after induction-chemotherapy and EPP in MPM patients with stage I–III disease. In part 1 of the trial, patients were treated with three cycles of chemotherapy and EPP. In part 2, after surgery, completely resected patients were randomly assigned (1:1) to receive high-dose RT or no further treatment. The results of SAKK 17/04 showed similar median locoregional relapse-free survival of 9.4 months (95% confidence interval [CI]: 6.5–11.9) in the RT group compared to 7.6 months (95% CI: 4.5–10.7) in the arm without RT [4]. According to the trial protocol, locoregional relapse was defined as relapse within the ipsiliateral hemithorax or death from any cause and not, as in many other studies, as relapse within the planning target volume (PTV) [1, 5, 6]. Further, heterogeneity of the radiation techniques allowed in the trial as well as the lack of a centralized review of RT plans were criticized in a letter to the editor following publication of the trial [4, 7]. To shed more light on the efficacy of RT applied within the SAKK trial we investigated tumor recurrences in relation to the high- and low-dose PTVs and to the total dose in patients randomized to RT.

MATERIAL AND METHODS

Patients

Altogether, 153 patients with pathologically confirmed malignant pleural mesothelioma; resectable TNM stages T1–3 N0–2, M0;WHO performance status 0–1; age 18–70 years were enrolled and 151 patients started treatment; 99 patients with R0-1 resections were candidates for randomization in part 2, and 54 patients could be randomized, 27 patients in each arm. Finally, follow-up images of 21 patients were available and could be evaluated for tumor control within the PTVs. All diagnostic follow-up radiologic images showing the site(s) of first relapse, RT treatment plans including PTVs, and clinical outcome data were collected from the participating centers or were provided by the SAKK coordinating center.

Radiotherapy target definition

Two clinical target volumes (CTVs) with corresponding planning target volumes (PTVs) were defined. The low-dose CTV2 was defined as the field of surgery, including the entire preoperative pleural and pulmonary structures, the surgical tracts and scars. The boost CTV, referred to as CTV1, was defined by the risk of residual postoperative microscopic disease or the area of highest risk for intrathoracic relapse as defined by the surgeon, the pathologist or as suggested by the tumor extension prior to surgery. The diaphragmatic borders as well as areas of primordial risk for relapse had to be marked with radiopaque clips during surgery. Additional clips were to be placed in areas where the surgeon did not feel confident about radicality. In case of metastatic nodal disease, contaminated lymph node areas were recommended to be included in CTV1. CTVs were expanded by 0.5-1 cm to the corresponding PTVs 1 and 2, which were used for RT planning.

Radiation techniques

In the 21 evaluable patients, 3D-conformal RT (3D-CRT) was used for 5 patients, intensity-modulated radiotherapy (IMRT) or volumetric modulated arc radiotherapy (VMAT) were used for 11 patients, helical tomotherapy for 2 patients, and a combination of 3D-CRT with IMRT was used for 3 patients [8]. Three types of dose and fractionation were allowed:

- 25 x 1.8 Gy = 45 Gy to the PTV1 followed by 7x 1.8 Gy = 12.6 Gy to the PTV2
- 23 x 2 Gy = 46 Gy to the PTV1 followed by 5x 2 Gy = 10 Gy to the PTV2
- 26 x 1.75 Gy = 45.5 Gy to the PTV2 including a simultaneous integrated boost of 26 x 2.15 Gy = 55.9 Gy to the PTV1

Patients were treated with different schedules and doses depending on the technologies available and treatment standards used in the participating centers when the trial was planned. Dosimetry was done for every first patient of each center using the EQUAL technique (thermoluminescent diodes) provided by ESTRO. In addition, minimal dosimetry was also required and done for each patient. These quality control measures were performed according to the national standards of the time.

Follow-up and recurrence analysis

During the first year, patients were seen at 4, 8, and 12 months after surgery including clinical examination and restaging using CT or PET/CT. Subsequently, the follow-up was performed every 6 months until 5 years after treatment. During the latter period, a diagnostic CT was performed only in case of suspected clinical relapse.

Local relapse as site of first relapse was defined as relapse within the high or low-dose PTV. Distant relapse was defined as relapse outside of the PTVs, intra and/or extra thoracic.

Marginal miss was defined as relapse just outside of the border of the low-dose PTV in an area that was supposed to be covered by the PTVs (e.g. diaphragmatic crus or edge of the recessus costodiaphragmaticus). All recurrences in the ipsilateral hemi-thorax were analysed by visually comparing the localization of tumor relapse on diagnostic images with PTVs in the original treatment plan. This was done unblinded by 2 senior clinicians with more than 15 years of experience each (OR, IC), and defined as a morphologically increasing radiographic abnormality.

Statistics

The follow-up time to local relapse and survival were calculated from surgery [1]. Time to local relapse was evaluated using the Kaplan Meier Method. For calculation of local control rates as site of first relapse patients were censored in the case of death as well as in the case of distant recurrence.

RESULTS

Of the 27 patients included in arm B and assigned to hemithoracic RT, 6 patients had to be excluded from the local recurrence analysis: 1 patient who had received only 12 Gy, 1 patient for whom follow-up CTs were no longer available and 4 patients, who died within three months after end of RT and before entering the follow-up phase (Figure 1).

Median follow-up of the 21 evaluable patients was 17 months (range, 3.4-61.5). Radiologic tumor recurrences were documented in 18 patients (86%) (Table 1). In these 18 patients the site of first relapse was exclusive locally in only 1 patient (5%), synchronous locally and distant in 4 patients (19%) and only distant in 13 patients (62%). In all 5 cases with local recurrence, the relapse was localized in the low-dose PTV (24%) and in 2 of the 5 patients

(10%) recurrences were simultaneously observed at multiple sites in the low- and high-dose PTVs. The anatomical localization of the local recurrences was costodiaphragmatic recessus (2 patients), lateral thoracic wall (1 patient), pericardium (1 patient), and multiple sites (1 patient). The median time to local tumor recurrence was 9.4 months (range, 6.2-12.1 months) (Figure 2). Of the 5 patients with local relapse, 4 patients had been treated with intensity-modulated radiation techniques (IMRT or VMAT,) and one patient with 3D conformal radiotherapy.

Altogether, 17 patients (81%) had radiologically documented recurrences outside of the PTV: 8 patients (38%) in the contralateral hemithorax, 4 patients (19%) in the mediastinum and 7 patients (33%) in the abdomen (Table 1). We found 2 recurrences at the lower border of the PTVs of which 1 recurrence was judged as geographic miss just outside of the PTV and the other one was overlapping with the PTV and therefore was counted as local recurrence.

Of the 3 patients without radiologically documented relapse during follow-up, 1 patient died after 27 months and 2 patients were still alive at 60 and 61 months after surgery. One patient with relapse in the contralateral lung had cyberknife stereotactic radiotherapy after 25 months and was still alive after 41 months.

If both study arms were compared, the ipsilateral hemithorax was less frequently involved as site of first relapse in arm B (irradiated) than in the control arm without RT (33% vs. 69%, $p = 0.02$, Supplementary Material Table S1 and Fig. S1).

Discussion

SAKK 17/04 trial was designed to investigate the role of trimodal therapy of patients with MPM in a multi-institutional setting. The primary endpoint to evaluate the effect of RT was

locoregional relapse-free survival. For the calculation of this endpoint, locoregional failure was defined in the protocol as relapse within the ipsilateral hemithorax regardless of the radiation field borders as well as death from any cause [4]. Here, we investigated in more detail the effect of RT on local control defined as tumor control within the radiation target volume at time of first relapse. In the 21 evaluable patients we found a local relapse rate of 24% and a distant relapse rate of 81%. Altogether all but one patient relapsed outside of the PTVs at first recurrence. Therefore, despite a relatively high local tumor control rate after complete resection and postoperative RT of the hemithorax, progression-free survival remained low mainly due to metastatic progression outside of the irradiated volume. Our local control rate of 76% within the PTVs is on the lower edge of values given in several single arm, single-center studies reporting local tumor control rates within the PTV of 84-95% [1, 2, 5]. Only 10% of irradiated patients in SAKK 17/04 trial recurred in the boost PTV treated to 55.9-57.6 Gy, which was defined as the region of highest risk for local relapse. This observation suggests that the boost dose used in the trial might be an effective dose for postoperative treatment. Further, considering a 76% tumor control in the low-dose PTV, 45 Gy might be on the lower edge as effective dose for control of subclinical disease. The local tumor control rate reported by us is lower than in the trial of Rice et al. who reported extremely favorable local tumor control in the PTVs of 95% after IMRT as part of trimodality therapy in a retrospective cohort of 61 patients, albeit with a median survival of only 14.2 months [1]. The median dose prescribed to the postoperative hemithorax was also 45 Gy, and a boost dose up to 60 Gy was given to the area of high risk for relapse. Later on, the same group published retrospective data of 86 patients treated with post-operative IMRT to the same dose and fractionation, and reported a local control rate of 84% [5]. The reason for the higher local control rate reported by the MD Anderson group can be explained by

patient selection, specialized care in an experienced single center (MD Anderson), the exclusive use of IMRT and the comparatively short median overall survival of 14.2 months. Recently, three phase II trials have been published also investigating the trimodality approach [9-11]. Doses given ranged from 50.4-54 Gy to the entire hemithorax without a boost in all three studies. Unfortunately, the local tumor control rates within the PTVs have not been reported. Progression free-survival rates of 6.9 to 13.9 months were comparable to the 9.4 months reported after RT in the present trial.

Technically, postoperative RT of MPM after EPP is challenging because radiation has to cover a large and anatomically complex volume extending from the apex of the lung down to the costodiaphragmatic recessus and, medially, including the diaphragmatic crus down to the lumbar vertebrae. In addition, the lower border of the clinical target volume in the costodiaphragmatic recessus is often difficult to define on postoperative CT images. The complexity of volume definition in this region is underlined by our finding of 2 recurrences at or outside of the lower field border, an area of potential underdosage and geographic miss. Remarkably, 4 patients could not be included in this analysis due to early death within the first 3 months after RT, of these 2 patients died for unknown reasons. The relatively high exclusion rate and/or early deaths without radiological documentation of relapse, the latter probably due to treatment related complications, are major caveats from the present analysis and illustrate that a close follow-up for the first 3 months after aggressive multimodal treatment is essential to detect and treat serious and life-threatening side effects.

Importantly, if both study arms were compared, the ipsilateral hemithorax was less frequently involved as site of first relapse if radiotherapy was part of the treatment. Unfortunately, it is impossible to answer the question if this effect was durable, because

most patients with relapse did not undergo regular imaging anymore. However, we can conclude that radiotherapy at least has the potential to delay local recurrence.

Trial SAKK 17/04 remains the only controlled prospective trial investigating the role of postoperative RT as part of trimodal therapy in MPM. However, the results have to be interpreted with caution because of the low number of patients randomized in part 2, the heterogeneity of radiotherapy techniques, the lack of a central plan review and the high proportion of irradiated patients with early death. This is reflected in the recent ASCO treatment guidelines for MPM according to which adjuvant radiotherapy after EPP may still be offered as treatment option in specialized centers based on the promising survival data of single arm phase II trials [12]. Though, independent of the results of SAKK 17/04, in clinical research there is currently a shift towards novel treatment combinations that are conceived as less toxic such as induction-accelerated hemithoracic IMRT before EPP or adjuvant pleural IMRT after pleurectomy-decortication [13]. Importantly, the high relapse rate in the SAKK 17/04 trial was not caused by ineffectiveness of hemithoracic RT but rather by tumor progression outside of the PTVs. Therefore, this analysis supports the further testing of radiotherapy in combination with novel surgical and pharmaceutical approaches for treatment of MPM.

In conclusion, we show that RT as given in SAKK trial 17/04 resulted in a reasonably high local tumor control rate, however RT remained futile for the majority of patients due to progression outside of the PTVs. Therefore, postoperative RT after chemotherapy and EPP cannot be recommended for routine clinical use in all patients with MPM but may still be offered to carefully selected patients. Novel treatment combinations are currently evaluated in clinical trials and more efficacious systemic treatment options and prognostic biomarkers

are needed to be able to select patients, who might benefit from radical local treatment including RT.

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