



Preoperative or postoperative radiotherapy versus surgery alone for retroperitoneal sarcoma: a case-control, propensity score-matched analysis of a nationwide clinical oncology database

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Summary

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Background Recruitment into clinical trials for retroperitoneal sarcoma has been challenging, resulting in termination of the only randomised multicentre trial in the USA investigating perioperative radiotherapy. Nonetheless, use of radiotherapy for retroperitoneal sarcoma has increased over the past decade, substantiated primarily by its established role in extremity sarcoma. In this study, we used a nationwide clinical oncology database to separately compare overall survival for patients with retroperitoneal sarcoma who had surgery and preoperative radiotherapy or surgery and postoperative radiotherapy versus surgery alone.

Methods We did two case-control, propensity score-matched analyses of the National Cancer Data Base, which included adult patients with retroperitoneal sarcoma who were diagnosed from 2003 to 2011. Patients were included if they had localised, primary retroperitoneal sarcoma. Patients were classified into three groups based on use of radiotherapy: preoperative radiotherapy, postoperative radiotherapy, and no radiotherapy (surgery alone). Patients were excluded if they received both preoperative radiotherapy and postoperative radiotherapy, or if they received intraoperative radiotherapy. Parallel propensity score-matched datasets were created for patients who received preoperative radiotherapy versus those who received no radiotherapy and for patients who received postoperative radiotherapy versus those who received no radiotherapy. Propensity scores were calculated with logistic regression, with multiple imputation and backwards elimination, with a significance level to stay of 0·05. Matching was done with a nearest-neighbour algorithm and matched 1:2 for the preoperative radiotherapy dataset and 1:1 for the postoperative radiotherapy dataset. The primary objective of interest was overall survival for patients who received preoperative radiotherapy or postoperative radiotherapy compared with those who received no radiotherapy within the propensity score-matched datasets.

Findings 9068 patients were included in this analysis: 563 in the preoperative radiotherapy group, 2215 in the postoperative radiotherapy group, and 6290 in the no radiotherapy group. Matching resulted in two comparison groups (preoperative radiotherapy vs no radiotherapy, and postoperative radiotherapy vs no radiotherapy) with negligible differences in all demographic, clinicopathological, and treatment-level variables. In the matched case-control analysis for preoperative radiotherapy median follow-up time was 42 months (IQR 27–70) for the preoperative radiotherapy group versus 43 months (25–64) for the no radiotherapy group; median overall survival was 110 months (95% CI 75–not estimable) versus 66 months (61–76), respectively. In the matched case-control analysis for postoperative radiotherapy median follow-up time was 54 months (IQR 32–79) for patients in the postoperative radiotherapy group and 47 months (26–72) for patients in the no radiotherapy group; median overall survival was 89 months (95% CI 79–100) versus 64 months (59–69), respectively. Both preoperative radiotherapy (HR 0·70, 95% CI 0·59–0·82; $p < 0·0001$) and postoperative radiotherapy (HR 0·78, 0·71–0·85; $p < 0·0001$) were significantly associated with improved overall survival compared with surgery alone.

Interpretation To the best of our knowledge, this is the largest study to date of the effect of radiotherapy on overall survival in patients with retroperitoneal sarcoma. Radiotherapy was associated with improved overall survival compared with surgery alone when delivered as either preoperative radiotherapy or postoperative radiotherapy. Together with the results from the ongoing randomised EORTC trial (62092-22092; NCT01344018) investigating preoperative radiotherapy for retroperitoneal sarcoma pending, these data might provide additional support for the increasing use of radiotherapy for patients with retroperitoneal sarcoma undergoing surgical resection.

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Introduction

The retroperitoneum represents the primary site of origin of approximately 15% of soft tissue sarcomas.^{1,2} Similar to

other soft tissue sarcomas, surgery is the only curative treatment for retroperitoneal sarcomas, and complete resection is the dominant predictor of long-term survival.^{3,4}

Research in context

Evidence before this study

Evidence for the use of radiotherapy for retroperitoneal sarcoma has to date come mostly from small retrospective studies, the majority of which are single centre studies. There are no randomised data assessing radiotherapy for retroperitoneal sarcoma, and thus support for its use has largely been extrapolated on the basis of its established role for soft tissue extremity sarcoma. We therefore considered all MEDLINE-listed journal articles written in English from any year until October, 2015, reporting the use of either preoperative or postoperative radiotherapy alongside surgery for retroperitoneal sarcoma as evidence before commencing this study. Search terms included “retroperitoneal sarcoma”, “sarcoma” AND “retroperitoneal”, and “sarcoma” AND “retroperitoneum”. The body of retrospective data available has thus far produced conflicting results, including several studies suggesting no improvements in either local recurrence-free survival or overall survival associated with radiotherapy, other studies showing improved local control without a corresponding improvement in overall survival, and finally, four small studies showing perioperative radiotherapy to be associated with both improved local recurrence-free survival and overall survival.

Added value of this study

To the best of our knowledge, in this study, we provide the largest sample size to date, including patients that received either preoperative or postoperative radiotherapy. This sample

size allowed us to perform two propensity-matched analyses specifically assessing the use of preoperative or postoperative radiotherapy, individually, compared with surgery alone. Additionally, by use of a nationwide clinical oncology database, we were able to limit these analyses to a 9-year period (2003–11) in which key advances in the treatment of retroperitoneal sarcoma have become well established. Here, we show that radiotherapy is associated with improved survival compared with surgery alone.

Implications of all the available evidence

Data from this study show a substantial improvement in overall survival when surgical resection is combined with either preoperative or postoperative radiotherapy for retroperitoneal sarcoma compared with surgery alone. These data support both the increasing use of radiotherapy for this disease, and ongoing randomised controlled trials assessing the role of radiotherapy. These data also suggest that the EORTC trial (NCT01344018) assessing preoperative radiotherapy versus surgery alone might be underpowered to identify a difference in overall survival, an important secondary endpoint. Thus, our results might provide additional evidence that radiotherapy is associated with improved overall survival. If the EORTC study shows an improvement in local recurrence-free survival with the use of preoperative radiotherapy, this would further support the increasing use of radiotherapy for patients with retroperitoneal sarcoma.

However, the anatomic constraints of the retroperitoneum often make complete resection difficult, and incomplete (R1 or R2) resection has been reported in up to half of patients who undergo surgery with curative intent.^{3–8} Moreover, even in completely resected retroperitoneal sarcomas, locoregional recurrence is common, occurring in up to 50% of cases.^{9,10} Thus, unlike other soft tissue sarcomas, mortality in those with retroperitoneal sarcomas frequently occurs after locoregional failure rather than distant metastasis.^{1,3,9–12}

Perioperative radiotherapy is the most widely used multimodality strategy directed at decreasing locoregional recurrence in retroperitoneal sarcoma. At present, however, data supporting the use of radiotherapy are limited, and the increasing use of radiotherapy for retroperitoneal sarcoma has largely been extrapolated based on its established role for soft tissue extremity sarcoma.^{13–15} Retrospective studies have reported inconsistent and equivocal results.^{9,16–28} In the USA, the only randomised controlled trial addressing the use of perioperative radiotherapy for retroperitoneal sarcoma did not accrue enough patients for completion (ACOSOG Z90312, NCT00091351). In Europe, an ongoing multicentre randomised controlled trial is assessing preoperative radiotherapy versus resection alone for primary retroperitoneal sarcoma (EORTC

62092-22092; NCT01344018); however, even if accrual is successful, results are not expected until 2020.

The Trans-Atlantic Retroperitoneal Sarcoma Working Group represents major European and North American sarcoma referral centres, and aims to develop consensus treatment standards on the basis of the strength of available evidence.²⁹ With a paucity of supporting data, the 2015 Consensus Approach established that postoperative radiotherapy is “of no study-proven value” and that preoperative radiotherapy should only “be considered after careful review by a multidisciplinary sarcoma tumor board”.²⁹ Despite these recommendations, data from the USA show an increase in the use of perioperative radiotherapy for retroperitoneal sarcoma.⁶ In the absence of randomised data supporting—and with controversy surrounding—the use of perioperative radiotherapy for retroperitoneal sarcomas, the main purpose of this study was to use a nationwide oncology registry to assess the association between preoperative or postoperative radiotherapy and overall survival for patients with retroperitoneal sarcoma.

Methods

Study design and participants

We did a case-control, propensity score-matched analysis of the National Cancer Data Base (NCDB).

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