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Original research article

Is Stereotactic Body Radiotherapy (SBRT) in lymph node oligometastatic patients feasible and effective?

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ABSTRACT

Objectives: To review the available data about stereotactic body-radiotherapy (SBRT) for oligometastatic lymph node cancer recurrence.
Methods: The inclusion criteria for this study were as follows: Medline search for the (1) English language (2) full paper (abstracts were excluded) on (3) adult oligometastatic solid cancer recurrence limited to lymph node that underwent SBRT (4) outcome data available and (5) published up to the 30th April 2014.
Results: 38 papers fulfilling the inclusion criteria have been found: 7 review articles and 31 patient series (20 and 11 retrospective and prospective studies, respectively) including between 1 and 69 patients (636 lymph nodes). Twelve articles reported only lymph node SBRT while in 19 – all types of SBRT including lymph node SBRT were presented. Two-year local control, 4-year progression free survival and overall survival was of up to 100%, 30% and 50%, respectively. The progression was mainly out-field (10–30% of patients had a recurrence in another lymph node/nodes). The toxicity was low with mainly mild acute events and single grade 3–4 late events. When compared to SBRT for any oligometastatic cancer, SBRT for lymph node recurrence carried better prognosis and showed lower toxicity.
Conclusions: SBRT is a feasible approach for oligometastatic lymph node recurrence, offering excellent in-field tumor control with low toxicity profile. The potential abscopal effect has been hypothesized as a basis of these findings. Future studies are warranted to identify the patients that benefit most from this treatment. The optimal combination with systemic treatment should also be defined.

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1. Introduction

Oligometastatic cancer recurrence is a recently established distinct clinical entity.[1,2] Indeed, local cancer treatment like surgical metastasectomy has been used in selected patients and histology types (sarcoma, breast cancer, colorectal cancer etc.) allowing for long term disease control in a good proportion of cases.[3–5] These findings confirm distinct biology of oligometastases based on the restricted tumor metastatic capacity.[2] In the last decade stereotactic body radiotherapy (SBRT) has become a new local treatment option for the limited volume primary cancer (non small cell lung cancer, hepatocellular carcinoma, renal cancer, prostate cancer etc.) or oligometastases.[6,7] As a non-invasive (or minimally invasive if fiducial positioning is required) short out-patient procedure it has been immediately introduced in the various scenarios of cancer patients for the treatment of primary or secondary lesions. Moreover, several benign conditions as arterio-venous malformations, epilepsy, trigeminal neuralgia or benign tumors including meningioma, vestibular schwannoma, pituitary tumors, are being treated successfully with stereotactic irradiation. Medline search using terms "stereotactic radiotherapy" showed 13,020 articles, out of which 8385 (64%) and 5136 (40%) have been published in the last 10 and 5 years, respectively. When "radiosurgery" (single fraction stereotactic radiotherapy) was used for Medline search, 11,215 articles were found, 7238 (65%) and 4405 (40%) published in the last 10 and 5 years, respectively.

Recurrent lymph node cancer after the primary treatment is considered a sign of disease dissemination and as such is rarely approached with local treatment like surgery or limited-field radiotherapy. Systemic therapy like chemotherapy, endocrine treatment or new biological agents are considered the golden standard in patients with lymph node recurrent cancer. At that time the cancer is rarely symptomatic, so the main symptoms reported by the patient will be treatment side effects lowering the quality of life and requiring hospital access. Therefore, local therapy if safe and effective is easily accepted by the patient. Recently published data suggest that SBRT might offer good local control in selected patients, although the majority of reports are retrospective and include small patients series with heterogeneous tumor sites.

The aim of our study was to evaluate the available literature on the SBRT as a therapeutic approach to lymph node recurrent cancer. SBRT is a novel radiotherapy modality, that takes advantage of the recently available image guidance technologies and radiation dose delivery techniques to administer ablative doses selectively to the target lesion, leading to acceptable toxicity with respect to conventional techniques. The available literature has been reviewed in order to evaluate the efficacy and toxicity profile of this innovative treatment in lymph node recurrent cancer.

2. Material and methods

2.1. Study protocol

This is a review study on the SBRT for recurrent oligometastatic solid cancer limited to lymph nodes.

2.2. Inclusion criteria

The inclusion criteria for this study were as follows: Medline search for the (1) English language (2) full paper (abstract were excluded) on (3) adult oligometastatic solid cancer recurrence limited to lymph node that underwent SBRT (4) outcome data available and (5) published up to the 30th April 2014.

The following Medline terms were used: stereotactic radiotherapy, stereotactic radiosurgery, lymph node, lymph node recurrence. The articles were checked for the availability of the information relative to SBRT outcome in terms of efficacy and/or toxicity profile. The articles dedicated exclusively to other aspects of SBRT (diagnostic, dosimetric or technical issues, incidental lymph nodal dose from SBRT etc.) were excluded.

2.3. Review and analysis of the available literature

The articles were reviewed in their full version by two authors (SR, BAJF). The papers were categorized as (1) review articles and (2) articles that included outcome information of the patient series.

3. Results

Thirty eight papers fulfilling the inclusion criteria have been found: 7 review papers[5,7–12] and 31 patient series reporting treatment (636 lymph nodes treated with SBRT).[13–43]

Out of 7 review articles, only 1 is dedicated exclusively to the lymph node SBRT,[8] and 2 describe treatment options for lymph node recurrence including SBRT.[11,12]

Thirty one clinical series reporting treatment outcome (in the series of 1–69 cases of lymph node recurrence) were divided in those including patients treated with SBRT only for lymph node recurrent cancer (12 articles)[32–43] and those on the patients treated for any oligometastatic cancer to any sites including lymph nodes (19 articles).[13–31] The first article of this series was published in 2005.[23] Twenty eight out of 31 articles (90%) have been published in the last 6 years (2008–2013).

Most probably some patients have been included in more than one article (along with updated follow-up) and whenever this information was clear in the text, it is also specified in the present review and tables.[13–15,28–31,38,42,43]

3.1. Clinical series reporting SBRT outcome

3.1.1. Series including SBRT for lymph node recurrence only

Twelve out of 31 clinical series reporting outcome included patients treated with SBRT for lymph node recurrence only[32–43] (Table 1). All but 2 series were retrospective.

3.1.1.1. Case profile and tumor sites. Altogether 290 patients (350 lymph nodes) were included in 12 articles. The majority (7 articles) included patients treated exclusively for abdominopelvic lymph nodes.[32–36,38,43] Three articles included patients treated exclusively for paraaortic lymph node.[40–42] Cervical lymph node and miscellaneous sites (mediastinum, abdomen and pelvis) were included in 1 and 1 series, respectively.[37,39]

Table 1 – Published clinical series including patients treated with SBRT for recurrent cancer limited to the lymph nodes only.

Authors, year of publication	No. of pts/treated LN mts	Nature of study	SBRT technique	Primary site/histology	Systemic therapy	Fiducial markers	Treated volumes
Bonomo et al., 2013[32]	26 pts, 32 abdomino-pelvic LN	Retrospective	LINAC (dynamic arcs) and CBK	Miscellaneous (mostly gynecologic and prostate)	Previous CHT in 12/32 treatments (37.5%)	Yes for pelvic targets with CBK	LN size < 2 cm: 11 (34.4%), 2–2.99 cm: 11 (34.4%), > 3 cm: 10 (31.2%)
Alongi et al., 2012[33]	25 pts, 28 abdomino-pelvic LN	Retrospective	VMAT RapidArc using FFF beams	Miscellaneous	Previous CHT in 20/25 pts	Not reported	Mean GTV volume 17.4 cm^3
Corvò et al., 2013[34]	36 pts, 36 abdomino-pelvic LN	Retrospective	IG-IMRT (helical Tomotherapy™ Hi-ART)	Miscellaneous (mostly pancreas and colon)	Previous CHT in 25/33 pts (70%)	Not reported	Not reported
Jereczek-Fossa et al., 2012[35 a]	69 pts, 94 abdomino-pelvic LN	Retrospective	LINAC, dynamic arcs	Miscellaneous (mostly gastrointestinal prostate, gynecologic)	Concomitant CHT in 9 cases, HT in 23 cases, both in 3 cases	Not reported	GTV mean 12.5 cm^3, median 29.1 cm^3
Bignardi et al., 2011[36]	19 pts with abdominal LN	Retrospective	3D-CRT and VMAT RapidArc	Miscellaneous	Previous CHT in 11 pts (58%)	Not reported	Mean GTV volume 14.8 cm
Casamassima et al., 2011[37]	25 pts with limited nodal recurrence	Prospective	LINAC, IMRT multiple coplanar and non-coplanar arcs	Prostate cancer	No	Not reported	Not reported
Jereczek-Fossa et al., 2009[38]	14 pts; 16 LN	Retrospective	LINAC and CBK	Prostate cancer	Concomitant ADT in 7 pts, docetaxel + LHRH in 1 pt	Yes in 7 pts treated with CBK	Not reported
Kim et al., 2010[39]	9 pts, 29 cervical LN	Retrospective	CBK	Nonanaplastic thyroid cancer	Previous radio iodine in 8 pts	Not reported	Total cumulative LN volume: range 1.6–43.6 ml
Kim et al., 2009[40]	7 pts treated for paraortic LN	Prospective	CBK	Gastric	Adj CHT after gastric resection in 4/7 pts, 5-FU before SBRT in all pts	Yes	CTV median volume 21 ml
Choi et al., 2009[41]	30 pts treated for para-aortic LN	Retrospective	CBK	Cervix, endometrial cancer	CHT in 25 pts: 2 pre-, 9 concomitant, 14 post-SBRT	Yes	PTV volume range 1.3–57.3 cm^3
Kim et al., 2009[42 b]	7 pts, 11 para-aortic LN	Retrospective	CBK	Colorectal	CT before SBRT for all pts, all non-responders	Yes	GTV median volume 22 ml
Kim et al., 2008[43 b]	23 pts treated for isolated pelvic LN	Retrospective	CBK	Rectal cancer	Salvage-CHT before SBRT for all pts	Yes	GTV median volume 26 cm^3

Authors, year of publication	Re-irradiation	SBRT dose (dose/fraction)	Median follow-up	Toxicity	Overall survival	Local control/pattern of failure
Bonomo et al., 2013[32]	Not reported	Most common 36 Gy in 3 fr (12 Gy/fr)	Mean 4.6 mo	No severe acute or late toxicity	All pts alive at last follow-up	Freedom of local PD: 100%. LC 90.9% in pts with prostate histology. Distant PD in 8 pts (25%)
Alongi et al., 2012[33]	No	45 Gy in 6 fr (7.5 Gy/fr)	195 days	Acute: G1–G2 in 4 pts; no ≥G3. Late: none.	Not reported	Overall response rate 82% (at median follow-up)
Corvò et al., 2013[34]	Yes in 3/33 pts (8%): median dose of previous RT 30 Gy	Median 35 Gy in 5 fr (7 Gy/fr) 1 fr/week	28 mo	Acute: G1–G2 in 24 pts, no ≥G3. Late: none	55% at median follow-up	LC in 30 pts (83%); 16 pts died at median follow-up (6 pts local PD, 10 pts distant PD)

Table 1 – (*Continued*)

Authors, year of publication	Re-irradiation	SBRT dose (dose/fraction)	Median follow-up	Toxicity	Overall survival	Local control/pattern of failure
Jereczek-Fossa et al., 2012[35] [a]	Yes for 20 lesions (21%). For 8 pts (9%) SBRT as boost	Mean 24 Gy in 3 fr (8 Gy/fr)	20 mo	Acute: G3: 2 events. Late: 8 pts (11.6%) G3: 2 G4: 1	3-year OS: 49.9%,	3-year LC: 64.3% 2-year PFS: 20% (dominant pattern of failure: out-field)
Bignardi et al., 2011[36]	No	Most common 45 Gy in 6 fr, (7.5 Gy/fr)	366 days	Acute: G1 in 1 pt, no ≥G2. Late: G1 in 1 pt, G3 in 1 pt	2-year OS: 93.3%	LC at 24 mo: 77.8% 2-year PFS 19.7% Patterns of failure: 2 pts local + distant; 2 pts only regional 7 pts distant PD
Casamassima et al., 2011[37]	Not reported	SBRT 30 Gy in 3 fr, (10 Gy/fr) in 18 pts; 24 Gy boost in 3 fr in 7 pts	29 mo	No ≥G1 events	3-year OS: 92%	Progression in 10 pts: - 2 pts bone - 8 pts LN (all out of field) (complete regression in 13 pts) 3-year DFS 17% 3-year LC 90%
Jereczek-Fossa et al., 2009[38]	No	Mean 30 Gy/3 fr (10 Gy/fr)	18.6 mo	Acute: none. Late: only G2 in 1 pt	8 NED, 4 AWD, 1 alive with biochemical failure, 1 died for other cause	No local recurrences; clinical PD in 5 pts after mean 12.7 mo No in-field PD Distant PD in 2 pts Regional PD in 3 pts
Kim et al., 2010[39]	Yes in 4 pts (44.4%)	30–39 Gy in 3 fr (10–13 Gy/fr)	23 mo	No ≥G3 toxicity	Not reported	5-year local PFS: 100% Regional failure in 4 pts (2 of them salvaged by additional SBRT) Distant PD in 4 pts
Kim et al., 2009[40]	No	Median 48 Gy in 3 fr (16 Gy/fr)	26 mo	Acute: G1 in 2 pts. Late: none	3-year OS: 43%	Local relapse in 1 pt (at 23 mo) Distant failure in 5 pts 3 year PFS: 29%
Choi et al., 2009[41]	SBRT as boost in 4 pts	33–45 Gy in 3 fr (11–15 Gy/fr) SBRT as boost: 13 Gy	Range 3–67 mo	Acute: ≥G3 in 5/30 pts during CHT (haematologic). Late: ≥ G3 in 1 pt	4-year OS 50.1%; median survival rate not reached	4 year LC: 67.4% 4 year PFS: 45% Relapse in 11 pts: locoregional alone 4 (13.8%), distant alone 3 (10.3%), locoregional + distant 2 (6.9%), recurrence at vaginal stump in 2 pts
Kim et al., 2009[42] [b]	No	Median 48 Gy (range 36–51 Gy) in 3 fr (16 Gy/fr)	26 mo	Acute: G1: 2/7 pts G4: 1 pt Late: none	3-year-OS 71.4%,	Local recurrence in 1 pt at 13 mo. after SBRT; regional recurrence in 1 pt; distant failure in 4 pts; 1 pt NED at 26 mo
Kim et al., 2008[43] [b]	In 4 pts	SBRT alone: median dose 39 Gy in 3 fr (13 Gy/fr); SBRT as boost: 16 Gy in single fr (NTD 65 Gy)	31 mo	Acute: G1–G2: 9 pts (39%) G4 in 1 pt None in the 4 reirradiated pts Late: none	5-year OS 23.2%	4 year LC: 74.3% PD in 45% (9/20) (2 local, 6 distant, 2 both). 4-year PFS 51.1%

Legend: Adj – adjuvant, ADT – androgen deprivation therapy, AWD – alive with disease, BED – biologically equivalent dose, CBK – CyberKnife, CHT – chemotherapy, CTV – clinical target volume, 3D-CRT – 3 dimensional conformal radiotherapy, DFS – disease free survival, EBRT – external beam radiotherapy, FFF – flattening filter free, 5-FU – 5-fluorouracil, fr – fractions, G1-G2-G3-G4 – grade 1, 2, 3, 4, GTV – gross tumor volume, IG-IMRT – image guided intensity modulated radiotherapy, IMRT – intensity modulated radiotherapy, LC – local control, LHRH – luteinizing hormone releasing hormone analogue, LN – lymph nodes, mo – months, mts – metastasis, NED – no evidence of disease, NTD – normalized total dose, OS – overall survival, PD – progressive disease, PFS – progression free survival, pts – patients, PTV – planning target volume, RT – radiotherapy, SBRT – stereotactic body radiotherapy, VMAT – Volumetric modulated Arc Therapy.

[a] Included updated information about 7 prostate cancer pts analyzed in previous report (Jereczek-Fossa et al., 2009[38]).

[b] Some patients are included in Kang et al. 2010[13] and Bae 2012[14].

Primary cancer was limited to miscellaneous origin, gastrointestinal malignancies, prostate, gynecological and thyroid cancer in 5, 3, 2, and 1, 1 articles, respectively (Table 1).

3.1.1.2. *Staging, target definition and concomitant therapy.* In the majority of the series staging was performed with use of total body contrast medium computer tomography (CT) and/or [^{18}F]fluoro-deoxy-glucose (or [^{11}C]choline in prostate cancer) positron emission tomography/CT scan (PET/CT). In only one series biopsy of target lesion was performed in a subset of patients.[35] In all cases patients received previous therapies and in some proportion SBRT was proposed as re-irradiation. Concomitant systemic treatment was allowed in some series.[35,38,41]

3.1.1.3. *SBRT technique and doses.* Various techniques were used for SBRT, including CyberKnife (in 5 articles all patients were treated with CyberKnife), Tomotherapy, RapidArc and other linacs. Fiducials were positioned mainly for CyberKnife treatment. Ablative doses were employed given in median 3 fractions (1–6 fractions) of 7–16 Gy each.

3.1.1.4. *Tumor outcome.* In all series overall response rate was excellent (up to 80%). Long term local control rate was very high and in some cases was 100%. The dominant pattern of failure was out-field: distant metastasis or regional lymph nodes. Regional lymph node recurrence occurred in about 10% of all patients and constituted about 50–80% of all events of progressive disease.

Three-year progression free survival (progression at any site) exceeded 20%[36,40] and seemed to be longer in gastrointestinal tumors.[40,43]

Overall survival rates up to 93.3% at 2 years[36] and 71.4% at 3 years[37] were observed.

3.1.1.5. *Toxicity.* Both acute and late toxicity was limited. Mainly mild (grade 1 or 2) acute events were observed and in the majority of the series no late toxicity was registered.[32–34,37,40–43] Median follow-up of about 2–3 years in all series might not allow for full toxicity evaluation.

3.1.2. *Series reporting SBRT for any oligometastatic site including lymph nodes*

Nineteen out of 31 clinical series reporting outcome included patients treated with SBRT for any site including lymph node recurrence[13–31] (Table 2). Nine studies (29%) were prospective, including 1 phase I trial.[22]

3.1.2.1. *Case profile and tumor sites.* Sixteen hundred lesions were treated with SBRT in 19 series and 286 were lymph nodes (18%). The treated sites included mainly abdomino-pelvic and miscellaneous areas. Three studies reported on the head and neck area only.[20,21,25] In the majority of series miscellaneous all primary cancer sites were treated and in some only gastrointestinal, genitourinary or head and neck malignancies were included (Table 2).

3.1.2.2. *Staging, target definition and concomitant therapy.* In the majority of the series staging was performed with use of total body contrast medium CT, magnetic resonance imaging (MRI) and/or [^{18}F]fluoro-deoxy-glucose (or [^{11}C]choline in prostate cancer) PET/CT scan. In only one series biopsy of target lesion was performed in a subset of patients.[15] In all cases patients received previous therapies and in some proportion SBRT was proposed as re-irradiation. Several SBRT courses were proposed in some series.[15–17,23,28–30] Concomitant systemic treatment was allowed in some series,[15–18] especially if prostate cancer patients were included (androgen deprivation).

3.1.2.3. *SBRT technique and doses.* In 7 reports CyberKnife was used for SBRT and in the remaining 12 – other linacs were employed. Fiducials were positioned mainly for CyberKnife treatment (in case of head and neck lesions – only for the tumors positioned below the 4th cervical vertebra).[21] Ablative doses were employed given in median 3 fractions (1–10 fractions) of 5–24 Gy each. Generally speaking higher median doses were employed in these reports when compared to the series including lymph node SBRT only (the doses to the lymph node and other lesions were not reported separately).

3.1.2.4. *Tumor outcome.* Local control rates were high and ranged from 61% to 67% at 1 year to 53–88%, 64–98%, 73–82% and 57% at 2, 3, 4 and 5 years after SBRT. Dose escalation was correlated with increase in local control.[22]

Progression was mainly out-field. Regional progression was reported in up to 36% of patients (including all sites of metastases).[14] In case of prostate and colorectal malignancies, recurrence limited to lymph nodes carried longer progression free survival when compared to the other recurrent sites (primary tumor or metastases).[13,15]

Overall survival rates were high and ranged from 80% at 1 year to 50–65%, 22–60% and 13–28% at 2, 3 and 5 years after SBRT (Table 2). Shorter overall survival was observed in lymph node recurrence from head and neck cancer when compared to other recurrence sites of this malignancy.[25]

3.1.2.5. *Toxicity.* Both acute and late toxicity was somehow higher than in the lymph node only series: acute toxicity was up to 77% and single late G4–G5 events were reported. Severe events included intestinal perforation or obstruction and were observed at high doses (48–51 Gy).[14] In particular, high toxicity was observed in the re-irradiation cases.[21]

4. Discussion

Our review showed that SBRT may be a safe and effective approach to oligometastatic lymph node recurrence, offering excellent in-field tumor control with low toxicity profile. The main limitations of our review include retrospective nature of the majority of the articles (65%), small number of patients included in each series (ranging from 1 to 69 patients), heterogeneity of histotypes, SBRT approaches and doses and recurrence site (lymph nodes versus all recurrence sites). To the best of our knowledge, no comparative studies (like case-control series etc.) have been published. The information on the patient- and treatment-related variables and outcome data (toxicity, tumor control) have been reported in incongruous manner. Therefore, we were able to perform only

Table 2 – Published clinical series including patients treated with SBRT for oligometastatic cancer (at any site, including lymph nodes).

Authors, year of publication	No. of LN treated/(the whole series)	Nature of study	SBRT technique	Primary site/histology	Systemic therapy	Fiducial markers	Treated volumes
Kang et al., 2010[13] [a]	41 (78): pelvic (29 ln) Para-aortic (11 ln, 7 pts) Mediastinal (1 ln, 1 pt)	Retrospective	CBK	Colorectal cancer	CHT before SBRT in 49/59 pts	Not reported	Cumulative CTV median volume for LN: 24 cm^3
Bae et al., 2012[14] [b]	19 (50); no. of pts treated on LN: 18 (41)	Retrospective	CBK	Colorectal cancer	Adj CHT in all pts; adj CHT after SBRT in 33 pts; neoadj CHT before SBRT in 21 pts	Not reported	Cumulative GTV volume for LN: median 18 cm^3; total cumulative GTV volume: median 13 cm^3
Jereczek-Fossa et al., 2012[15] [c]	18 (38) total number of pts: 34	Retrospective	CBK	Prostate cancer	ADT in 18 pts/21 lesions (12/18 LN mts lesions), estramustine in 1 pt	Yes in 26 lesions (68%), of which 9 LN mts (9/18)	Not reported
Jereczek-Fossa et al., 2013[16]	11 (118)	Prospective	CBK	Miscellaneous (excluded prostate cancer; mostly breast, lung, head/neck cancer)	Concomitant in 47/118 treatments (40%): CHT 32, HT 3, both 12	Yes in 8/118 total lesions (6.8%)	Not reported
Berkovic et al., 2013[17]	22(49), (11/24 pts)	Prospective (single arm study)	LINAC	Prostate cancer	Yes: single short acting LH-RH analog + antiandrogen 1 month before SBRT	Not reported	Not reported
Ahmed et al., 2013[18]	1/21	Prospective	IMRT and 3D-CRT	Prostate cancer	In 15 pts (88%) ADT after completion of SBRT	Not reported	Not reported
Hoyer et al., 2006[19]	3 pts/64 pts (5%)	Prospective phase II trial	LINAC	Colorectal cancer	Neoadj CT before SBRT in 33/64 pts (52%)	Not reported	GTV median diameter 35 mm
Kodany et al., 2011[20]	6 (34), 17% of total sites (cervical LNs)	Retrospective	CBK	Miscellaneous, mostly squamous cell carcinoma	No concomitant	Not reported	GTV median volume 11.6 cm^3
Roh et al., 2009[21]	11 (44): 8 neck LN and 3 retropharyngeal LN	Retrospective	CBK	Miscellaneous	In 21 pts (58.3%) previous CHT in 6 pts CHT after SBRT	Yes in pts with lesion below C4 level	Median GTV volume 22.6 cm^3
Greco et al., 2011[22]	14 (124)	Prospective, phase I	LINAC, single-dose IGRT, 6–15 MV photons, 7–9 coplanar fields	Miscellaneous (mostly prostate, renal cell, colorectal)	Not reported	Yes, if deemed necessary	PTV median volume 54.9 cm^3
Wersall et al.2005[23]	6 (162)	Retrospective	LINAC	Renal cell carcinoma	Prior systemic treatment in 15 pts	Not reported	Not reported
Salama et al., 2012[24]	22(113)	Prospective dose escalation study	LINAC (non overlapping axial and non coplanar fields), RPM when needed	Miscellaneous (mostly lung, breast, renal, squamous K of head and neck)	CHT not allowed, only HT allowed. Prior systemic therapy in 49 pts (80.3%)	Not reported	Median lesion size 2.5 cm
Kawaguchi et al., 2010[25]	8 of the 22 pts had LN mts (1 limited recurrence with LN)	Prospective	CBK	Squamous cell carcinoma of head&neck	Low dose oral 5-FU from 1 mo after SBRT	Not reported	GTV median volume 24.5 cm^3

Table 2 – (*Continued*)

Authors, year of publication	No. of LN treated/(the whole series)	Nature of study	SBRT technique	Primary site/histology	Systemic therapy	Fiducial markers	Treated volumes
Scorsetti et al., 2011[26]	4(70), isolated abdominal LN	Prospective	VMAT (RapidArc) with FFF beams	Not reported	Not reported	Not reported	PTV volume in abdominal lesions: $115 \pm 82\ cm^3$
Scorsetti et al., 2011[27]	12 (37) retroperitoneal LN	Retrospective	VMAT RapidArc	Miscellaneous (mostly colorectal, pancreatic)	No	Not reported	Max axial diameter: median 35 mm, for abdominal LN: median 23.5 mm
Milano et al., 2008[28]	28 pts (121) (24 pts thoracic LN, 4 pts pelvic/abdominal LN)	Prospective	LINAC conformal arcs or multiple fixed coplanar beams	Miscellaneous (mostly breast, colorectal)	No	Not reported	Median sum of GTVs $28\ cm^3$ mean $52\ cm^3$
Milano et al., 2008[29 d]	39 (293) (33 thoracic, 6 abdomino-pelvic LN)	Retrospective	LINAC conformal arcs or multiple fixed coplanar beams	Miscellaneous (mostly breast, colorectal)	Not reported	Not reported	Thoracic LN: median $19\ cm^3$ abdomino/pelvic LN: median $7.2\ cm^3$
Milano et al., 2009[30 e]	21 (155) 32 pts (of 121 total pts) undergoing ≥2 SBRT courses/total of 155 lesions	Retrospective	Conformal arcs or multiple fixed coplanar beams	Miscellaneous	Not reported	Not reported	GTV median volume $6\ cm^3$, mean $4\ cm^3$

Authors, year of publication	Re-irradiation	SBRT dose	Median follow-up	Toxicity	Overall survival	Local control/pattern of failure
Kang et al., 2010[13 a]	Not reported	SBRT alone (26 pts): 36–51 Gy in 3 fr, NTD 66–115 Gy. SBRT as boost (5 pts): 16 Gy in single fr, NTD 35 Gy (+40–45 Gy EBRT)	32 mo	Pelvic LN: G1–G2: 9/23 pts; G4: 1/23 pts[a] Para-aortic LN: G1–G2: 2/7 pts; G4: 1/7 pts[a]	3-year OS 49%	3-year LC 66% 3 year PFS 25% Failure pattern NED 21 pts PD 35 pts (local 8, distant 11, regional 8)
Bae et al., 2012[14 b]	In 1 case, after previous SBRT	For LN mts: median 48 Gy, (45–51 Gy) in 3 fr	28 mo	Acute G1–G2: 17 pts (39%) Late ≥G3 in 3 pts (7%): liver, pelvic LN, paraortic LN[b]	3-year and 5-year OS: 60% and 38%	3-year and 5-year LC: 64% and 57% PD in 23/41 pts (56%): 14 local, 15 regional, 14 distant, 9 local + regional + distant
Jereczek-Fossa et al., 2012[15 c]	In 27/38 lesions (71%), of which 8 LN mts (8/18)	Median 30 Gy in 4.5 fr (for LNs: 33 Gy/3 fr)	16.9 mo	None in 68% of pts. Acute: 1 G3 LN SBRT (1/16 = 6%) Late G3: 2 (6%)	At the time of analysis: 19 pts NED, 15 pts AWD	PFS at 12 mo 68.1% at 18 and 30 mo. 42.6% (63.5% in LN group) PFS longer in case of LN recurrence (median PFS > 30 mo) than for other sites (11–14 mo) In-field PD only in 3 cases (not LN or M), 8%
Jereczek-Fossa et al., 2013[16]	Yes in 47/118 total lesions (40%)	Median 24 Gy in 3 fr	12 mo	Acute: none in 85% of treatments. G1–G2: 14 G3: 4 Late: G1–G2: 3 G3: 5	3-year OS 31.2% 3-year CSS 39.6%	3-year LC: 67.6% 3-year PFS: 18.4%

Table 2 – (*Continued*)

Authors, year of publication	Re-irradiation	SBRT dose	Median follow-up	Toxicity	Overall survival	Local control/pattern of failure
Berkovic et al., 2013[17]	Not reported	Median 50 Gy in 10 fr BED: 80 (if $\alpha/\beta = 3$); 92 (if $\alpha/\beta = 1.5$)	24 mo	Acute: G2: 14% No ≥G3 Late: G2 9% No ≥G3	12 pts AWD at last FU, 1-year ADT-FS 82%, 54% at 2 years; median deferment of ADT: 38 mo	LC 100%, no in-field PD Pattern of recurrence: 11 pts oligometastatic, 6 pts multiple metastasis, 3 pts only biochemical 2-year PFS: 42%
Ahmed et al., 2013[18]	Not reported	Dose to LN: 50 Gy in 5 fr	For LN: 4.4 mo	Acute: G1–G2: 3 cases (for LN no acute toxicity) No late toxicity	12 mo CSS 100%	2 pts died for distant PD at last FU 12 months FFDP 40%
Hoyer et al., 2006[19]	Yes in 1 pt	45 Gy in 3 fr	4.3 years, 1 pt lost to FU	(within 6 mo): G4: 1 pt G3: 3 pts	3-year and 5-year OS: 22% and 13%	2 year LC: 79% Local failure in 10/141 lesions progression pattern: 1 pt only local, 9 pts local + distant 2-year PFS 19%
Kodany et al., 2011[20]	Yes in 21/34 pts (65%). Median dose of previous RT 60 Gy, median interval 51 mo	Median 30 Gy in 5 fr	16 mo	Acute: none Late: severe in 6 pts (18%), all in re-RT	1-year OS 70.6%, 2-year OS 58.3% median survival 28 mo	Overall response rate 61.9%
Roh et al., 2009[21]	Yes (all 11 LN). Median dose of previous EBRT 70.2 Gy, median interval 24 mo	Median 30 Gy in 3–5 fr	17.3 mo. 35 of the 44 sites followed at last assessment (80%)	Acute in 24 pts (G1-G3) Late in 3 pts 8.6% 1 treatment-related death (33 Gy in 3 fr to retropharyngeal LN)	1-year OS and 2-year OS 52.1% and 30.9%	1-year and 2-year LC: 61% and 52.2% Pattern of failure: local in 17 pts (in field 14.5%, out field 8.6%, marginal 5.7%), regional 2 pts (5.7%), distant 3 pts (8.6%)
Greco et al., 2011[22]	No	Median 24 Gy in single fr (starting from 18 to 20 Gy, than from 2006 22–24 Gy)	18 mo, no pts lost to FU	Acute G3 in 2 cases Late ≥G3 in 11/103 pts, overall incidence of G3 late tox < 4%	Not reported	2 year LC 64% 29 local failures 2 year LC 82% for high doses (23–24 Gy), 25% for low doses (18–20 Gy), 69% for intermediate doses (21–22 Gy). 2 year LC for LN: 67%
Wersall et al.2005[23]	Not reported	Most frequent: 10 Gy × 3–4 (2–5 fr, with 5–16 Gy/fraction)	37 mo for pts alive at censor date; 13 mo for uncensored pts	In 23/58 pts 50% G1–G2; G4 in 1 pt	Median survival time: 19- > 58 mo	LC rate: 98% Distant failure in 73%
Salama et al., 2012[24]	Not allowed	Starting dose: 24 Gy (8 Gy × 3); dose ceiling was 60 Gy (20 Gy × 3) for all cohorts	20.9 months	Acute: G3: 2 Late: G3: 6 (1 GI bleeding for para-aortic LN treated with 24 Gy)	1-year, 2-year OS: 81.5%, 56.7%	1-year and 2-year LC: 67.2% and 52.7%; 1 year, 2 year PFS: 33.3%, 22% Patterns of failure: In 7 pts (11.7%) in field PD as first progression 33 pts (55%) only distant PD

Table 2 – (*Continued*.)

Authors, year of publication	Re-irradiation	SBRT dose	Median follow-up	Toxicity	Overall survival	Local control/pattern of failure
Kawaguchi et al., 2010[25]	Yes in 14 pts; previous RT dose 40–65 Gy in 1.5–2 Gy daily fractions, median interval 11 mo	Median 33.73 Gy (range 20–42 Gy) in 2–5 fractions	24 mo	Acute: G2: 17 pts (77.3%) G3: 5 pts (all in re-RT) Late: G1: 11 ptsG2: 3 pts	2 year OS in pts without LN mts 78.6% vs 12.5% in pts with LN mts	CR maintained at a median 2-years follow-up in 10/22 pts (45.5%)
Scorsetti et al., 2011[26]	Not reported	45 Gy in 6 fractions	Minimum follow-up 3 mo	Acute tox: 2 G2 in abdomen	Not reported	Early LC in 89% Outcome at 1st evaluation (55 pts evaluable of 70): CR 10, PR 26, SD 13, PD 6
Scorsetti et al., 2011[27]	Not reported	45 in 6 daily fractions (7.5 Gy/fr) for LN mts	12 mo	Acute: G1 in 5 pts Late: G3 in 1 pt G1 in 1 pt	Not reported	6-mo crude LC rate: 79.2%
Milano et al., 2008[28]	In 6 pts	Preferred schedule 50 Gy in 5 Gy-fractions over 2 weeks	41 mo	G1 in 1 pt G2 in 3 pts	2-year and 4-year OS: 50% and 28%	2-year and 4-year LC: 77% and 73% 2-year and 4-year PFS: 26% and 20% 15/121 pts only local failure 29/121 pts distant + local failure
Milano et al., 2008[29] [d]	8 thoracic LNs received SBRT as a boost after mediastinal RT	For SBRT: 30–68 Gy (3–8 Gy/fr) BED 31–72 Gy (median 62.5 Gy, mean 57.5 Gy)	41 mo		Alive at last follow-up: 89 pts Censored (death): 147	2-year and 4-year LC: 77% and 73% Local failure in 57/293 lesions No documented local failure in 236/293 lesions
Milano et al., 2009[30] [e]	12 lesions undergoing salvage repeated SBRT	Not reported (see previous studies)	Not reported(see previous studies)	No ≥ G2 toxicity in the 9 pts reirradiated for a locally recurrent lesion	2-year and 4-year OS: 65% and 33%	2-year and 4-year LC: 88% and 82% 2-year and 4-year PFS: 54% and 28% 18/155 lesions failed locally 19/32 pts developed DM not amenable to curative-intent treatment

Legend: Adj – adjuvant, ADT – androgen deprivation therapy, ADT-FS – androgen deprivation therapy free survival, AWD – alive with disease, BED – biologically equivalent dose, CBK – CyberKnife, CHT – chemotherapy, CR – complete response, CSS – cancer specific survival, CTV – clinical target volume, 3D-CRT – 3 dimensional conformal radiotherapy, DFS – disease free survival, DM – distant metastases, EBRT – external beam radiotherapy, FFF – flattening filter free, fr. – fractions, 5-FU – 5-fluorouracil, G1–G2–G3–G4 – grades 1, 2, 3, 4, GTV – gross tumor volume, HT – hormonal therapy, IG-IMRT – image guided intensity modulated radiotherapy, IGRT – image guided radiotherapy, IMRT – intensity modulated radiotherapy, LC – local control, LHRH – luteinizing hormone releasing hormone analogue, LN – lymph node, mo – months, mts – metastasis, NED – no evidence of disease, Neoadjuv – neoadjuvant, NTD – normalized total dose, OS – overall survival, PD – progressive disease, PFS – progression free survival, PR – partial response, pts – patients, PTV – planning target volume, RT – radiotherapy, SBRT – stereotactic body radiotherapy, SD – stable disease, tox – toxicity, VMAT – Volumetric modulated Arc Therapy.

[a] It includes some patients considered in Kim et al., 2009[42] (the patient with G4 toxicity treated on para-aortic node is the same) and Kim et al. 2008[43] (the patient with G4 toxicity treated on pelvic node is the same).

[b] It includes some patients considered in Kim et al., 2009[42] (the patient with G4 toxicity treated on paraortic node is the same), Kim et al., 2008[43] (the patient with G4 toxicity treated on pelvic node is the same), it evaluates the results of high doses > 45 Gy (escalation up to 60 Gy for liver and lung metastases, not for lymph nodes due to G4 toxicity at 48 and 51 Gy).

[c] 7 pts with lymph node recurrence included in the preliminary report, Jereczek-Fossa et al., 2009,[38] have included in this series with updated follow-up.

[d] Descriptive analysis of the 121 pts considered in the previous prospective study Milano et al., 2008.[28]

[e] Analysis of oligometastatic patients undergoing 2 or more curative-intent SRT courses: about 32 of 121 pts considered in the prospective study Milano et al., 2008,[28] those treated with 2 or more SBRT courses.

descriptive analysis. The impact of dose (physical or normalized) and fractionation on tumor control remains to be established.[22,29] The effect of tumor volume on the local control has been observed in some studies,[29] but clear conclusion cannot be drawn at present. Despite these constraints, we do believe that our review adds new insight to the current knowledge on cancer recurrence and its therapeutic options. Ablative dose SBRT has revealed as an high-precision, non-invasive, short, well tolerated and convenient approach in the patients that otherwise would be offered long lasting systemic palliative treatment like chemotherapy, androgen deprivation etc. Progress in cancer imaging (early diagnosis of small volume primary or metastatic tumors) and the development of high precision radiotherapy will probably lead to further intensification of local treatment, increasing its role in cancer management.[44–46]

According to our review, cure may be obtained in a small but constant patient percentage (20–30% at 2 years) and in many long treatment-free interval can be observed.[17] This last endpoint has been only recently introduced in the cancer research methodology and reflects the importance of quality of life issues, cost-effectiveness evaluation and last but not least, possibility of making cancer a chronic condition.[47] Indeed, a new paradigm of the "chronic curable cancer" has been recently proposed.[47]

Lymph node only recurrence constitutes a particular clinical situation. A patient is usually asymptomatic and burden of the disease is extremely low. Surgery for lymph node recurrent tumor might be challenging, and is limited by the previous therapies that could lead to the high morbidity and the risk of macro- or microscopic residual disease. Extended field external beam radiotherapy can also carry a risk of normal tissue injury especially if the treated volumes are overlapping with the previous surgical or radiotherapy area and high doses are used. SBRT with extremely limited normal tissue irradiation may overcome these difficulties. As shown in our review, acute toxicity was low and only single severe late events were reported, limited to the cases of high SBRT dose to the near visceral organs (mainly bowel). These findings are easily explained by both intrinsic features of SBRT (i.e. extremely high precision in dose delivery) and typically small volume of lymph node recurrence. In fact, the toxicity was somehow higher in the series reporting SBRT for any tumor site including lymph node where the toxicity was not reported separately for lymph nodes and other sites. Non-lymph node recurrences have usually bigger volumes leading to higher toxicity rates in the mixed series when compared to the lymph node series only.

Regional progression (disease occurrence in other, non irradiated lymph node) is greatly feared when SBRT is employed. Indeed, some authors suggest elective conventional radiotherapy to the lymph node region combined with SBRT boost to the positive lymph node.[12] Based on the current review, between 10% and 30% of the patients treated with SBRT for single lymph node recurrence will recur in other lymph node and in these cases further SBRT is often feasible.[17,35] The risk factors for regional progression cannot be defined due to the small number of cases in each series. However, higher risk of regional progression (30%) was reported in all-sites series when compared to the isolated lymph node recurrence only (10%). This finding suggests that more advanced cases were included in the former series. Distant metastases, primary recurrent, visceral metastases etc. are well known to have worse prognosis when compared to the isolated lymph node recurrence.

The mechanism of effect of SBRT on the cancer lesions is not yet clear. Apart from the direct effect of SBRT on clonogenic cancer cells, an abscopal effect (a regression of non-irradiated lesions distant from the irradiated tumor site) was also hypothesized.[6] This out-of-field systemic phenomenon has been observed in numerous malignancies (renal cancer, melanoma, lung cancer), however, its mechanisms are not yet well understood and include several post-radiation anti-tumor immune processes and inflammatory reactions.[48–50] Reduction of cancer cell seeding was also suggested.[5] These effects might be enhanced when targeted drugs and SBRT body radiotherapy are combined.[48–50]

In conclusion, our review suggests feasibility and efficacy of SBRT in the isolated lymph node cancer recurrence. Future studies are urgently warranted to identify the patients that benefit most from this treatment. The optimal combination with systemic treatment should also be defined. The mechanisms of SBRT interaction with cancer cells and the potential effect of the drug-SBRT combination should also be investigated.

Conflict of interest

None declared.

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