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CLINICAL INVESTIGATION

ROLE OF RADIOTHERAPY IN THE MANAGEMENT OF DESMOID TUMORS

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Purpose: To identify high-risk patients with desmoid tumors who could benefit from postoperative radiotherapy (RT) and to determine the efficacy of postoperative and definitive RT.

Materials and Methods: Retrospective analysis of clinical data for all patients with desmoid tumors who underwent definitive local therapy at the University of Michigan from 1984 through 2008. Estimates for local control were calculated using the product–limit method of Kaplan and Meier, and associations with patient, tumor, and RT characteristics were explored using Cox proportional hazard regression.

Results: Treatment for 95 patients who qualified for the study included surgery, RT, or both in 54, 13, and 28 cases, respectively. With a median follow-up of 38 months, the actuarial 3-year local control (95% confidence interval [CI]) was not significantly different ($p = 0.3$) among the three treatment groups: 84.6% (70.2–92.4), 92.3% (56.6–98.9), and 69.0% (43.1–84.9), respectively. Tumor site in the head/neck ($p = 0.03$) and history of previous surgical therapy ($p = 0.01$) were associated with increased recurrence risk (HR = 2.8, 95% CI 1.1–7.4, and HR = 3.2, 95% CI = 1.3–7.8), whereas gender, age, use of RT, and positive margins were not ($p > 0.2$).

Conclusions: Our findings suggest equivalent local control rates after surgery, RT, or a combination of both. Although history of previous surgical therapy or site of origin in the head/neck region were found to be associated with increased risk of recurrence after local therapy, there was no clear association between surgical margin status and local control. © 2010 Elsevier Inc.

Desmoid tumors, radiotherapy, surgery, local control, surgical margins.

INTRODUCTION

Desmoid tumors are rare, slow-growing mesenchymal tumors with a high predilection for local recurrence. The management of desmoid tumors is controversial. Although surgery remains the mainstay of therapy, options include observation, radiotherapy (RT), chemotherapy, hormonal and anti-inflammatory therapy, or a combination thereof. Because of their rarity, high-level evidence (such as from prospective randomized trials) of efficacy does not exist, and treatment recommendations are based on retrospective reviews and expert opinions; consequently, controversy is common. Decision making is further complicated by the seemingly variable natural history of this disease.

In patients treated with resection alone, local relapse is common. In a review of 22 series including 780 patients, Nuyttens *et al.* (1) reported a relapse rate of 39%. Since relapse and the consequent salvage therapy is associated with reduction or loss of function, identification of predisposing

factors has been a major thrust of clinical research. Many such factors have been suggested, including tumor size, site, number of prior treatments, age, association with familial adenomatous polyposis (FAP), and margins of resection (2). On this topic, also, there is little agreement between various publications.

One of the key questions that remain unsettled is the prognostic significance of microscopic positive margins and the need for RT in this setting. Whereas Nuyttens *et al.* (1), Spear *et al.* (3), Ballo *et al.* (4), and Stoeckle *et al.* (5) reported a significant increase in the risk of local relapse associated with positive resection margins, Gronchi *et al.* (6), Merchant *et al.* (7), and Lev *et al.* (8) demonstrated no such effect.

RT alone has been used in patients with unresectable tumors or in patients in whom resection would result in high morbidity and major loss of function. In general, most reviews suggest a high rate of local control, equivalent or at times superior to that achieved with surgery (2). This high rate of control is achieved despite a frequent selection bias

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in favor of surgery, as RT is typically used for large aggressive tumors, often after failure of other therapies.

To identify risk factors for relapse after resection, and to determine the usefulness of RT as an adjunct to surgery and as the sole treatment for unresectable tumors, we have undertaken a retrospective review of our institutional experience.

METHODS AND MATERIALS

Patient population

With the approval of the Institutional Review Board, we retrospectively examined the medical records of all patients treated at the University of Michigan for desmoid tumors between 1984 and 2008. All patients were evaluated by the University of Michigan Cancer Center multidisciplinary connective tissue oncology group, who also rendered treatment recommendations. Of 104 patients identified, 95 received curative-intent local therapy with surgery, RT, or both and were the focus of this analysis. The remaining 9 patients received primary medical therapy. Patients with FAP were not included in the study. We collected data regarding the following: patient age and sex; tumor site, size, and presentation (*i.e.*, primary vs. recurrence); treatment detail including surgical resection margins, RT technique, dose and schedule, types and duration of medical therapy; and outcome (local and distant failure and death). Table 1 summarizes the main patient and tumor characteristics by treatment group.

Treatment

Surgical resection was performed with the intent of achieving wide margins (several centimeters), when possible. If it was judged that such resection would result in significant loss of function, a marginal resection was performed. Adjuvant RT was offered only to patients who were thought to be at high risk for local relapse, mostly because of positive margins. Patients with unresectable tumors and those in whom surgery was judged to result in significant loss of function were treated with definitive RT.

Full RT detail was available for 29 of 41 patients. Nine patients received RT in other hospitals affiliated with the University of Michigan, and RT records for another 3 patients were not available. Megavoltage radiation of 6 to 15 MV was delivered in all cases. On rare instances, this was combined with 9- to 12-MeV electron radiation. The surgical bed (or primary tumor in unresectable cases) was treated with wide margins, and a boost has been used in 46% of the cases. Special immobilization devices were used in 79% of patients, including a mask for tumors in the head and neck region and a cradle for extremity tumors. The majority of patients were treated in the supine position, but patients with pelvic tumors or tumors in the back were treated in the prone position. CT scan for treatment planning was performed in 83% of cases, and in two-thirds of cases it was used for three-dimensional planning. Median radiation dose was 55.8 Gy (range 50–68.4) delivered in 1.8- to 2-Gy fractions.

Statistical methods

Freedom from local recurrence was the primary endpoint of this study and was estimated using the product-limit method of Kaplan and Meier. Time to local recurrence was calculated from the date of treatment until documented local recurrence (event), or last clinical visit (censor). The association between the primary endpoint and patient, tumor, and treatment characteristics (including RT)

were explored using Cox proportional hazard regression. Wald-type *p* values were calculated per characteristics, with values less than 5% considered meaningful evidence for significant association.

RESULTS

Table 1 provides a summary of patient and tumor characteristics by treatment group. The median age of the patients was 38 years (range, 8–87 years). Of the 95 patients who received curative-intent therapy, 54 had surgery alone, 28 had surgery and RT, and 13 had RT alone. As reflected in Table 1, RT was used mostly as adjuvant therapy for patients with positive surgical resection margins or other factors judged to indicate high risk for relapse, or alone in patients with unresectable tumors.

With a median follow-up time of 38 months (range, 1 month to 23 years), the crude rate of recurrence for surgery alone, RT alone, and surgery plus RT was 8 of 54 (14.8%), 2 of 13 (15.4%), and 9 of 28 (32.1%), respectively. The actuarial 3-year freedom from recurrence (95% CI) was 84.6% (70.2–92.4), 92.3% (56.6–98.9), and 69.0% (43.1–84.9), respectively. These differences were not statistically significant (*p* = 0.300). Figure 1 depicts freedom from recurrence by treatment group. For those with local recurrence, the median time to recurrence was 21.9 months (range 7 months to 12 years), with only two recurrences diagnosed more than 5 years after therapy.

Time to recurrence was significantly associated with body site and prior surgical treatment (Table 2). Seven of 19 (36.8%) head-and-neck cancer patients experienced recurrence during follow-up. The recurrence rate was much lower for patients with tumors in the trunk, extremities, and pelvis/mesentery/retroperitoneum: 9 of 54 (16.8%), 2 of 12 (16.8%), and 1 of 10 (10.0%), respectively (HR = 2.8, 95%

Table 1. Patient and tumor characteristics by treatment

Characteristic	Treatment: <i>n</i> (%)		
	Surgery alone	Radiotherapy alone	Surgery and radiotherapy
Frequency	54	13	28
Male sex	22 (40.7)	5 (38.5)	9 (32.1)
Age >38 years	29 (53.7)	5 (38.5)	16 (57.1)
Body site			
Trunk	34 (63.0)	3 (23.1)	17 (60.7)
Extremities	2 (3.7)	5 (38.5)	5 (17.9)
Head and neck	11 (20.4)	3 (23.1)	5 (17.9)
Pelvis/mesenteric/retroperitoneal	7 (13.0)	2 (15.4)	1 (3.6)
Prior surgery	4 (7.4)	5 (38.5)	14 (50.0)
Tumor size (median)	5.5	10.0	7.7
Surgical margin status			
Positive	24 (44.4)		26 (92.9)
Negative	22 (40.7)		2 (7.1)
Indeterminate/unknown	8 (14.8)		0

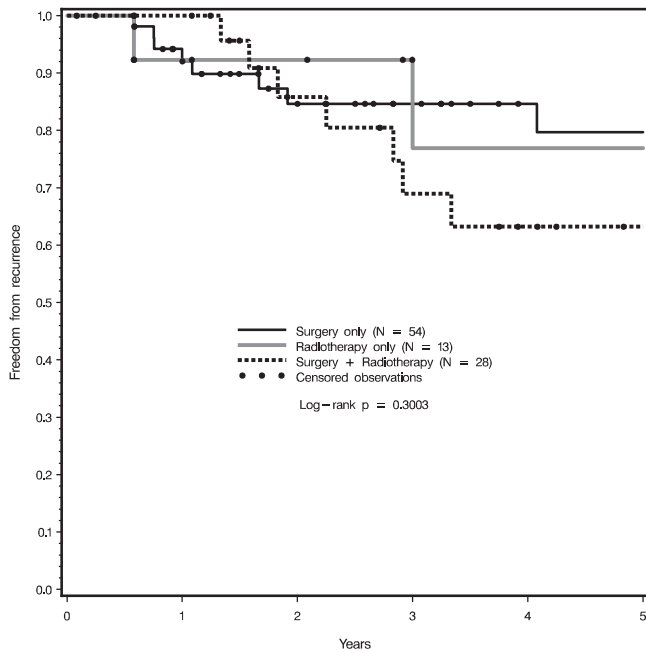


Fig. 1. Freedom from recurrence estimates for surgical, radiotherapy, and combination patients ($N = 95$).

CI = 1.1–7.4, $p = 0.03$). Nine of 23 (39.1%) patients with a prior definitive surgery experienced recurrence, whereas only 10 of 72 (13.9%) patients without such a preceding therapeutic attempt recurred (HR = 3.2, 95% CI = 1.3–7.8, $p = 0.01$). Figures 2 and 3 present estimates for freedom from recurrence for patients with desmoid tumor originating in the head-and-neck region vs. other body sites and for patients with prior surgery vs. others, respectively.

Margin status was not significantly associated with time to recurrence in this population. However, when considering only surgical cases for which surgical margin status was known ($N = 74$), the point estimate for the hazard ratio was 2.67, with 95% confidence interval 0.60 to 11.85, sug-

Table 2. Univariate associations between patient and tumor characteristics and time to recurrence.

Characteristic	p Value
All cases ($N = 95$)	
Radiotherapy (yes vs. no)	0.2252
Sex	0.7534
Age (continuous)	0.5399
Age >38 years (median)	0.3003
Body site	0.0357
(head and neck vs. all others)	
Earlier definitive	0.0123
surgical treatment (yes vs. no)	
Surgical cases only ($n = 82$)	
Surgical margin	0.2329
status (+ vs. -, indeterminate)	
Surgical cases with defined margins ($N = 74$)	
Tumor size (median)	0.5897
Surgical margin	0.1969
status (+ vs. -)	

gesting that the effect of surgical margins was large but not large enough to be discerned with high power, given the sample size. We hypothesized that the effect of surgical margins might have been blunted by the administration of RT in patients with positive margins. Therefore we performed univariate analysis to assess the effect of post operative RT on local control separately in patients with positive margins (50 patients, of whom 26 received RT), which did not reveal an association between RT delivery and local control ($p = 0.989$). Multivariate modeling to simultaneously account for surgical margin status and RT use was not attempted because only 2 patients with surgery and RT had negative margins. Therefore the effect of RT is almost entirely confounded by the presence of positive surgical margins.

Next we have examined the relationship between radiation dose and risk of local relapse. Patients who had RT only received a mean dose of 50 Gy. Within this group, there have been only two failures (at doses of 50 Gy and 54 Gy). For patients treated with surgery and RT, the mean RT dose in those experiencing recurrence locally was 56.1 Gy (minimum = 50.0, maximum = 59.4), and patients not experiencing recurrence locally had a mean RT dose of 53.4 Gy (minimum = 48.6, maximum = 68.4). The data do not suggest a meaningful relationship between dose and local recurrence. A t test for the comparison of the means yielded a p value of 0.2062.

RT had to be discontinued because of acute toxicity in only a single case, in which RT was delivered to the foot. Long-term toxicity was mostly observed in patients who underwent both surgery and RT at various stages of their disease. This included Horner's syndrome, dysphagia and frozen shoulder (1 patient), osteonecrosis (1 patient), large muscular defect (1 patient), nonhealing tissue defect requiring surgical interventions (2 patients), limb contracture (2 patients), lower limb weakness and edema (1 patient), chronic pain (4 patients), limitation of motion (3 patients), and pain combined with limitation of motion (2 patients). There were two patients with equines deformity requiring surgery after RT alone, and 1 patient with chronic pain after surgery alone and one amputation. There was one death from secondary malignancy (gastric cancer) in a patient who received RT to the retroperitoneum. This patient also experienced chronic malabsorption, but had a history of systemic lupus erythematosus as a risk factor.

Patients who had disease recurrence after local therapy were able to undergo salvage therapy in the majority of cases; of 7 patients who had relapsed after surgical therapy, 3 patients underwent reoperation, 1 patient received medical therapy, and another 3 were lost to follow-up. Two patients who had relapse after RT subsequently received medical therapy. Of 8 patients who had relapsed after surgery and RT, 2 underwent reoperation, 3 received medical therapy, 1 was lost to follow-up, and 2 received no further treatment. At the time of their last follow-up, 87 patients were alive and free of disease, 1 patient had died of secondary malignancy, and six patients continued to have active disease.

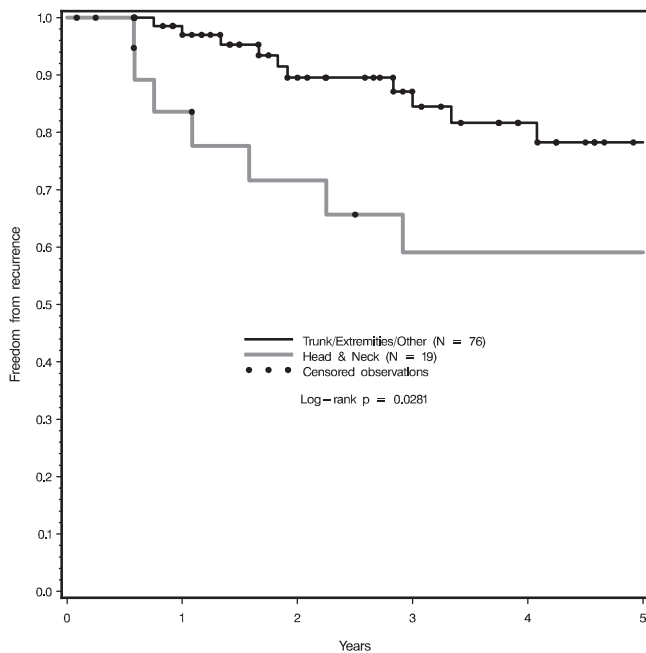


Fig. 2. Freedom from recurrence estimates by body site location ($N = 95$).

To define the pattern of relapse after RT, we examined the location of the relapse in relation to the treatment fields. Of 10 patients who had recurrence of disease after RT, 8 were treated at the University of Michigan and a complete radiation record was available. In-field recurrence was documented in 5 cases and marginal recurrence in 3 cases.

DISCUSSION

The main finding of this study is that surgery, RT, or a combination of surgery and RT result in similar rates of

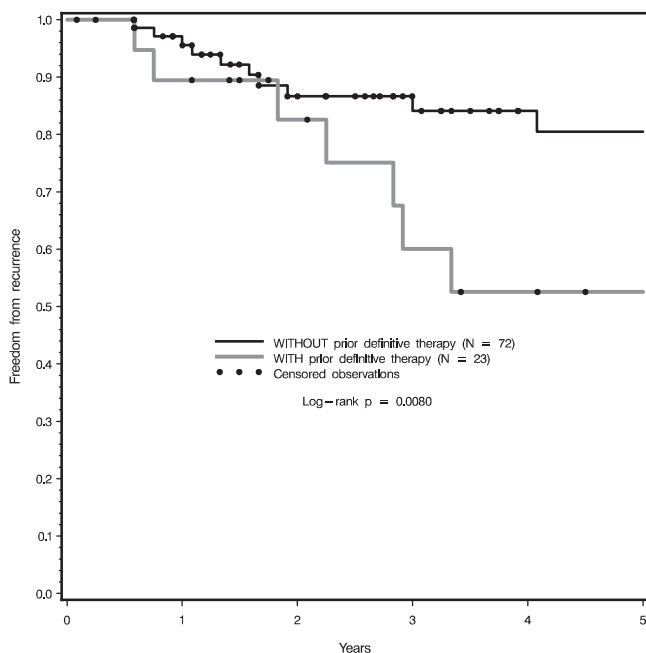


Fig. 3. Freedom from recurrence estimates by occurrence of prior definitive treatment ($N = 95$).

local control 3 years after therapy. Because combining surgery and RT often increases the risk of serious long-term toxicity, single-modality therapy would be preferred when feasible. In our experience, reported herein, patients with history of previous surgeries or those with primary tumor in the head and neck are more likely to have disease recurrence after local therapy, whereas resection margins are not clearly associated with recurrence after surgery. Thus we have identified subsets of patients who should be considered strongly for adjuvant RT. Others can be safely monitored. Salvage therapy for recurrent disease is often successful, and ultimate local control was achieved in the vast majority of patients.

Surgery is still the treatment of choice for the majority of patients who present with desmoid tumors; however, across all published series, at least 20% of the patients will experience disease recurrence. There is no unanimous agreement today regarding the factors associated with an increased risk of local relapse. Considering that, in most neoplasms, the adequacy of the surgical resection margins is one of the best predictors of recurrence, it is intriguing that the results for desmoid tumors are so inconsistent: Nuyttens *et al.* (1) published a comparative review of 22 articles published before 1999 that included 780 patients. They found local control rates of 72% vs. 41% after surgery alone and 94% vs. 75% after surgery and RT, for patients with negative or positive margins, respectively. The validity of these results is limited by the age of, and the small numbers of, patients in the individual series. However similar results were also reported in 1997 by Goy *et al.* (9) and updated, more recently by Singh *et al.* (10) who found increased recurrence rate in the presence of positive margins (31% vs. 11%, $p = 0.004$, respectively) for 137 patients who underwent surgery (+ adjuvant RT in 21 cases) at the University of California–Los Angeles. Stoeckle *et al.* (5) found local recurrence in only 2 of 22 patients with negative margins and in 19 of 56 patients with positive margins. Outcomes of patients treated at MD Anderson Cancer Center before 1994 were reported by Ballo *et al.* (4), who found, in 118 patients after surgery, increased recurrence rate in the presence of positive margins (10-year recurrence rate of 54% vs. 27%, $p = 0.003$, for positive vs. negative margins, respectively); however, in a more contemporary publication by Lev *et al.* (8) summarizing the outcomes of 189 patients treated between 1995 and 2005 (93 of whom were treated with surgery alone), margin status did not emerge as a significant risk factor for recurrence. Similarly, Merchant *et al.* (7) published in 1999 the results of therapy in 103 patients, with primary desmoid tumors, who underwent gross total resection at Memorial Sloan-Kettering Cancer Center (31 also received RT) and found in 45 patients with positive margins, a recurrence rate (22% vs. 24%) similar to that in patients with negative margins. Gronchi *et al.* (6) summarized the results of surgery in 203 patients (40 received adjuvant RT) and found that margin status had no effect on local control in 128 patients with primary disease and only borderline effect in 75 patients with recurrent disease. Lack of correlation between

margin status and recurrence risk was reported by Phillips *et al.* (11) in 109 patients treated at Royal Marsden, as well. In our study, there was a suggestion of a negative impact of positive margins on local control (HR = 2.67); however this could not be confirmed, probably because of the small patient numbers.

We found that presentation with recurrent disease after previous surgery was significantly associated with increased risk of local recurrence. The data published so far regarding this issue are equivocal as well; several series found that presentation is a significant risk factor for recurrence (3, 5, 6, 10, 12), whereas others have not (13–16). Moreover Nuyttens *et al.* (1) and Goy *et al.* (9) suggested interaction between presentation and surgical margins in patients treated with surgery alone, implicating a particularly poor prognosis if both risk factors are present.

There is controversy regarding the importance of other risk factors, such as age, tumor site, and tumor size. As recently reviewed by Melis *et al.* (2), several studies suggested that origin in the extremities is associated with increased risk of recurrence. In our study, tumor site in the head and neck was found to predict higher risk for recurrence. It is possible that inferior outcome for tumors in these sites is related to proximity to critical structures, which does not allow adequate resection with negative surgical margins; however it is also possible that there are biological differences among desmoid tumors in various locations, as suggested by Stoockle *et al.* (5).

The role of RT in the treatment of desmoid tumors is controversial, as well. Some series report clear benefit from the addition of RT to surgery (1, 3, 17); others suggest that RT abrogates the negative effect of positive margins (4, 9, 10), whereas some authors report no improvement at all in disease control after RT (5, 7, 13, 18). Our results suggest that subsets of patients can be identified who are at high risk for local failure. These include patients with site of origin in the head and neck, recurrent disease after previous surgery, and possibly those with positive resection margins. Such patients stand to benefit most from adjuvant RT. Careful analysis of the pattern of failure in our series suggests that most failures are within-field. This is in agreement with most previously published series reporting that in-field recurrences are at least as common as marginal recurrences (16, 19) or even represent the dominant pattern of failure after RT (1, 4, 9, 15, 20). Noted exceptions are series by Leibel *et al.* (21) and Zlotecki *et al.* (12), who found a very low rate of in-field recurrences. In our own series, we did not find evidence for a meaningful relationship between dose and local recurrence. In patients treated with RT only to a mean dose of 50 Gy, we have observed only two local failures (15%). Based on this finding and the published literature, we believe that a dose of 50 to 54 Gy is adequate in this setting. In patients treated with surgery and RT, there was a higher local failure rate despite the use of higher doses (mean dose of 56.1 Gy in those who experienced failure vs. 53.4 Gy in those who did not). A reasonable interpretation

of these data is that patients who were thought to be at high risk for local relapse were treated to higher doses. This observation suggests that increasing the radiation dose, in this setting, to more than 56 Gy in selected patients who are at high risk for local failure, might improve outcomes. Clearly, the utmost attention should be paid to the conformality of dose if such escalation is contemplated, so as to reduce the risk of long-term complications.

All series that compared RT alone to postoperative RT found at least equivalent results (1, 4, 8), or even an advantage to the administration of RT as single therapy (3, 12, 15), suggesting that if surgery is likely to be incomplete and to require adjuvant RT, it might as well be omitted from the treatment scheme to avoid unnecessary side effects. In our series, RT was delivered either postoperatively to patients with positive margins or as a single therapy to unresectable tumors; the RT yielded equivalent local control rates in both groups, supporting the notion that there is no advantage from the addition of surgery to RT in such cases.

The strength of our study is in the rather consistent approach to the management of desmoid tumors at our institution during the study period. As stated before, surgical resection was the preferred treatment when it was judged that such resection would not result in significant loss of function. Adjuvant RT was offered only to patients thought to be at high risk for local relapse, mostly because of positive margins (only 2 of 28 patients who received adjuvant RT had negative resection margins). Patients with unresectable tumors and those in whom surgery was judged to result in significant loss of function were treated with definitive RT. For each patient, the treatment strategy was discussed and formulated by a multidisciplinary musculoskeletal tumor board. Our study is subject to limitations common to most publications regarding this rare disease. These include the small number of patients and the retrospective nature of the study. Although the length of follow-up in our patients is adequate, as previous publications suggest that most recurrences after surgery and/or RT occur within 3 years, longer follow-up is needed to assess the outcome after salvage therapy.

CONCLUSIONS

In summary, our findings support surgery as the treatment of choice for desmoid tumors that are likely to be removed with negative surgical margins and no functional impairment. Adjuvant RT should be considered for patients at high risk for local failure, such as those with site of origin in the head and neck, those with recurrent disease after previous surgery, and possibly those with positive resection margins. Patients with unresectable disease can be managed well with RT alone. Although the use of RT is likely to improve local control, it is also more likely to result in long-term complications; therefore individual decision making and special attention to organs at risk is warranted.

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