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FULL PAPER

The role of stereotactic body radiation therapy (SBRT) in the treatment of oligometastatic disease in the elderly

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Objective: To report about clinical outcome of stereotactic body radiation therapy (SBRT) in the treatment of oligometastatic disease in elderly patients.

Methods: Patients with 1–4 inoperable metastases were treated with SBRT. Dose prescription ranged from 40 to 75 Gy in 3–8 fractions. SBRT was delivered using the volumetric modulated arc therapy technique with flattening filter-free photon beams. The primary end points were in-field local control (LC) and toxicity. Secondary end points were overall survival (OS) and disease-specific survival (DSS).

Results: 82 patients with 111 total metastases were treated. Median age was 79 years. 64 patients (78%) had a single lesion; the remaining patients had 2–4 lesions. 16 (14.4%) lesions were localized in the abdomen, 50 (45.0%) in the liver and 45 (40.5%) in the lungs. Local response was observed for 87 lesions (78.4%) while

local progression was observed in 24 lesions (21.6%). Actuarial 1-year LC was $86.8\% \pm 3.3\%$. Actuarial 1-year OS was $93.6\% \pm 2.7\%$. 2-year findings were $76.3\% \pm 4.4\%$ and $72.0\% \pm 5.6\%$, respectively. Actuarial 1- and 2-year DSS results were $97.5\% \pm 2.0\%$ and $81.6\% \pm 4.9\%$, respectively. Treatment-related Grade 2–3 toxicity was observed in five patients (4.2%); Grade 1 toxicity in seven patients (5.9%) and no toxicity was observed in 85.4% of the cases.

Conclusion: SBRT is a safe and effective therapeutic option for the treatment of oligometastatic disease in the elderly with acceptable rates of LC and low treatment-related toxicity.

Advances in knowledge: The use of SBRT for oligometastatic disease in the elderly can be considered as a valuable approach, particularly for patients with fragile status or refusing other approaches.

INTRODUCTION

The analysis of global cancer data with the projection of demographic ageing of populations, particularly in western countries, shows a remarkable increasing trend in the number of elderly patients affected by some type of cancer. World Health Organization data show an estimated increase of total number of new cancer patients of about 25% for 2030 in Europe, and this increase is expected to be predominantly (91%) observed in patients aged 65 years or above.¹ Similar results were projected for the USA by Smith et al² from 2010 to 2020 with a net increase of 22% in the number in patients.

In resonance with the increased life expectancy, the desirable improvement in the efficacy of diagnosis and therapy contributes to shift cancer management from an acute to a chronic profile. In the frame of palliative care, oligometastatic status will ask for effective approaches, particularly for

elderly patients who are normally fragile owing to concomitant comorbidities and poor prognostic factors. The Charlson comorbidity index³ is a validated scoring system to determine the “intensity” of these factors and can be used as an indicator for the selection of more appropriate treatment regimens.

Smith and Smith⁴ proposed a conceptual framework for the selection of radiation therapy for older patients with cancer. In this framework, the recommendation for radiation therapy derives from an accurate assessment of the risk–benefits, the patients' expectations and the availability of alternative options. In their conclusions, the authors identified, among future directions, the need to determine how advanced technologies can be judiciously applied in this field.

Kunkler et al⁵ reported the results of a task force of the International Society of Geriatric Oncology demonstrating the limited Level I evidence for radiotherapy in the elderly,

and provided recommendations for curative treatments but not for the metastatic disease conditions. In general, this report suggests that stereotactic treatments can be a valid approach in several cases.

Rosenblut⁶ reviewed the use of radiation therapy in the geriatric population and concluded that these patients are capable of tolerating and possibly benefitting from proper radiation treatments. In addition, he suggested that no cut-off age could be identified in the selection of the best treatment option.

Stereotactic body radiation therapy (SBRT) is a technique capable of delivering high biologically equivalent dose to the tumour in a small number of fractions (3–6) with a steep dose fallout on surrounding healthy tissues. The small number of fractions of SBRT reduces the need for patients' family support; elderly patients are frequently not independent in self care and transportation, as they often require a relative to help them to reach the hospital. Recently, the use of SBRT in patients >75–80 years of age with non-small-cell lung cancer (NSCLC) Stage I, unfit for surgery was investigated. SBRT demonstrated improved local control (LC) and survival rates compared with observation and with standard radiotherapy.^{7–9} As per the authors' knowledge, there are no studies on the use of SBRT in oligometastatic patients focusing on an elderly and fragile population.

The aim of the present study was to investigate the outcome and the tolerability of SBRT treatments, performed with volumetric modulated arc therapy (VMAT) and with risk-adapted fractionation schemes, in a group of elderly patients. The primary objective was to demonstrate the level of LC achievable in the absence of significant toxicity.

METHODS AND MATERIALS

Patients selection and treatment

This retrospective observational study, approved by local institute review board committee, based on treatment chart examination, was carried out on a population of patients aged 70 years or more with oligometastatic status to be treated with SBRT. Patients were eligible for the study if metastases (from any primary tumour) were localized in the liver, in the lung or in the abdominal cavity. All patients included in the review were unfit for chemotherapy treatments owing to various reasons (comorbidity, age, own preference). Additionally, a maximum tumour diameter of <6 cm was required, no prior radiotherapy in the same site and Eastern Co-operative Oncology Group performance status of ≤ 2 and a Charlson comorbidity index <8. All patients underwent a CT scan of chest, abdomen, pelvis and bone or positron emission tomography scan no more than 2 months before SBRT.

The patient's projected life expectancy, based on Charlson's index, had to be greater than 12 months owing to non-cancer risks.^{10,11} Written informed consent was obtained before beginning radiation therapy.

Primary end points of the investigation were LC and toxicity, secondary end points were overall survival (OS) and disease-specific survival (DSS).

The SBRT technique used for the treatments has been reported in detail in previous publications for all indications.^{12–14} Patients with liver and abdominal lesions/cancer were immobilized with a thermoplastic body mask including a Styrofoam block for abdominal compression to minimize respiratory organ motion. No abdominal compression was applied to lung patients; as per institutional policy in these cases, 4D planning was required. The clinical target volume (CTV) was defined for all patients on planning CT images as equal to the gross target volume (GTV). In all patients who underwent 4D-CT scan (lung patients), an internal target volume (ITV) was defined as the envelope of all GTVs in the different respiratory phases. The planning target volume (PTV) was generated from either the GTV or the ITV by adding an overall isotropic margin of 7 mm in the lung and 5 mm in the abdominal cases.

According to the localization, lesions' size and patients' status, several risk-adapted treatment regimens were prescribed. Total dose ranged from 40 to 75 Gy in 3–8 fractions. In particular, 75 Gy in 3 fractions was prescribed to liver metastasis, 48–60 Gy in 4–8 fractions to lung lesions and 40–45 Gy in 4–6 fractions to adrenal metastases and abdominal lymph nodes. Dose reductions were allowed if judged necessary to cope with organs at risk (OAR) sparing. The dose was prescribed as the mean dose to PTV. Treatment was delivered on a Varian® TrueBeam™ linear accelerator (Varian® Medical Systems, Palo Alto, CA) using a 6–10 MV flattening filter-free beam. The adopted technique was RapidArc™ (Varian® Medical Systems), the Varian solution for VMAT. Daily image guidance (IGRT) was performed by means of CBCT acquisitions, and patients' positioning was verified in 3D prior to irradiation.

The plan objective was to cover at least 98% of the CTV (ITV) volume with 98% of the prescribed dose ($D_{98\%} = 98\%$) and for the PTV to cover 95% of the volume with 95% of the dose ($V_{95\%} = 95\%$). Hot spots with doses >107% were accepted only if inside the target. Planning constraints for OAR were defined according to the number of fractions, as shown in Table 1.

Assessment

After conclusion of SBRT, all patients were assessed at 1 month and every 3 months during the first year and every 6 months after 1 follow-up year. CT or MRI was performed at each follow-up. Acute and late toxicity were scored by the Common Terminology Criteria for Adverse Events v. 3.0 (CTCAE). Any increase in grade from baseline was considered toxicity related to the treatment. Tumour response and LC were defined using European Organization for Research and Treatment of Cancer Response Evaluation Criteria in Solid Tumours (EORTC-RECIST) criteria v. 1.1.¹⁵

Survival and time to LC were calculated from the date of start of the SBRT treatment. Patients were observed for LC, even if new distant lesions developed. Kaplan–Meier method was used to generate the actuarial data. LC was defined as stable disease, partial or complete remission as observed at follow-up examinations. OS was measured by accounting for any death while DSS was computed based on cancer-specific causes while other causes were censored. Univariate analysis was performed for age,

Table 1. Planning constraints for organs at risk

Organ at risk	Constraints
Healthy liver	$>700 \text{ cm}^3 < 15 \text{ Gy}$
Spinal cord	$D_{0.1 \text{ cm}^3} < 18 \text{ (20) Gy}$
Kidneys	$V_{15 \text{ Gy}} < 35\%$
Stomach	$D_{1 \text{ cm}^3} < 21 \text{ (36) Gy}$
Duodenum	$D_{1 \text{ cm}^3} < 21 \text{ (36) Gy}$
Small bowel	$D_{1 \text{ cm}^3} < 21 \text{ (36) Gy}$
Large bowel	$D_{1 \text{ cm}^3} < 21 \text{ (36) Gy}$
Heart	$D_{1 \text{ cm}^3} < 30 \text{ Gy}$
Lungs	Mean $< 4 \text{ Gy}$ $V_{20 \text{ Gy}} < 10\%$
Oesophagus	$D_{0.1 \text{ cm}^3} < 30 \text{ Gy}$

$D_{\times \text{cm}^3}$, dose received by $\times \text{cm}^3$ of the organ; $V_{\times \text{Gy}}$, volume receiving at least $\times \text{Gy}$ of the dose.

Numbers in brackets indicate more relaxed constraints for the fractionation schemes with 4–8 fractions.

sex, Charlson index, number and size of treated lesions, primary tumour histology, treated site and biological equivalent dose (BED).

RESULTS

A total of 82 patients with 111 metastases were irradiated and included in the analysis. Table 2 shows the patients' characteristics, treatment localization, primary tumour site and fractionation scheme. About 22% of the patients were treated for 2–4 synchronous or metachronous metastases. The main primary tumour in the cohort was colorectal cancer followed by lung cancer (NSCLC) covering in total about two-thirds of the patients. About half of the patients received no chemotherapy treatment prior to the SBRT while the other half received 1, 2 or more cycles of systemic treatment. Approximately, 79% of the patients were treated with the most aggressive schemes with 3–4 fractions (in the lung and in the liver) while 6–8 fractions were applied mostly to abdominal and central lung lesions. The mean Charlson index was 4.14 ± 0.93 (median: 4; range: 3–6). The median time from primary tumour diagnosis to SBRT treatment was 41 months (range from 2 months to 16.5 years). The median time from diagnosis of the metastasis and its SBRT treatment was 2.2 months (range 0–48 months).

Median follow-up was 21.9 months (mean 25.4 ± 12.5 ; range 3–53 months).

Analysis of dose plans based on dose volume histograms confirmed that they were, with respect to planning constraints for all patients, consistence with the previously published data.

Local response

Table 3 shows the summary of the LC data. Complete response was observed in more than one-third of the cohort while LC (inclusive of complete, partial and stable response) was achieved in 78.3% of the treated lesions. The median time to local progression from time of metastases diagnosis, for the 24 in-field local failures, was 11.1 months. Of the 22 progressive lesions,

6 (27% of the progressions, 5% of the total) were in the abdomen, 5 (23% or 4.5% of the total) were in the liver and 11 (50% or 9.9% of the total) were in the lung. The median time to progression was 11.5 months (range: 0.5–26.0 months). The time to progression was shorter ($p = 0.05$) for the lung cases (median 9.1 months) than for abdomen and liver (12.4 and

Table 2. Patients' demographics and treatment characteristics

Parameter	Number of cases (frequency)
Number of patients	82
Number of lesions	111
Median age (range) [years]	78.8 (73.0–88.5)
Sex male/female	64 (78%)/18 (22%)
Primary tumour	
Colorectal	40 (48.8%)
Lung	13 (15.9%)
Kidney–urethra	7 (9.5%)
Liver	4 (4.9%)
Prostate	3 (3.6%)
Pancreas	3 (3.6%)
Other	12 (14.6%)
Treatment site	
Abdomen	16 (14.4%)
Liver	50 (45.0%)
Lung	45 (40.5%)
Chemotherapy cycles received before SBRT	
0	42 (51.2%)
1	12 (14.6%)
2	16 (14.4%)
>2	12 (14.6%)
Number of treated lesions	
1	64 (78.0%)
2	10 (12.2%)
3	6 (7.3%)
4	2 (2.4%)
SBRT prescription dose	
40–45 Gy	18 (16.2%)
48–60 Gy	57 (51.3%)
75 Gy	36 (32.4%)
Number of fractions	
3	48 (43.2%)
4	40 (36.0%)
5–8	23 (20.7%)

Table 3. Local control (over lesions cohort) and distant failure (over patients cohort). Time is computed from diagnosis of treated metastasis

Status	Number of cases (frequency)
Complete response	42 (37.8%)
Partial response	41 (36.9%)
Stable disease	6 (5.4%)
Progressive disease (local)	22 (19.8%)
Mean time to progression (range) [months]	11.1 $\pm$ 6.2 (1–26)
Distant progression	71 (64.0%)
Time to distant progression (range) [months]	14.7 $\pm$ 10.3 (0–55)

11.5 months, respectively). Distant progression was observed in 64% of the patients with a median time to progression of 12.6 months (range: 0–55).

Mean LC time was 42.7 ± 1.9 months [95% confidence limit (CL): 38.9–46.5 months]; median was not reached. Actuarial LC at 12, 24 and 36 months was $86.8\% \pm 3.3\%$, $76.3\% \pm 4.4\%$ and $74.1\% \pm 4.8\%$, respectively (Figure 1a). Figure 1b–d shows the LC stratified per treatment site, per site of primary tumour (reduced to 4 groups) and dose group (divided into BED lower or higher than 100 Gy). No statistical significance was found between strata although in the case of treatment site, the $p = 0.09$ suggested a tendency towards significance. 1-year LC for the patients treated in the abdomen, liver and lung was $86.7\% \pm 8.8\%$, $91.8\% \pm 3.9\%$ and $81.2\% \pm 6.0\%$, respectively. The 1-year LC was $88.4\% \pm 3.6\%$ for lesions treated with BED >100 Gy and $79.0\% \pm 7.7\%$ for BED <100 Gy; the difference was not statistically significant ($p > 0.4$). Univariate analysis did not show any significant impact on LC for any variable. In particular, Figure 1e shows LC for lesions smaller or greater than 3 cm^3 ($p = 0.10$). No significant threshold was found for the lesion's size.

Survival

Crude survival rate was 68%. 14 patients (17%) died due to tumour-related causes. Disease-related cause of death was determined when a patient developed progressive disease with important decline of general conditions leading to death. 12 patients (15%) died due to other causes (heart disease: 6 patients; cerebrovascular disease: 2 patients; respiratory disease: 2 patients; and

one each for sepsis or neurocognitive disease). None died due to treatment-related causes. The actuarial OS at 12, 24 and 36 months was $93.6\% \pm 2.7\%$, $72.0\% \pm 5.6\%$ and $61.2\% \pm 6.9\%$, respectively (Figure 2a). Despite a short median follow-up of 21 months, the median OS was 45.4 ± 2.5 months. Univariate analysis showed no significance in survival for any of the investigated variables. Figure 2b shows an example of the OS stratified for primary tumour.

Of the 26 patients (31.7%) who died during the observation period, 11 (42.3%) died because of non-cancer-related causes. Mean median DSS was not reached. Actuarial DSS at 12, 24 and 36 months was $97.5\% \pm 1.8\%$, $81.6\% \pm 4.9\%$ and $78.5\% \pm 5.6\%$, respectively (Figure 2c).

Acute toxicity

A very mild pattern of acute toxicity was observed in the cohort of patients (Table 4). Reported G2 toxicity was only 6%. A Grade 2 radiological (asymptomatic) case of pneumonitis was observed. Of the other four cases of G2, three occurred in liver patients (two with nausea and one with an increased bilirubin level) and one in a lung patient (pain). No correlation with any dose–volume parameter was found in these cases. In 98% of the patients, no change of the already ongoing pharmacological support therapy was needed. In some cases, additional support drugs or corticosteroid therapy was prescribed for short periods.

Formal Quality-of-Life questionnaires were not administered to the patients during their treatments and follow-up. A subjective self-assessment was asked at all visits (“Is your standard of life improved/worsened after SBRT treatment?”) and $>90\%$ of patients reported either no change or improvements (symptom-related impairment reduction).

DISCUSSION

Takeda *et al*¹⁶ reported on SBRT with ablative intent in patients aged >80 years and affected by NSCLC. With a median follow-up of 2 years, authors reported very limited toxicity. 90% of patients had Grade 0–1 radiation pneumonitis. 17% had Grade 2–3 and one patient had a Grade 5 event and died of respiratory failure. Transient chest pain was observed in some patients, and two events of Grade 2 rib fracture were observed. The 3-year local, regional and distant metastatic-free survival rates were 82.3%, 90.1% and 76.8%, respectively. These results suggested that SBRT in octogenarians could be feasible and safe. Similarly, Sandhu *et al*¹⁷ reported on a retrospective analysis on 24 Stage I patients with NSCLC with median age of 85 years. Patient tolerance and DSS data

Table 4. Toxicity; results are for overall cohort and divided per treatment site

Patients' subgroup	G0, <i>n</i> (%)	G1, <i>n</i> (%)	G2, <i>n</i> (%)	G3, <i>n</i> (%)
All patients	70 (85.4)	7 (8.5)	5 (6.1)	0 (0)
Liver patients	32 (84.2)	3 (7.9)	3 (7.9)	0 (0)
Abdomen patients	15 (83.3)	3 (16.7)	0 (0)	0 (0)
Lung patients	23 (88.5)	1 (3.8)	2 (7.7)	0 (0)

Figure 1. (a) Local control (LC); (b) LC stratified per dose group; (c) LC stratified per primary tumour; (d) LC stratified per treated site; (e) LC stratified per lesion size. BED, biological equivalent dose; HCC, hepatocellular carcinoma; NSCLC, non-small-cell lung cancer.

suggested that SBRT could be attractive for these patients (no $\geq$ Grade 3 early or late toxicity was observed). Haasbeek et al⁷ showed on a cohort of 193 patients aged ≥ 75 years, that SBRT in Stage I NSCLC lead to high LC (88% at 1 year) rates with minimal toxicity despite the presence of major comorbidities. 60% of patients reported no early toxicity; the main reported effect at 3 months was fatigue (33%). Nausea and respiratory symptoms were present in about 4–6% of the cases. Also late toxicity was rare: 2% of the cases had $\geq$ Grade 3 radiation pneumonitis and $<2\%$ presented late rib fractures. More recently, Haasbeek et al⁸ conducted a population-based study of the changes in treatment options and survival based on the Netherlands cancer registry. The study was limited to early stage lung cancer. The main point of the study was the demonstration that introduction of SBRT correlated with a remarkable reduction of untreated patients with a highly significant improvement of 8 months in median survival.

Kim et al¹⁸ discussed the role of SBRT in the treatment of pancreatic cancer in the elderly in a retrospectively analysed group of 26 patients with median age of 86 years. No acute or late Grade 3+ toxicity was observed. 6 months and 12 months actuarial LC were 60.1% and 41.2%. Median OS was 7.6 months. A trend for improved LC with prescription dose

>20 Gy was observed. Authors concluded that definitive SBRT was feasible, effective and safe. Yechieli et al¹⁹ confirmed the effectiveness of SBRT in elderly patients in a retrospective analysis of 20 patients. Median age was 83.2 years, adult comorbidity evaluation-27 co-morbidity index score was 3 (severe) in 55% of patients and 2 (moderate) in 30%. Median survival was 6.4 months. Grade 3–4 toxicity during follow-up was observed in 3 (15%) of the patients (gastrointestinal bleeding and dehydration). Authors considered SBRT an excellent treatment option in elderly patients also with severe comorbidities.

Watanabe et al²⁰ compared patients 80 years of age or older (Group A) and patients aged 65–79 years old (Group B) treated with stereotactic radiosurgery (SRS) for brain metastases. Median OS was 5.3 and 6.9 months in Group A and B, respectively. Their results suggested that octogenarians could be candidates for SRS, in particular more aggressive treatment of brain metastases could be utilized in these patients with modified-RPA Class I+IIa or IIb disease.

SBRT can achieve high rates of LC in many treatment sites: lung, liver, abdominal lymph nodes and adrenal glands. In a recent review,²¹ the role of SBRT in oligometastatic patients was investigated. The LC for isolated or few lung metastases was 70–100% at 1 year. For liver metastases, in retrospective studies,

Figure 2. (a) Overall survival (OS); (b) OS stratified per primary tumour; (c) disease-specific survival. HCC, hepatocellular carcinoma; NSCLC, non-small-cell lung cancer.

LC was 56–100% at 1 year. Recent prospective studies demonstrated that higher radiation dose using SBRT was promising in oligometastatic liver patients with LC rate 95% at 12 months.^{12,22} In both studies, none of the patients demonstrated high grade (4 or 5) radiation toxicity and very few had Grade 3 effects. There are few published data for SBRT in abdominal metastases, lymph nodes or adrenal glands, there are no standard total dose and fractionations, and 1-year LC was 55–90%.^{14,23,24} Jereczek-Fossa *et al*²³ report stereotactic treatment of isolated metastases from prostate cancer, no acute toxicity was reported but one patient had rectal tenesmus that was likely induced by earlier radiation treatment. Casamassima *et al*,²⁴ in the treatment of adrenal gland metastases reported only one case of Grade 2 adrenal insufficiency but follow-up was too short to report on late events.

The results presented here, demonstrate a very high LC, confirming earlier reported data for the same technological approach but on broader cohorts of patients. Treatment tolerance and compliance was good/satisfactory, and a limited need of supportive therapy was observed. In contrast with earlier data published for SBRT (not specific for elderly patients), this study did not confirm the dependence of LC on BED and size of the

treated lesions. For the latter, a tendency to significance ($p = 0.10$) was found at the conventional threshold of 3 cm³. For the BED, possible confounding factors like age, histological heterogeneity and BED values not far from 100 Gy also in the lower group, could have masked the dependence visible in other studies.

All treatments were completed in a short course out-patient setting (within 1 or 2 weeks) with a positive impact on the logistic management of the treatment for both the institute and the patients' family. Each fraction, using the high intensity photon beams, was completed in a few minutes (less than 15 min on couch, including imaging and positioning) with a high degree of compliance and satisfaction from the patients.

Since life expectancy is today quite prolonged, Quality of life plays a crucial role in treatment choice. Given the retrospective nature of the study, no formal investigation was performed on quality of life but the subjective self-assessment reported by patients suggested that the SBRT treatment was well tolerated and lead to a perceived improvement of the living conditions. More appropriate investigation shall be conducted in a formal prospective trial in the future to confirm this evidence.

CONCLUSION

SBRT can be considered an effective and safe treatment for oligometastatic patients in the elderly, with sustained LC, associated with encouraging survival rates and low toxicity. A prospective Phase II trial will be conducted to confirm this retrospective evaluation and to also formally assess

quality of life and correlation of outcome results with life expectancy.

CONFLICT OF INTEREST

L Cozzi acts as Scientific Advisor to Varian Medical Systems and is a Clinical Research Scientist at Humanitas Cancer Center.

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