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CLINICAL INVESTIGATION **Metastasis**

CLINICAL OUTCOME OF HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY FOR ABDOMINAL LYMPH NODE METASTASES

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Purpose: We report the medium-term clinical outcome of hypofractionated stereotactic body radiotherapy (SBRT) in a series of patients with either a solitary metastasis or oligometastases from different tumors to abdominal lymph nodes.

Methods and Materials: Between January 2006 and June 2009, 19 patients with unresectable nodal metastases in the abdominal retroperitoneal region were treated with SBRT. Of the patients, 11 had a solitary nodal metastasis and 8 had a dominant nodal lesion as part of oligometastatic disease, defined as up to five metastases. The dose prescription was 45 Gy to the clinical target volume in six fractions. The prescription had to be downscaled by 10% to 20% in 6 of 19 cases to keep within dose/volume constraints. The first 11 patients were treated with three-dimensional conformal techniques and the last 8 by volumetric intensity-modulated arc therapy. Median follow-up was 1 year.

Results: Of 19 patients, 2 had a local progression at the site of SBRT; both also showed concomitant tumor growth at distant sites. The actuarial rate of freedom from local progression was 77.8% ± 13.9% at both 12 and 24 months. Eleven patients showed progressive local and/or distant disease at follow-up. The 12- and 24-month progression-free survival rates were 29.5% ± 13.4% and 19.7% ± 12.0%, respectively. The number of metastases (solitary vs. nonsolitary oligometastases) emerged as the only significant variable affecting progression-free survival ($p < 0.0004$). Both acute and chronic toxicities were minimal.

Conclusions: Stereotactic body radiotherapy for metastases to abdominal lymph nodes was shown to be feasible with good clinical results in terms of medium-term local control and toxicity rates. Even if most patients eventually show progressive disease at other sites, local control achieved by SBRT may be potentially significant for preserving quality of life and delaying further chemotherapy. © 2011 Elsevier Inc.

SBRT, Lymph node metastases, IMRT, Volumetric modulated arc therapy, RapidArc.

INTRODUCTION

Stereotactic body radiotherapy (SBRT) has proved its efficacy in several patient populations with primary and metastatic limited tumors (1). In particular, SBRT may be appropriate for selected patients with oligometastatic disease, defined as fewer than five lesions (2). Abdominal SBRT has been reported with reference mainly to primary and secondary liver tumors, as well as pancreatic and renal tumors (1). Stereotactic body radiotherapy for metastases to abdominal lymph nodes has rarely been reported, with only three articles reporting on it as a specific topic (3–5) and with it most often comprising a few cases in mixed series (6–10). In one article reporting the outcome of SBRT for isolated lymph node recurrence from prostate cancer, the target lesion was within the pelvis in most cases, which poses different technical problems (11).

The rationale for administering SBRT with a curative intent to patients with limited nodal metastatic disease may be the same as that in selected patients with liver or lung metastases. Whereas most patients with metastases to abdominal nodes are unfit for surgery, it is known that in the setting of limited metastatic burden, SBRT leads to local control rates higher than 70% to 80% (1, 10), which may turn into increased survival and better quality of life. Conversely,

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conventionally fractionated non-stereotactic radiotherapy is generally believed to attain poorer results, because doses are limited by normal tissue tolerance. Actually, few published data do exist on local control rates of conventional radiotherapy in this context. Although several articles dealt with conventional radiotherapy of isolated para-aortic lymph node recurrence from cervix cancer, most of them reported only survival rates (12–15). A 33% to 50% rate of progressive disease in the para-aortic lymph node–treated area was reported in two studies (16, 17).

Between January 2006 and June 2009, 19 patients with unresectable nodal metastases in the abdominal region were treated with SBRT. We have previously reported early results in a series of 15 patients with abdominal nodal metastases, including 12 treated by SBRT alone with three-dimensional conformal radiotherapy (CRT) techniques (18). In that series no major toxicity was observed, and 6-month local control was achieved in 10 of 12 cases. Because in 6 of 12 cases our standard dose of 45 Gy in 6 fractions had to be downscaled by 10% to 20% to keep within dose/volume constraints for organs at risk (OARs), we also investigated the potential role of volumetric intensity-modulated arc therapy given by RapidArc (Varian Medical Systems, Palo Alto, CA) in this patient population (19). RapidArc has been investigated previously for some other clinical cases (20–25), showing significant improvements over other advanced techniques. Because we also found advantages in dose distribution in this setting, since November 2008, SBRT to abdominal nodes has been delivered by volumetric intensity-modulated radiotherapy.

This retrospective study is an update of our previous report. Our aim was to evaluate the clinical effectiveness of SBRT for patients with solitary or nonsolitary oligometastases to abdominal lymph nodes. Medium-term (12–24 months) local control and acute and late toxicity were considered as the main endpoints.

METHODS AND MATERIALS

Patient selection

From October 2005 to June 2009 at Istituto Clinico Humanitas, Rozzano, Italy, 80 patients were treated by linear accelerator–based hypofractionated SBRT to abdominal targets, including liver, pancreatic, and lymph nodal lesions. Since January 2006, 29 consecutive patients with unresectable nodal metastases in the abdominal region were treated. Six patients treated with a single-dose SBRT boost after external beam fractionated radiation over an extended volume are not the subject of this report. In addition, among the 23 patients treated by SBRT alone, we excluded 4 cases because the nodal site was at the hepatic hilum, which entails special issues in terms of organ motion. Thus, on the whole, this report regards 19 patients.

Disease extension was evaluated in all the cases by computed tomography (CT) with or without magnetic resonance imaging. The presence of metabolic active tumor in the nodal site was confirmed by fluorodeoxyglucose positron emission tomography (PET) performed in 17 of 19 patients. In all patients the target metastasis was in the abdominal retroperitoneal region, with either a solitary lesion (11 patients) or a dominant nodal lesion as part of oligometastatic disease (nonsolitary oligometastases) (8 patients). Among the latter 8 cases, nontarget metastases were either PET negative after previous chemotherapy (3 patients: 1 with a single lung metastasis, 1 with a single liver metastasis, and 1 with multiple abdominal lymph nodes) or after SBRT at other sites (3 patients: 1 with a single lung metastasis, 1 with a single liver metastasis, and 1 with a single adrenal metastasis) or PET positive and thereafter treated by chemotherapy (2 patients: 1 with a single liver metastasis and 1 with multiple mediastinal lymph nodes).

The anatomic site was defined according to the most involved nodal station: left para-aortic in 5 patients; right para-aortic in 7; posterior to inferior vena cava in 2; posterior to head of pancreas, or celiac, or near the origin of the superior mesenteric artery in 5. In 8 patients the clinical target volume (CTV) was in close proximity to some part of the duodenum, with a minimal distance of 8 mm or less. Computed tomography images of four representative cases are shown in Fig. 1.

All the patients had been considered unfit for surgery at the time of radiation. In 3 patients the lesion was a nodal recurrence after nonradical surgery at the same site. Chemotherapy was stopped at least 3 weeks before SBRT and withheld until disease progression. Other relevant patient, tumor, and treatment characteristics, stratified by radiation technique, are reported in Table 1.

CT simulation

During CT simulation, the patients were positioned supine, with their arms above the head, and were immobilized by means of a vacuum bag combined with a thermoplastic body mask including a Styrofoam block for abdominal compression to minimize organ motion. Contrast-enhanced planning CT scans were acquired in free quiet breathing mode with a 3-mm slice thickness with a stereotactic body frame composed of a bridge-like removable cover coupled to a carbon fiber basement (Stereotactic Body Frame; Elekta [Milan, Italy]). Oral contrast was given 30 to 60 minutes before CT scan to visualize the duodenum and small bowel.

Contouring and dose prescription

The gross tumor volume included macroscopic nodal disease apparent on CT as well as on PET if available. The CTV was kept equivalent to the gross tumor volume. The planning target volume (PTV) was defined by taking into account both the internal margin and the setup margin (26). The internal margin depends on intrafraction organ motion and interfraction organ motion, which are not expected to be substantial in a short course of radiation for retroperitoneal nodes adjacent to the spine and large vessels. Scarce data are available regarding organ motion of retroperitoneal nodes: in a similar setting regarding the celiac axis, Wysocka *et al*. (27) calculated a median intrafraction craniocaudal displacement of 3.8 mm and lower displacements in the other axes. The setup margin was estimated to be lowered close to 0, given the cone-beam computed tomography (CBCT) systematic verification of setup variations. This led us to cut down the CTV–PTV margin to 6 mm in the cranial–caudal axis and 3 mm in the anterior–posterior and lateral axes, allowing mainly for residual intrafraction organ motion, as well as for inaccuracies in CBCT image interpretation.

The main OARs considered were the spinal cord, kidneys, stomach, duodenum, small bowel, and liver. The stomach, duodenum, and small bowel were contoured when appropriate. Organ motion was taken into account for the small bowel by contouring the intestinal cavity (the volume containing bowel loops as defined in a specific comparison) (28), a method that seems both practical and robust (28, 29). For the duodenum, on the contrary, we decided to avoid either

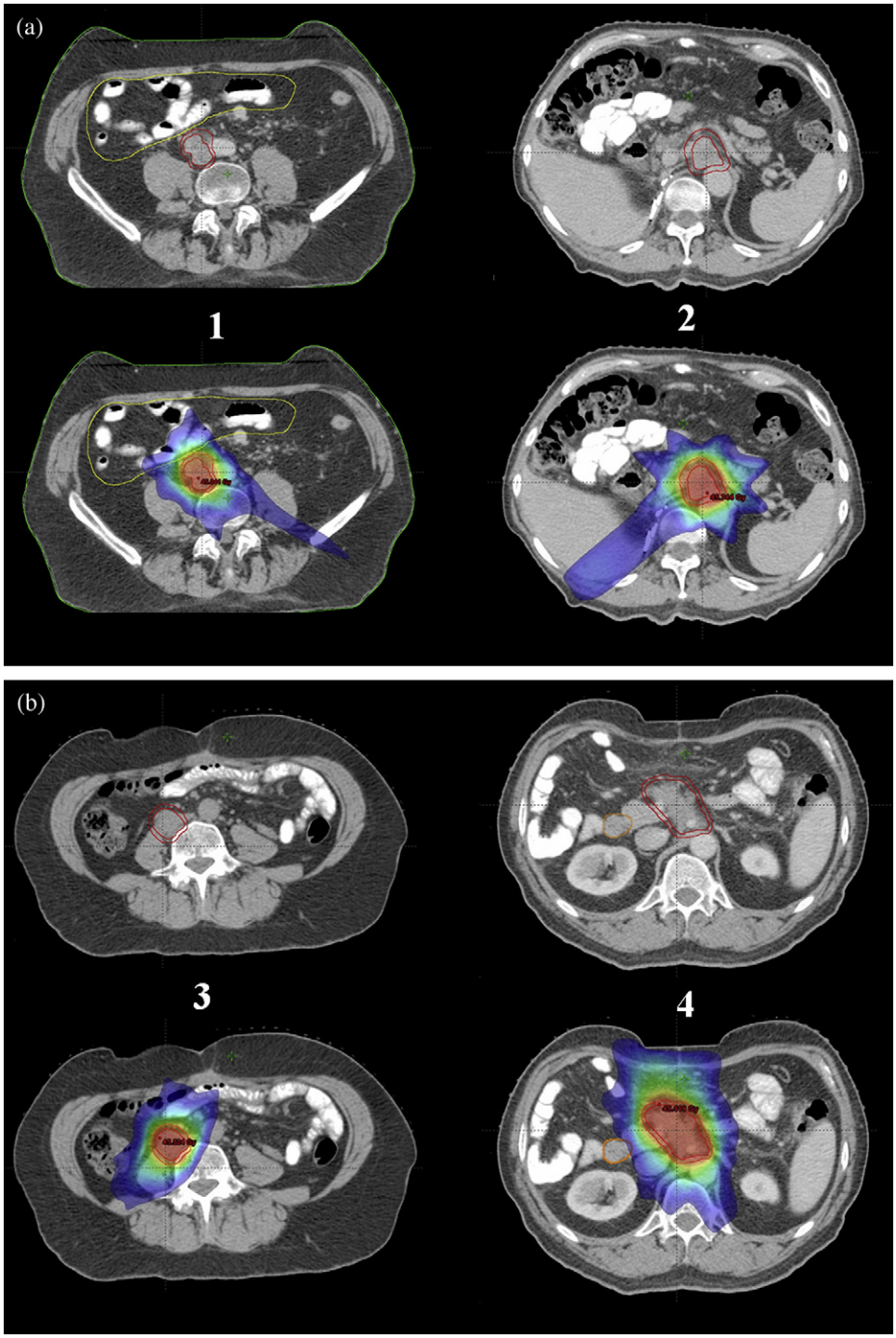

Fig. 1. Computed tomography images of four representative cases and their dose distribution displayed in color wash between 15 Gy and 46 Gy (CTV volume: 24.5 cm^3 in Case 1, 20.5 cm^3 in Case 2, 14.8 cm^3 in Case 3, and 49.6 cm^3 in Case 4; planning technique: three-dimensional conformal in Cases 1 and 2 and RapidArc in Cases 3 and 4).

a ''cavity method'' or a fixed margin, because of its particular anatomy and a different magnitude of motion among its segments.

The dose prescription to the CTV was set to 45 Gy in 6 daily fractions of 7.5 Gy. In CRT plans the dose was prescribed to the isocenter, whereas in RapidArc plans the same dose was prescribed as the mean dose to the CTV. In both CRT and RapidArc plans, the encompassing peripheral dose had to be 42.75 Gy (95% of the prescribed dose) for the CTV and 36 Gy (80% of the prescribed dose) for the PTV. However, the 45-Gy standard dose had to be downscaled by 10% to 20% in 6 of 11 CRT cases to keep within constraints of gastrointestinal serial-like OARs and thus avoid unacceptable risk of radiation damage. Dose prescriptions according to planning technique are reported in Table 2. No dose reduction was required in RapidArc plans.

Table 1. Patient characteristics

Variable group	Characteristics	Whole group	CRT patients	RA patients
Patient	Gender (No. of patients)			
	Male	10	6	4
	Female	9	5	4
	Age (y)			
	Median	62	61	64
	Range	38–78	38–78	54–77
	ECOG Performance Status			
	0	15	9	6
	1	4	2	2
Tumor	Primary tumor (No. of patients)			
	Colon–rectum	5	3	2
	Esophagus	1	0	1
	Stomach	1	1	0
	Biliary tract	2	1	1
	Pancreas	1	0	1
	Breast	1	1	0
	Kidney (clear cell)	2	1	1
	Renal pelvis (transitional cell)	2	1	1
	Lung	1	1	0
	Ovary	3	2	1
	No. of metastases			
	Solitary	11	6	5
	Oligometastases	8	5	3
	Maximal axial tumor diameter (mm)			
	Median	30	30	30
	Range	20–55	20–47	20–55
	CTV volume (mm^3)			
	Median	14.8	20.5	14.3
	Range	3.8–98.3	3.8–37.3	5.9–98.3
	Median solitary	13.8		
	Median oligometastases	21.8		
	PTV volume (mm^3)			
	Median	31.8	39.6	31.5
	Range	9.9–146.4	9.9–69.0	16.4–146.4
	Previous chemotherapy (No. of patients)			
	Yes	11	7	4
	No	8	4	4
	Previous surgery at target site (No. of patients)			
	Yes	3	1	2
	No	16	10	6
	Total (No. of patients)	19	11	8

Abbreviations: CRT = three-dimensional conformal radiotherapy; RA = rapidarc; ECOG = eastern cooperative oncology group; CTV = clinical target volume; PTV = planning target volume.

Treatment planning

All plans were designed and optimized for a Varian Clinac 2100CD system equipped with a Millennium multileaf collimator (Varian Medical Systems) with a leaf width of 5 mm at the isocenter. Conformal radiotherapy plans were designed by use of either four to eight fixed gantry beams or three to five dynamic conformal short arcs, with a single isocenter. In RapidArc plans a single volumetric modulated arc or two arcs were optimized according to the RapidArc technique, which uses continuous variation of the instantaneous dose rate, multileaf collimator leaf positions, and gantry rotational speed to optimize the dose distribution (19).

For OARs, both RapidArc and conformal plans were required to meet the following objectives: $D_{0.1\ cm3}$ for spinal cord lower than 18 Gy, $V_{15\ Gy}$ lower than 35% for both kidneys, $V_{36\ Gy}$ lower than 1% for duodenum, $V_{36\ Gy}$ lower than 3% for stomach and small bowel, and $V_{15\ Gy}$ lower than for liver (total liver volume, 700 cm^3). In addition, $D_{0.5\ cm3}$ lower than 30 Gy for the duodenum, stomach, and small bowel was considered as a secondary objective. No definitive consensus currently exists regarding constraints for serial OARs in abdominal SBRT (30). We derived our planning objectives from the

Table 2. Dose to CTV according to planning technique

	CRT plans (No. of patients)	RapidArc plans (No. of patients)
Total CTV dose		
45.0 Gy	5	8
40.5 Gy (10% reduction)	3	0
36.0 Gy (20% reduction)	3	0
Total	11	8

Abbreviations: CTV = clinical target volume; CRT = conformal radiotherapy.

The treatment course was delivered in six fractions in all patients.

literature, making some adjustments for fraction dose (8, 31–35). Dose distributions on axial views in four representative cases are shown in Fig. 1.

Treatment delivery

Treatment was delivered on 6 consecutive working days, with the patient keeping a 3-hour fast to avoid gross displacement of the stomach and bowel. Treatment delivery included stereotactic frame localization in the first session aiming at preliminary isocenter positioning, and then the frame cover was removed to avoid disturbing CBCT acquisition; from that point onward, setup accuracy relied on CBCT image guidance with online couch adjustment at each fraction. Couch repositioning was performed after automatic matching of CBCT images to reference planning CT images, followed by manual refining. Internal analysis of 60 CBCT scans from 10 patients showed mean shifts of 0.2 ± 0.2, 0.3 ± 0.3, and 0.4 ± 0.2 cm in the vertical, longitudinal, and lateral directions, respectively.

Follow-up and statistics

Acute and late radiation-induced toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0). Patients were followed up in 3-month interval in the first and second year and every 6 months thereafter. Local control was evaluated on CT images at 3, 6, 12, 18, and 24 months. In patients who had a PET scan before SBRT, metabolic response was also evaluated at 6 and 12 months.

Response was evaluated on CT images at first follow-up according to World Health Organization criteria (36). Local control was evaluated in terms of freedom from local progression (FFLP), defined as no evidence of tumor growth inside the target lesion. Secondary endpoints included progression-free survival (PFS) and overall survival. Progression-free survival was defined as the time to progression (either local or distant) or death, whichever came first. All endpoints were calculated from the date of the last radiation treatment.

Actuarial analysis of endpoints was conducted by the Kaplan-Meier method. Log-rank statistics were used to test for differences in outcomes when stratifying by relevant factors. The median follow-up was 366 days (range, 180–1,400 days) in the whole series, 648 days (range, 219–1,400 days) in the CRT group, and 247 days (range, 180–376 days) in the RapidArc group.

RESULTS

Patient population

The comparison between the CRT and RapidArc groups (11 and 8 patients, respectively) showed a rather well-balanced distribution of patient and tumor variables (Table 1). Given the small numbers, no formal statistic was applied to check the balancing. An unbalancing between the two groups is evident in the median duration of follow-up, obviously caused by different time periods. Similarly, the subgroup of 6 patients with downscaling of total dose did not show any specific difference in distribution of variables, because dose reduction was usually forced by some critical anatomic relationship between target and normal tissues.

Tumor response

A complete response was found in 2 patients, according to World Health Organization criteria (36). A partial response was achieved within 3 months after radiation in 9 patients (overall response rate, 57.9%). Eight patients had stable disease.

Freedom from local progression

Two patients had a local progression at 273 and 295 days, respectively. Both of these patients also showed concomitant tumor growth at distant sites. In the Kaplan-Meier analysis, both the 12- and 24-month FFLP rates were 77.8% ± 13.9% (mean ± standard error [SE]) (Fig. 2). In this context the log-rank comparison of groups was of limited value, given the small number of patients as well as the occurrence of only two events. In particular, no significant difference was found in relation to treatment technique (CRT vs. RapidArc) or actual total dose (downscaled cases vs. standard 45-Gy cases).

Progression-free survival

Of the patients, 11 showed local and/or distant progressive disease (PD) at follow-up: 2 showed local and concomitant distant PD, 2 had only regional PD at different retroperitoneal nodal sites outside the treated volume, and 7 had PD at distant visceral sites. Time to progression ranged from 32 to 370 days. The 12- and 24-month Kaplan-Meier PFS rates were 29.5% ± 13.4% and 19.7% ± 12.0% (mean ± SE), respectively (Fig. 3). The log-rank univariate statistics for patient and tumor variables showed number of metastases (solitary vs. nonsolitary oligometastases) as the only significant variable (24-month PFS rate, 41.7% vs. 0%; $p < 0.0004$) (Fig. 3). In patients with the largest nodes (either CTV volume >15 cm^3 or largest diameter >30 mm), the observed trend for lower PFS was not statistically significant. Again, no significant difference was found in relation to treatment technique or actual total dose.

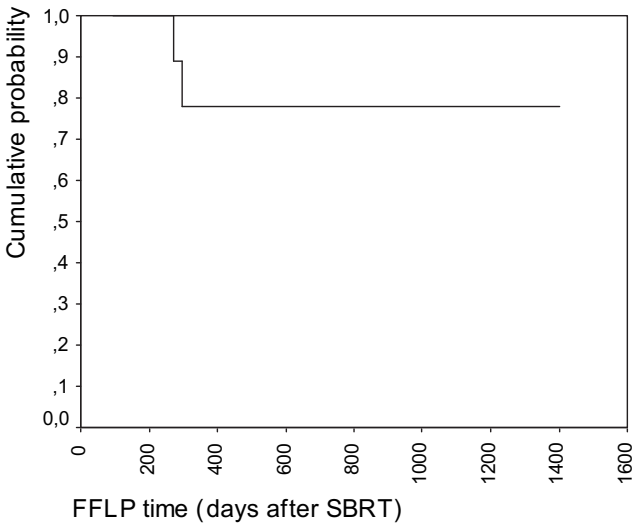

Fig. 2. Kaplan-Meier curve of freedom from local progression (FFLP). SBRT = stereotactic body radiotherapy.

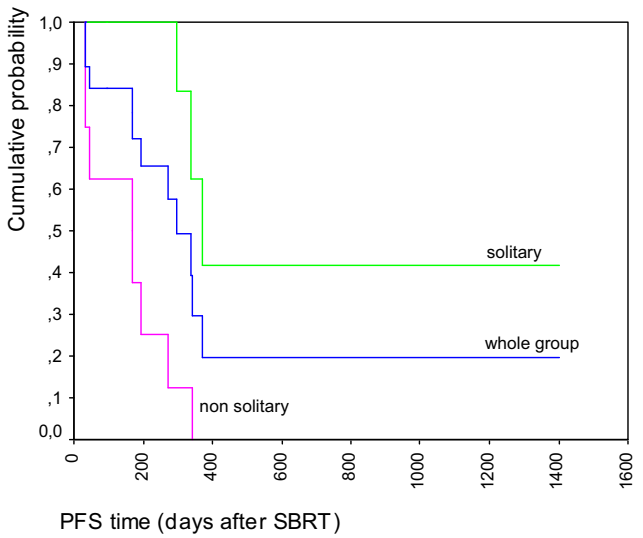

Fig. 3. Kaplan-Meier curve of progression-free survival (PFS): whole group vs. solitary metastases vs. nonsolitary oligometastases. SBRT = stereotactic body radiotherapy.

Overall survival

The actuarial rate of overall survival both at 1 and 2 years was 93.3% ± 6.4% (mean ± SE). A total of 2 patients died, as a consequence of uncontrolled metastatic cancer.

Toxicity

Both acute and chronic toxicities were minimal. Four patients showed mild and transient Grade 1 acute enteritis, which recovered spontaneously within 3 months after radiotherapy. Another 2 patients complained of late effects. The first had chronic enteritis causing Grade 1 diarrhea and Grade 1 abdominal pain. The second had some sub-occlusive events (ascribed to peritoneal adhesions), which always recovered after nonsurgical treatment. This sole Grade 3 late complication occurred in a patient treated by CRT. In this patient, who underwent previous surgery at the site of nodal metastasis, the causative role of radiation remains uncertain. Symptomatic gastrointestinal bleeding, ulceration, or stenosis did not develop in any patient.

DISCUSSION

Locally curative treatment of oligometastases is regarded as an important resource for improving survival in a clinically significant subset of cancer patients (1, 2). In this framework, SBRT for patients with oligometastatic disease in abdominal lymph nodes may play a major role. Early data from our series showed promising local control rates. However, a dose reduction was needed in several cases because of the close proximity of the CTV to the gastrointestinal OARs, where severe radiation damage may occur after doses lower than typical SBRT prescriptions even if limited to small volumes. Although CBCT image guidance provided a margin reduction, in several patients the spatial relation between nodal metastasis and OARs was too close to allow their exclusion from high-dose regions in CRT plans. Conversely, dose escalation over our standard 45 Gy may be needed especially for very large and/or hypoxic lesions (37). We have shown previously that volumetric intensity-modulated arc therapy given by RapidArc achieves more favorable dose distributions, particularly in terms of lower doses to serial-type gastrointestinal OARs adjacent to target (19). Because tumor control should be improved by avoiding dose reduction, since November 2008, RapidArc has been selected as the treatment of choice for this category of patients at Istituto Clinico Humanitas.

This study was performed to investigate the clinical outcome of SBRT in this patient population. In the context of metastatic disease, the median follow-up of about 1 year may be enough for a preliminary report. Long-term results will be evaluated after a more prolonged follow-up.

Our data showed a fairly good rate of overall response at 3 months. The comparison of response rates after SBRT has shortcomings because of inhomogeneity in the evaluation criteria. Because the finding of residual nonactive disease is common after SBRT, looking also at morphologic changes on CT and uptake changes on PET should allow a more reliable evaluation of response compared with standard criteria. Of course, medium-/long-term local control, defined as no evidence of tumor growth inside the target lesion, is a more reliable endpoint for evaluating the effectiveness of SBRT.

Medium-term (1–2 years) local control in this series was found to be higher than 75%, in accordance with our previous results as well as with sparse data in the literature (3, 4, 11), despite a larger median PTV volume (31.8 cm^3) compared with the largest series (17 cm^3) (3). High rates of local control seem consistent with the delivery of moderately high biological doses, because our schedule (45 Gy in 6 fractions) may be estimated to be biologically equivalent to about 65 Gy conventionally fractionated if time factor is not considered (37).

In this series the relation between dose, tumor size, and outcome remains uncertain. However, on a theoretic basis, dose escalation over a 65-Gy normalized total dose should affect local control. On the other hand, half of the patients had a tumor diameter greater than 30 mm, a size for which a 65-Gy dose is not expected to be radical in many solid tumors (37). As a matter of fact, we intend to explore dose escalation in selected cases with larger solitary lesions.

Poorer PFS rates in this series compared with the rate observed by Choi *et al.* (3) may be explained by substantial differences in the patient populations regarding several aspects. First, our study included mixed tumor types, with most of them bearing a worse natural history than cervix cancer; in addition, it was not restricted to solitary metastases. It has been shown that new metastases will develop in most oligometastatic patients treated with SBRT (38). The prevailing distant pattern of recurrence in our group is in agreement with this observation. Even if obtaining local control might salvage only a few patients, it could be clinically relevant to reduce tumor burden or delay further chemotherapy, as well as to preserve quality of life, by avoiding symptomatic tumor growth in retroperitoneal nodes.

The potential benefit in terms of quality of life is also supported by the low incidence of acute and late toxicity. Low toxicity rates have also been reported in other reports dealing with similar populations (3, 4, 11). Clearly, the risk of damaging normal tissue is expected to be related to the site of target and its size. In 8 of our 19 patients, the CTV was located at a distance less than 8 mm from some part of the duodenum. A significant rate of gastrointestinal major toxic effects has been reported in some articles dealing with SBRT for biliary tract or pancreatic tumors (30, 33, 39), whereas in this group of patients, we did not observe events such as bleeding, ulceration, or stenosis. Several factors could account for this difference. First, the median PTV volume was lower compared with the aforementioned articles: 31.8 cm^3 vs. 97 cm^3 (30), 46.6 cm^3 (33), and 136 cm^3 (39). In addition, the lower fraction dose in our less hypofractionated schedule should be considered. Lastly, in our experience the use of advanced technologies such as volumetric intensity-modulated arc therapy, as well as CBCT image guidance, proved of great value for the purpose of keeping toxicity to a minimum without compromising target dose.

Although this work aimed at evaluating the role of SBRT irrespective of radiation technique, we have also reported a comparison between treatment groups (CRT vs. RapidArc), without finding any significant difference in terms of FFLP, PFS, and toxicity. The same holds true for the comparison between the subgroup with dose downscaling and the full-dose subgroup. Clearly, these comparisons were quite limited by the limited follow-up, as well as by the very small number of events. Regardless, the fact remains that no dose reduction was required in RapidArc plans. Though not detected in this series, it is conceivable that the ability to deliver the planned dose might affect outcome in a larger population.

CONCLUSIONS

Hypofractionated SBRT for metastases to abdominal lymph nodes was feasible and able to provide good clinical results, supporting its role in aggressively treating selected cases with limited metastatic disease. A more prolonged follow-up will be required to confirm our results in the long term. Even if most patients eventually show progressive disease at other sites, local control achieved by SBRT may be potentially significant for quality of life and delaying further chemotherapy. In the subgroup of patients with a solitary metastasis, investigating dose escalation may be worthwhile.

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