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REVIEW

Long-term outcomes of interventions for radiation-induced xerostomia: A review

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Abstract

Xerostomia, or dry mouth, is a significant problem affecting quality of life in patients treated with radiation therapy for head and neck cancer. Strategies for reduction of xerostomia burden vary widely, with options including: sialagogue medications, saliva substitutes, acupuncture, vitamins, hyperbaric oxygen, submandibular gland transfer, and acupuncture or associated treatments. In this review, we sought to evaluate long-term outcomes of patients treated with various interventions for radiation-induced xerostomia. A literature search was performed using the terms "xerostomia" and "radiation" or "radiotherapy"; all prospective clinical trials were evaluated, and only studies that reported 1 year follow up were included. The search results yielded 2193 studies, 1977 of which were in English. Of those, 304 were clinical trials or clinical studies. After abstract review, 23 trials were included in the review evaluating the following treatment modalities: pilocarpine (three); cevimeline (one); amifostine (eleven); submandibular gland transfer (five); acupuncture like transcutaneous electrical nerve stimulation (ALTENS) (one); hyperbaric oxygen (one); and acupuncture (one). Pilocarpine, cevimeline, and amifostine have been shown in some studies to improve xerostomia outcomes, at the cost of toxicity. ALTENS has similar efficacy with fewer side effects. Submandibular gland transfer is effective but requires an elective surgery, and thus may not always be appropriate or practical. The use of intensity-modulated radiation therapy, in addition to dose de-escalation in select patients, may result in fewer patients with late xerostomia, reducing the need for additional interventions.

Key words: Xerostomia; Radiation therapy; Radiotherapy; Head and neck cancer; Quality of life

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Core tip: Xerostomia is a common side effect of radiation for head and neck cancer, and can impact patient quality of life even years after treatment. In this review, we sought to evaluate the current literature regarding long-term outcomes of interventions for radiation-induced xerostomia, including medical management, submandibular gland transfer, acupuncture, acupuncture like transcutaneous electrical nerve stimulation, and hyperbaric oxygen.

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INTRODUCTION

Head and neck cancer patients treated with radiation experience changes in their quality of life due to radiation-induced dry mouth or xerostomia[1]. Complications include trouble eating, speaking, and swallowing, which can lead to depression and limited social activities[2,3]. Xerostomia can be avoided by reducing the mean radiation dose delivered to parotid and submandibular glands[4-9]. Intensity-modulated radiation therapy (IMRT) to spare parotid glands has been shown to reduce the incidence of xerostomia and improve quality of life[10-16]. However, despite the improvements seen in quality of life, select patients report persistent xerostomia after IMRT[17,18].

Standard care for radiation-induced xerostomia in head and neck cancer patients remains sialogogue medications, such as pilocarpine and cevimeline[19]. However, these medications have been shown to cause complications such as nausea and sweating[20], in some cases leading to patients withdrawing from the study[21,22] Numerous alternatives have been studied for xerostomia treatment, including amifostine[23], bethanechol[24], saliva substitutes[25], palifermin[26], alpha-tocopherol[27], vitamin C/E[28], thyme honey[29], herbal products, acupuncture[30], transcutaneous electrical nerve stimulations, submandibular gland transfer surgery[31], gene therapy[32], hyperbaric oxygen[33], and hyperthermic, supersaturated humidification—many of which have been reviewed previously in a meta-analysis by Mercadante *et al*[19]. However, few studies have long-term follow up data for interventions. We performed this review to evaluate various interventions for the long-term management of radiation-induced xerostomia.

LITERATURA RESEARCH

We performed a review of journal articles in English in July 2018. Our inclusion criterion was any prospective clinical trial reporting clinical outcomes of interventions for radiation-induced xerostomia, with evaluation for late xerostomia at least 1 year after the radiation or intervention. The exclusion criteria were: (1) review articles, retrospective studies, letters, or case reports; (2) studies that did not show the most updated results when multiple journal articles published from the same patient cohort; (3) xerostomia unrelated to prior radiation therapy; and (4) the use of radioiodine or radionucleotide as a treatment.

PubMed electronic databases were queried in July 2018 for search terms such as "xerostomia", "radiotherapy", and "radiation". This database query initially resulted in 2193 studies. Of these, 304 studies were prospective trials written in English. With our exclusion criteria, these studies and their reference lists were reviewed to be considered for inclusion (Figure 1).

Twenty-three studies are selected for analysis (Tables 1-6). Of these, three studies evaluated pilocarpine; one evaluated cevimeline; eleven studies evaluated amifostine; five evaluated submandibular transfer; one evaluated ALTENS; one evaluated hyperbaric oxygen; and one evaluated acupuncture. Below we review the results of the studies.

Figure 1 Literature research flowchart.

PILOCARPINE AND CEVIMELINE

Pilocarpine, a cholinergic agonist, has shown mixed results in the treatment of radiation related xerostomia. Burlage *et al*[34] evaluated 170 patients randomized to either oral pilocarpine or placebo during radiation therapy. Based on LENT SOMA score, there was no statistical difference between the two arms at one year. However, based on patient reported xerostomia, pilocarpine significantly reduced symptoms in patients who received > 40 Gy mean dose to the parotid. Toxicity was relatively low in this, with 2 patients withdrawing from the study–one in the pilocarpine group (due to sweating) and one in the placebo group due to a suspected adverse event. The only grade 2 reported toxicity was excessive sweating in one patient. In study by Mateos *et al*[35], 49 patients were divided into two groups. One group received pilocarpine during RT and throughout the year that followed, while the other received radiation alone. Visual analogue scale (VAS) revealed no subjective difference between the two groups. Dynamic salivary scintigraphy also showed no statistically significant advantage to pilocarpine. In contrast, Valdez *et al*[36] reported a series of 9 patients receiving either pilocarpine for 3 mo or placebo. Based on patient reports surveys, there were significantly fewer symptoms of xerostomia in the pilocarpine group. Interestingly, in this small number of patients, there was a statistically significant difference between the groups in stimulated parotid salivary function at 3 mo. No pilocarpine related toxicities were reported.

Cevimeline has also been studied as an oral agent for treatment of xerostomia. Chambers *et al*[37] reported a single arm trial of 255 patients taking cevimeline for 1 year. At final evaluation, 59.2% of patients had improved symptoms based on mean global evaluation score, with 37.3% showing no change, and 3.5% with worsening symptoms compared to initial visit. The rate of grade3 toxicity was 20.4% and consisted mostly of sweating; 7.1% of patients experienced a severe adverse event, one of which (miscarriage) was possibly attributed to the study drug. Overall the authors conclude that cevimeline was well tolerated and may provide relief of xerostomia in head and neck cancer patients.

AMIFOSTINE

Eleven papers studying amifostine met inclusion criteria. Büntzel *et al*[38] reported on 39 patients randomized to either IV amifostine 500 mg with carboplatin (days 1-5 and days 21-25) during concurrent chemoradiation, or to chemoradiation alone. The authors report that grade 3 mucositis, grade 2 xerostomia, and grade 3 thrombocytopenia were all significantly decreased in the amifostine group. Brizel *et al*[39] also found an advantage with amifostine, reporting on 303 patients treated with either radiation along or amifostine 200 mg/m^2 15-30 min prior to each RT dose.

Table 1 Pilocarpine and Cevimeline

Author	Type of study	*n*	Intervention	Xerostomia symptoms	Salivary Function	Toxicity
Burlage *et al*[34], 2008	Double-blind, randomized, placebo-controlled trial	170	PC during RT *vs* placebo	LENT SOMA: no difference at 1 yr; Patient-reported xero: significantly lower scores in pilocarpine group at 12 mo only if mean parotid dose > 40 Gy	Parotid flow rate complication probability (PFCP): at 1 yr, no diff between arms (except in subset of pts with > 40 Gy mean parotid dose-reduced loss of flow in pilocarpine group)	2 patients didn't complete treatment, excessive sweating for PC and suspected AE for placebo pt; 1 G2 excessive sweating
Mateos *et al*[35], 2001	Prospective non-randomized study	49	PC 5 mg TID during RT and for 1 yr *vs* no PC	No significant difference in visual analogue scale between groups	Dynamic salivary scintigraphy: no SS differences between groups	NA
Valdez *et al*[36], 1993	Double-blind, randomized, placebo-controlled trial	9	PC 5 mg four times daily for 3 mo during RT *vs* placebo	Significantly fewer subjective oral symptoms in pilocarpine group on survey during treatment; no difference at 1 yr (25% in both arms)	Salivary flow rate (resting and stimulated): smaller losses in stim function in PC group at 3 mo (SS)	none reported
Chambers *et al*[37], 2007	Open-label prospective single-arm study	255	Cevimeline for 1 yr 45 mg TID orally	Used mean global eval. score (0-3), at final eval. 59.2% improved, 37.3% no change, 3.5% worse compared with first visit ($P < 0.0001$ change from baseline to visit 8)	NA	20.4% G3 AE, most common was sweating; 7.1% severe AE, one possibly attributed to study drug (miscarriage)

PC: Pilocarpine; G: Grade; AE: Adverse event; xero: Xerostomia; pts: Patients.

Grade 2 xerostomia was significantly improved in the amifostine group compared with control (51% *vs* 78%, $P < 0.0001$); in addition, a higher threshold dose of radiation was required to cause grade 2 xerostomia in the amifostine group. This study also quantified whole saliva production (WSP) during RT and at follow up; there was significantly higher saliva production in the amifostine patients at 1 year. In terms of amifostine toxicities, 53% of patients experienced nausea and vomiting (5% of total amifostine administrations, with 3% grade3 nausea and 5% grade3 vomiting). Other complications included hypotension, venous catheter complications, infections, and clotting/vascular disorders. Many of these were related to the IV method of administration. The authors concluded that amifostine reduces xerostomia, although alternative delivery methods should be evaluated. In contrast, a separate study did not report significant administration-related toxicities with the use of IV amifostine 300 mg/m^2 prior to RT[40]. This randomized trial assigned patients to either chemoradiation alone or chemoradiation with prophylactic amifostine. Toxicities reported included nausea/vomiting (1 patient) and transient hypotension (13.6%). By week 3 of radiation treatment, 100% of the control group and 9.1% of the study group had grade 2 mucositis; by week 5, 97.5% of control group was reported to have moderate to severe mucositis, and 63.6% of the study group. Additionally, treatment duration was significantly shorter in the amifostine group, due to more treatment interruptions from grade 4 mucositis.

Two additional studies evaluated the efficacy and safety of IV amifostine. A randomized trial by Buentzel *et al*[41] included 132 patients randomized to either IV amifostine 300 mg/m^2 on days 1-5 and 200 mg/m^2 on other days of RT, or placebo. In contrast to prior studies mentioned, there was no difference in acute or late xerostomia based on RTOG criteria. There was, however, a difference in toxicity, with a 43% *vs* 20% grade 3 toxicity rate (amifostine and placebo groups, respectively). Of note, less than 1/3 of patients were evaluated at the 1 year time point. Wasserman *et al*[42] included 303 patients randomized to either amifostine 200 mg/m^2 prior to each radiation fraction, or radiation alone. With 2 years of follow up, the amifostine group had: lower grade 2-4 chronic xerostomia, increased unstimulated saliva scores, and

Table 2 Amifostine: Xerostomia

Author	Type of study	*n*	Intervention	Xerostomia symptoms	Effect Size
Bardet *et al*[46], 2011	Phase III randomized trial	291	Amifostine IV *vs* SC	RTOG grading: G2+ xero significantly higher in SC at 1 yr, but not at 2-3 yr	37% IV *vs* 62% SC
Haddad *et al*[45], 2009	Phase II randomized trial	58	SC amifostine 500 mg daily (for median 28 doses) no amifostine	CTCAE: no significant difference in Gr2+ xero (minimum follow up 26 mo)	41% both arms
Law *et al*[44], 2007	Phase II prospective nonrandomized trial	20	SC 500 mg amifostine 30-60 min before RT	G2 xero 42% at 12 mo, 29% at 18 mo; no G3+ xero. G3+ mucositis in 30% of pts.	
Anné *et al*[43], 2007	Phase II single arm multicenter trial	54	SC amifostine	RTOG scoring: G2+ xero = 56%; late G2+ in 45% ; G3+ acute 33%	
Jellema *et al*[23], 2006	Phase II randomized trial	91	No amifostine *vs* 200 mg/m^2 IV daily (3 wk) *vs* 5 wk	RTOG scoring: significant difference in late G2+ xero at 6 mo between arms; no difference in xero at 12 mo or 24 mo; no dif in acute xero EORTC QLQ-H and N35: significantly higher mean xerostomia score in no amifostine group	Late G2+ xero 74% *vs* 67% *vs* 52%
Buentzel *et al*[41], 2006	Phase III randomized placebo-controlled trial	132	IV amifostine 300 mg/m^2 days 1-5 and 21-25, 200 mg/m^2 on other days *vs* placebo	RTOG criteria: no significant difference in G2+ acute or late xero	39% amifostine *vs* 34% placebo (acute); 39% amifostine *vs* 24% placebo (late)
Wasserman *et al*[42], 2005	Phase III randomized trial	303	IV amifostine 200 mg/m^2 15-30 prior to each RT fraction *vs* no amifostine	RTOG scoring: significantly lower G2+ xero in amifostine group on longitudinal analysis	20% *vs* 36% at 24 mo
Thorstad *et al*[47], 2004	Pilot clinical trial	27	Amifostine concurrent with RT (500 mg SC daily)	not reported	NA
Antonadou *et al*[40], 2002	Randomized controlled trial	50	Amifostine 300 mg/m^2 15-30 min prior to RT (daily) *vs* no amifostine	RTOG/EORTC scoring: significantly lower xero in amifostine group at 18 mo (G1+)	30.4% *vs* 4.5%
Brizel *et al*[39], 2000	Phase III multiinstitutional randomized trial	303	Amifostine 200 mg/m^2 15-30 min prior to each RT tx *vs* no amifostine	RTOG scoring: significantly higher G2+ xero (acute and late) in control *vs* amifostine; higher dose required to cause G2 xero in amifostine pts (60 Gy *vs* 42 Gy);	78% *vs* 51% (acute); 57% 43% (1 yr)
Büntzel *et al*[38], 1998	Phase II randomized trial	39	Amifostine IV 500mg prior to carboplatin (days 1-5 and 21-25) *vs* no amifostine	Acute G2 xero, G3 mucositis, and G3 thrombocytopenia all significantly decreased with amifostine; at 12 mo, trend toward xero improvement with amifostine	Xero: G2 100% *vs* 12% (acute); 55% *vs* 17% (late; P = 0.05)

SC: Subcutaneous; G: Grade; xero: Xerostomia; pts: Patients.

better patient reported mouth dryness.

As an alternative delivery method, subcutaneous administration of amifostine has been evaluated in four trials with mixed results. Two phase II single arm trials, with 54 and 20 patients each, treated patients with subcutaneous amifostine and compared results to prior studies using IV, and showed similar results in terms of efficacy[43,44]. One phase II randomized study of 58 patients compared subcutaneous amifostine with no amifostine, and found no significant difference between the two arms[45]. A phase III randomized controlled trial assigned 291 patients to either IV or subcutaneous amifostine[46]. The authors found no significant benefit in terms of

Table 3 Amifostine: Salivary function, quality of life, toxicity

Author	Salivary Production	QOL	Toxicity
Bardet *et al*[46], 2011	No difference in unstimulated and stimulated salivary flow rate =	No difference in patient-reported salivary function or Gr 2+ xero	No difference in compliance between arms (69% IV *vs* 71% SC). Acute toxicity 25% IV *vs* 27% SC (NS). SS higher rate of hypotension in IV arm; significantly higher skin rash and local pain in SC arm.
Haddad *et al*[45], 2009	No difference in unstimulated or stimulated saliva at all endpoints (up to 1 yr)	No difference in penetration, aspiration, and pharyngeal residue on swallow eval.	G3 mucositis in 75% (amifostine) and 70% (no amifostine); Gr3 skin toxicity in 12 patients in amifostine group (main reason for withholding amifostine)
Law *et al*[44], 2007	NA	NA	G2 weight loss for all pts, Gr2 or less N/V in 7 pts (35%). No grade 3+ amifostine-related AEs.
Anné *et al*[43], 2007	NA	PBQ: mean score 8.5 baseline, 6.1 at 4 wk, 7.5 at 1 yr	Nausea, emesis, injection site reaction most common G1-2; G3 dehydration 11%, rash 6%, weight decrease, mucositis, dyspnea, allergic reaction 4% each; one G4 anaphylaxis
Jellema *et al*[23], 2006	NA	QLQ-C30, QLQ-H and N35: no differences in sticky saliva or other QOL data	Significantly higher N/V in amifostine groups; 28% of patients discontinued amifostine early
Buentzel *et al*[41], 2006	not assessed: fewer than one-third in each arm had salivary assessment at 1 yr	NA	42% G3+ toxicity (amifostine) *vs* 20% (placebo) (SS)
Wasserman *et al*[42], 2005	no dif. in stimulated; unstimulated higher in amifosine group at 12 mo (SS)	PBQ: amifostine group had SS better mouth dryness at 12, 18, and 24 mo; better score for "use of oral comfort aids" with amifostine at 24 mo	not enough to analyze
Thorstad *et al*[47], 2004	not reported	not reported	reasons for discontinuing amifostine: nausea (33%), rash (15%), fever (7%), other (11%)
Antonadou *et al*[40], 2002	NA	NA	SS lower acute mucositis and acute dysphagia in amifostine group; in amifostine group, 1 pt had N/V, 3 pts had transient hypotension
Brizel *et al*[39], 2000	Whole saliva production higher in amifostine pts at 1 yr (SS)	PBQ: overall score favored amifostine at 1 yr (SS)	53% nausea and vomiting (5% of total administrations; 3% G3 N, 5% G3 V)); G3 N/V in 7% of pts; median weight loss higher in control group (SS); hypotension 15% (3% G3; < 1% of all doses); venous catheter complications 5%; infections 14%; clotting/vascular 3% (1 pt G4); allergic reaction 5%
Büntzel *et al*[38], 1998	NA	NA	No significant difference in N/V between groups; hypotension 40% amifostine arm (max drop 20 mmHg)

QOL: Quality of life; SC: Subcutaneous; G: Grade; AE: Adverse event; xero: Xerostomia; NA: Not available; PBQ: Patient benefit questionnaire; pts: Patients.

patient compliance or efficacy with subcutaneous administration, suggesting that IV should remain the standard treatment. Thorstad *et al*[47] report toxicity results of a pilot study of 27 patients assessing subcutaneous amifostine delivered concurrently with IMRT. Although compliance rate was not reported, the authors report that not all patients tolerated the treatment, with nausea, rash, and fever being the main complaints that caused discontinuation of amifostine.

SALIVARY GLAND TRANSFER

Five studies evaluating salivary gland transfer met criteria for inclusion. In a phase II single arm study of 57 patients, Jha *el al*[48] reported that submandibular salivary gland transfer to the submental space is feasible and safe, with 81% of patients reporting none or minimal xerostomia with median follow up of 14 mo. One phase II prospective non-randomized trial of 38 patients showed improved stimulated and

Table 4 Submandibular gland transfer: Xerostomia

Author	Study design	*n*	Intervention	Xerostomia symptoms	Effect size
Zhang *et al*[31], 2014	Randomized controlled trial	65	Submandibular transfer *vs* control	Significantly lower incidence of xerostomia (RTOG/EORTC staging criteria) at 1 yr and 5 yr in transfer group *vs* control. Significantly lower VAS at 5 yr for transfer group	Xerostomia 18.7% *vs* 81.8% at 1 yr; 15.4% for transfer *vs* 76.9% at 5 yr; VAS 3.7 for transfer *vs* 5.8 for control
Rieger *et al*[51], 2012	Phase III randomized controlled trial	69	Submandibular transfer *vs* oral PC	EORTC QLQ H and N35: significantly worse dry mouth and sticky saliva at 1 yr in PC group *vs* submandibular transfer at 1 yr	Dry mouth score 42.6 *vs* 85.8; sticky saliva score 37.2 *vs* 66.7
Liu *et al*[50], 2011	Prospective non-randomized controlled trial	70	Submandibular transfer *vs* control	At 5 yr, significantly higher mod-to-severe xerostomia in control group; significantly better VAS in transfer group *vs* control	Mod-to-severe xerostomia 78.6% *vs* 12.9%
Seikaly *et al*[49], 2004	Phase II prospective non-randomized	38	Submandibular gland transfer *vs* control	UW-QOL: significantly better xerostomia symptoms (amount and consistency) at 2 yr	83% *vs* 0% reporting normal amount of saliva
Jha *et al*[48], 2003	Phase II prospective single arm	76	submandibular gland transfer	UW-QOL: 81% minimal or no xero at end of RT; 65% at 2 mo; 71% at 6 mo (in unshielded pts, 71% had severe xero at 6 mo)	-

VAS: Visual analogue scale; PC: Pilocarpine; xero: Xerostomia; UW-QOL: University of Washington quality of life scale; pts: Patients.

unstimulated saliva as well as improved patient reported xerostomia in the transfer group compared to patients who did not receive transfer[49]. Similarly, in another study including 70 patients, those treated with salivary gland transfer had an incidence of 12.9% of moderate-to-severe xerostomia compared with 78.6% in the control group[50]. Two randomized controlled trials, of 65 and 69 patients each, evaluated submandibular transfer, one comparing to a control group, and the other to oral pilocarpine[31,51]. The first showed a significant reduction in the incidence of xerostomia with salivary gland transfer; the second also showed a significant advantage for salivary gland transfer over pilocarpine with respect to dry mouth and sticky saliva. In all of the above studies, surgery was well tolerated, with no reported complications.

OTHER MODALITIES

Other studies include treatment with hyperbaric oxygen, which was shown in a randomized trial to improve patient reported dry mouth and sticky saliva[52]. In a sham-controlled study of acupuncture for xerostomia, Blom *et al*[53] treated patients either with acupuncture or superficial acupuncture, and found no difference in xerostomia outcomes or salivary flow rate between the two groups. Finally, Wong *et al*[54], in a 148 patient phase III study, reported on the use of acupuncture-like transcutaneous electrical nerve stimulation (ALTENS) compared to oral pilocarpine. While there was no difference in whole salivary production, there was a significantly higher proportion of patients in the ALTENS group that responded positively to treatment. In addition, the rate of adverse events was 61.6% in the pilocarpine group compared with 20.9% in the ALTENS group, although the difference in adverse events was not significant at 9 mo (P = 0.67). There were three grade 3 toxicities overall (dry mouth and blurred vision in the pilocarpine group, headache in the ALTENS group).

Table 5 Submandibular gland transfer: Salivary function, quality of life, toxicity

Author	Salivary function	Quality of life	Toxicity
Zhang *et al*[31], 2004	Transfer 1.39 g and 1.6 g saliva *vs* 0.66 and 0.68 g control at 1 yr and 5 yr, respectively. Significantly higher submandibular gland secretion in transfer group at 5 yr (radionuclide scintigraphy).	Significantly improved speech, chewing, swallowing, changes in eating habits, nighttime xero, need to wake up to drink frequently, sleep quality in transfer group	No surgical death or complications occurred in transfer group
Rieger *et al*[51], 2012	NA	NA	Not reported
Liu *et al*[50], 2011	Significantly better trapping and excretion (scintigraphy) in transfer group at 5 yr; Significantly higher mean weight of unstimulated saliva in transfer group at 5 yr	Transfer group improved significantly *vs* control in dry mouth, night rest, drink to speech, drink to eat, water intake, change in feeding pattern, tooth decay, and visual analogue scale	No major complications of surgery (one pt taken back 2 yr later for removal of wire used to mark borders of transferred gland due to pain)
Seikaly *et al*[49], 2004	Significantly higher stimulated and unstimulated saliva in transfer group at 16 mo	NA	No surgical complications from submandibular transfer
Jha *et al*[48], 2003	stimulated and unstimulated saliva decrease gradually, then increase at 16 mo (graphical)	NA	No surgical complications

xero: Xerostomia; NA: Not available.

DISCUSSION

Although there have been prior reviews on the management of radiotherapy-induced xerostomia, to our knowledge there has been no review of the current literature with a focus on late xerostomia following radiotherapy for head and neck cancer[19,55,56]. We found a very heterogeneous group of studies in this review, with many different modalities, doses, routes of administration, timing with respect to treatment, and differing quality of life (QOL) endpoints as well as different objective saliva measurements.

In most of the studies reviewed above, amifostine appears to be beneficial in reducing the risk of long term xerostomia, although it likely requires IV administration. Severely limiting clinical utilization, however, toxicity was noted in close to half of the patients treated[39,41]. Similarly toxicity limits the clinical utilization of pilocarpine and cevimeline, which have been shown to improve xerostomia, with treatment related adverse events exceeding 91.4% (20.4% grade 3) with cevimeline[37].

In contrast, ALTENS treatment was shown to be as effective as pilocarpine, with fewer adverse events (20.8% in ALTENS group *vs* 61.6% in pilocarpine group)[54]. At 15 mo, the treatment response rate was significantly higher in the ALTENS group. ALTENS represents a non-invasive, well tolerated option for treatment of late xerostomia. However, ALTENS devices are not widely available and when offered in a clinical setting, require patients to travel to the clinic twice weekly for 12 wk. Both of these issues limit availability. To address this issue, Iovoli *et al*[57] have described a case report of excellent improvement in dry mouth with home use of a new, cheap, commercially available device.

Submandibular gland transfer has shown promise in several studies as mentioned above. The use of salivary gland transfer in select patients appears to be effective with regard to xerostomia prevention. Additionally, none of the studies evaluated here reported complications from surgery. However, the use of this procedure is somewhat limited based on several factors including patient selection criteria (for example, it would not be feasible in patients with bilateral positive neck nodes), experience of each surgeon and willingness to perform the procedure, as well as time constraints and potential delay of definitive treatment for an elective procedure.

With the advancement of radiation delivery techniques, the use of IMRT has been shown to reduce dose to selected salivary glands, therefore sparing salivary function. It is generally thought that damage to major salivary glands (submandibular and parotid) is the major cause of xerostomia following radiation therapy, as evaluated with MRI, CT, and ultrasound[58-62]. Pacholke *et al*[63] retrospectively reviewed 210 patients with xerostomia at least one year following completion of radiation therapy, as measured by the University of Michigan xerostomia QOL score. Higher xerostomia scores were associated with higher salivary gland dose. On multivariate analysis, radiation technique was an independent predictor of xerostomia, favoring IMRT. The PARSPORT trial was a randomized phase III randomized controlled trial that

Table 6 Other

Author	Type of study	Sample size	Intervention	Xerostomia symptoms	Salivary function	Quality of life	Toxicity
Wong *et al*[54], 2015	Phase III randomized controlled trial	148	ALTENS *vs* oral PC (5 mg TID for 12 wk)	NA	Basal WSP and stimulated WSP: no sig difference	XeQOLs: no difference at 15 mo. 83% ALTENS positive responders *vs* 62.8% PC, SS at 15 mo.	2 G3 events in PC (dry mouth, blurry vision) *vs* 1 G3 event in ALTENS (headache). 61.6% of PC had Grade 3 or less non-hematologic AEs *vs* 20.9% of ALTENS
Teguh *et al*[52], 2009	randomized controlled trial	19	Hyperbaric O2 (30 sessions at 2.5 ATA with O2 breathing for 90 min daily, 5 d a week) *vs* control	Visual analogue scale dry mo better on O2 (SS)	NA	EORTC QLQ-C30 and H and N35; Sticky saliva better on O2 (SS) and less dry mouth on O2 (SS)	NA
Blom *et al*[53], 1996	randomized placebo-controlled trial	38	acupuncture *vs* placebo (superficial acupuncture)	NA	salivary flow rate: no dif. between groups; both groups showed increased flow rates after treatment	No specific endpoints	Tiredness, small haematomas at acupuncture sites

ALTENS: Acupuncture like transcutaneous electrical nerve stimulation; NA: Not available; G: Grade; PC: Pilocarpine; AE: Adverse event; WSP: Whole salivary production; XeQOLs: Xerostomia quality of life scale.

assigned patients with pharyngeal squamous cell carcinoma to either conventional radiotherapy or parotid-sparing IMRT, and found a significant reduction in xerostomia in the IMRT group[10]. In addition to IMRT, the use of intensity modulated proton beam therapy (IMPT) has also been studied in a 150 patient case-matched analysis comparing IMPT to IMRT[64]. With respect to xerostomia, the authors found improved patient-reported symptoms at 3 mo, but no difference at 1 year.

In many cases, however, complete sparing of the parotid or submandibular glands is not possible due to proximity of primary tumor or grossly involved lymph nodes. Recently, there is new evidence that sparing even a portion of the parotid gland may be helpful in preventing xerostomia. Parotid stem cells are thought to be capable of regenerating salivary function, and are located in a concentrated area in the parotid gland around the main salivary ducts, as demonstrated in a study in rats[65]. In this same study, the authors identified a volume in the human parotid gland posterior to the mandible that was most associated with saliva production one year following radiation therapy, and demonstrated that it is possible to spare this area in some patients where sparing the entire parotid is not feasible[65].

Because of the increasing incidence of HPV positive head and neck cancer, there has been interest in de-escalating therapy for this subset of patients[66-68]. By reducing the total radiation dose, xerostomia may become less prevalent in this population, thus reducing the need for alternative treatment of salivary dysfunction.

While pilocarpine, cevimeline and amifostine have been shown to improve late xerostomia outcomes, these treatments often cause side effects that are not tolerable for patients. ALTENS represents a less toxic alternative therapy for prevention of late xerostomia, but has not been widely available until recently[57]. Similarly, submandibular gland transfer is effective, but may not be appropriate for all patients. Salivary gland sparing with improved radiation techniques (IMRT)—in particular sparing of parotid stem cells—is a practical way to reduce late salivary dysfunction. As IMRT becomes more widely available, in conjunction with potential dose de-escalation, the need for alternative xerostomia treatments may become less relevant.

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MINIREVIEWS

Stereotactic body radiation therapy for non-small cell lung cancer: A review

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Abstract

Stereotactic body radiation therapy (SBRT) is the treatment of choice for medically inoperable patients with early stage non-small cell lung cancer (NSCLC). A literature search primarily based on PubMed electronic databases was completed in July 2018. Inclusion and exclusion criteria were determined prior to the search, and only prospective clinical trials were included. Nineteen trials from 2005 to 2018 met the inclusion criteria, reporting the outcomes of 1434 patients with central and peripheral early stage NSCLC. Patient eligibility, prescription dose and delivery, and follow up duration varied widely. Three-years overall survival ranged from 43% to 95% with loco-regional control of up to 98% at 3 years. Up to 33% of patients failed distantly after SBRT at 3 years. SBRT was generally well tolerated with 10%-30% grade 3-4 toxicities and a few treatment-related deaths. No differences in outcomes were observed between conventionally fractionated radiation therapy and SBRT, central and peripheral lung tumors, or inoperable and operable patients. SBRT remains a reasonable treatment option for medically inoperable and select operable patients with early stage NSCLC. SBRT has shown excellent local and regional control with toxicity rates equivalent to surgery. Decreasing fractionation schedules have been consistently shown to be both safe and effective. Distant failure is common, and chemotherapy may be considered for select patients. However, the survival benefit of additional interventions, such as chemotherapy, for early stage NSCLC treated with SBRT remains unclear.

Key words: Lung cancer; Non-small cell lung cancer; Stereotactic body radiation therapy;

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Stereotactic ablative radiotherapy; Distant failure

Core tip: Stereotactic body radiation therapy (SBRT) offers excellent local and regional control for early stage non-small cell lung cancer (NSCLC), and is often the treatment of choice for medically inoperable patients. This literature review provides an updated analysis of prospective clinical trials evaluating clinical outcomes following SBRT for early stage NSCLC.

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INTRODUCTION

Early studies have demonstrated the efficacy of conventionally fractionated radiotherapy for the treatment of stage I non-small cell lung cancer (NSCLC). Haffty *et al*[1] reported on 43 patients with stage I NSCLC from 1970-1983 who had been deemed medically inoperable or who had refused surgical resection. When treated with a median of 59 Gy in 2 Gy per fraction, 5 year overall survival was reported at 21%. Subsequent studies have demonstrated efficacy for radiation doses exceeding 60 Gy[2,3]. In particular, T1 tumors treated with > 65 Gy had significantly reduced risk of recurrence compared to T2 and T3 tumors or doses ≤ 65 Gy[3]. A more modern analysis of stage I, node negative patients staged with computed tomography (CT) and treated with a median dose of 63.2 Gy showed increased cause-specific survival in the subset of patients who received ≥ 65 Gy[4]. While conventionally fractionated radiotherapy can provide a reasonable alternative to surgical resection in medically inoperable patients, the 5-year overall survival rates reported in these early studies were suboptimal at 10%-30%[1-4]. As the delivery of radiation has improved over time, SBRT has emerged as an alternative to very precisely deliver a high dose of radiation in a small number of fractions[5].

Surgery remains the standard of care for medically operable early stage NSCLC. Stereotactic body radiation therapy (SBRT) also referred to as stereotactic ablative radiotherapy (SABR), has become the preferred treatment option for medically inoperable patients with significant comorbidities or for patients who decline surgery. This article will review major concepts in the use of SBRT for primary early-stage NSCLC, including technical considerations and reported outcomes and toxicities from major clinical trials, with a specific emphasis on fractionation and future directions.

SBRT AS DEFINITIVE TREATMENT FOR NSCLC

We conducted a comprehensive literature search for journal articles written in English and published between January 2000 and July 2018. The inclusion criterion was any prospective clinical trial reporting clinical outcomes of primary early stage NSCLC definitively treated with SBRT. The exclusion criteria were the following: (1) review articles, case reports, or letters to editors; (2) studies that did not report the most updated outcomes when multiple publications resulted from the same patient cohort; (3) duration of follow-up shorter than one year; (4) sample size fewer than 30; (5) multiple primary lung tumors; and (6) lung oligometastasis or advanced stage NSCLC.

The search was completed in July 2018. Studies included were identified by performing a search of literature existing in the PubMed database. The PubMed electronic database was queried for search terms including "SBRT", "stereotactic body radiotherapy", and "SABR", along with their respective acronyms, and "lung" or "NSCLC". This database query initially produced 3920 results. Of these, 3631 studies were in the English language. Limiting this selection to prospective clinical trials reduced the results to 269 entries. After a thorough review of the literature, any study

meeting the above criteria but not listed in PubMed was additionally included. By applying our inclusion and exclusion criteria, these studies and their reference lists were evaluated by two reviewers to determine their suitability for inclusion (Figure 1).

Nineteen studies meeting our criteria were selected for inclusion in this review (Table 1). Publication years ranged from 2005 to 2017. The mean number of patients included in the trials was 75 (range 31 to 180), with a median follow-up between 16 to 86 mo. Dose fractionation schedules varied widely. Using a α/β ratio of 10, the total biologically effective doses (BED) included were > 100 Gy_{10} in almost all studies, except for two. Shibamoto *et al*[6] treated four patients, whose tumors were less than 1.5 cm in diameter, with 44 Gy in 4 fractions. Similarly, a small number of patients were treated with BED < 100 Gy in the dose escalation study authored by McGarry *et al*[7].

Survival and tumor control

Two of the earliest studies for early stage NSCLC treated with SBRT were reported by McGarry *et al*[7] and Nagata *et al*[8], who both showed promising local and regional control rates, and distant failure only recorded in patients with T2 disease. In the United States, Timmerman *et al*[9] reported initial results of a phase I study, demonstrating that SBRT was well tolerated, with updated results finding that the majority of local failure was seen in patients receiving ≤ 48 Gy[7]. Of the included studies that estimated 3-year results, reported overall survival percentages ranging from 43% to 95% and local control rates as high as 98%[10-17]. In the four studies with 5-year outcomes, local control was reported between 79%-85%[6,18-20]. Distant control at three years ranged from 76%-97%[10-17]. Reported outcomes from the included studies are tabulated in Table 1.

Fractionation for peripheral tumors

Radiation Therapy Oncology Group (RTOG) 0236 was a phase II North American multicenter study of 55 medically inoperable patients with peripheral NSCLC treated with 54 Gy in 3 fractions. The study initially reported 3-year local control rate of 91% and distant failure in 22%[21]. Updated 5-year results showed 5-year local control of 80% and distant failure of 31%[18]. With promising results from the RTOG 0236 3-fraction regimen for peripheral NSCLC, a multicenter, phase II study, I-124407, was undertaken to compare 30 Gy in 1 fraction and 60 Gy in 3 fractions. This study evaluated 98 patients with a median follow up of 27 mo and showed 2-year overall survival of 71% for single fraction and 61% for 3 fraction regimens. There was no difference in survival or toxicity between the regimens[22].

Similarly, building on the results of the 4 fraction regimen by Nagata *et al*[8], the comparison of 34 Gy in 1 fraction and 48 Gy in 4 fractions was investigated in a multicenter phase II study, RTOG 0915, by Videtic *et al*[13]. The study assessed 94 patients with a median follow up of 30 mo, showing 2-year overall survival of 61% for single fraction and 78% for 4 fraction regimens. No difference in overall survival, primary tumor control, and toxicity was seen between these regimens.

As conventionally fractionated radiation therapy has also improved over time, the multicenter Scandinavian phase II SPACE trial is the only publication that has reported results comparing SBRT (66 Gy in 3 fractions) to conventionally fractionated radiotherapy (70 Gy in 35 fractions). Despite an imbalance in the number of patients with T2 tumors and of male gender (both of these negative prognostic factors were increased in the SBRT arm), there was no statistically significant difference in 1-, 2-, or 3-year overall survival (81% *vs* 89%, 68% *vs* 72%, 54% *vs* 59%, respectively, for SBRT *vs* conventionally fractionated arms). Favorable results were also reported for local control (86.4% in the SBRT arm *vs* 85.7% in the conventional fractionation arm)[14].

Central tumors

Timmerman *et al*[23] reported a phase II study of 70 medically inoperable patients with both peripheral and central tumors treated with 60-66 Gy in 3 fractions. With a median follow up of 17.5 mo, the study initially reported 2-year local control of 95% with grade 3-4 toxicity seen in 8 patients (11%) and treatment-related death in 6 patients (9%). Central location was initially shown to be an adverse prognostic factor for toxicity, but this did not remain significant in the updated report by Fakiris *et al*[17].

The NRG/RTOG 0813 phase I/II trial evaluated NSCLC patients with centrally located tumors, defined as within 2 cm of the proximal bronchial tree or adjacent to the mediastinal or pericardial pleura. Successively accruing patients into a dose-escalating 5-fraction SBRT schedule, ranging from 10-12 Gy/fraction, the study was designed to determine the maximal tolerated dose. The highest dose level allowed by the protocol, 12 Gy/fraction, was achieved, with only 7.2% dose-limiting toxicities reported in the preliminary phase I analysis. Two-years overall survival rates were

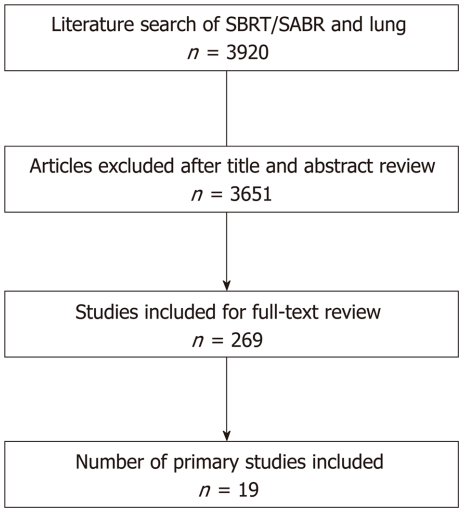

Figure 1 Methods flow chart. SBRT/SABR: Stereotactic body radiation therapy/stereotactic ablative radiotherapy.

reported at 70%[24].

SBRT for operable patients

While many of these trials included medically inoperable patients only, a multicenter Japanese phase II Japan Clinical Oncology Group (JCOG) 0403 study stratified patients who received SBRT for T1N0M0 non-small cell lung tumors into medically operable and inoperable categories. All patients received 48 Gy in 4 fractions. Overall survival at 3 years was reported as 59.9% in the inoperable group *vs* 76.5% in the operable group[12]. Despite being comprised of a relatively older population (median age of 79 years), their results were similar to other studies with younger median age populations[15,25].

Among operable patients only, lobectomy was compared with SBRT in two phase III trials, STARS (NCT00840749) and ROSEL (NCT00687986), both of which were closed early due to slow accrual. Nonetheless, Chang *et al*[15] reported a pooled analysis of 58 patients who were enrolled, with a median follow up of 40 mo for SBRT and 35 mo for surgery. In the STARS trial, peripheral and central lung tumors received 54 Gy in 3 fractions and 50 Gy in 4 fractions, respectively. In the ROSEL study, only peripheral lung tumors were included and received either 54 Gy in 3 fractions or 60 Gy in 5 fractions. Overall survival at 3-years was 95% for SBRT and 79% for surgery. Local control at 3 years was 96% for SBRT and 100% for surgery. Distant failure at 3 years was 3% for SBRT and 7% for surgery.

Toxicity

In the collected studies, several toxicity measures were analyzed, with all papers citing National Cancer Institute Common Criteria grading of lung toxicity. The reported toxicities from included studies can be referred to in Table 2.

Grade 3 toxicity ranged from 3%-20%, with grade 5 (or fatal) toxicities only detailed by three studies. Fakiris *et al*[13] noted 12 grade 3-5 toxicities, with the potential treatment-related grade 5 toxicities reported as pneumonia (n = 3), hemoptysis (n = 1), and respiratory failure (n = 1). RTOG 0915 reported one patient death in the single-fraction arm approximately 2 wk after treatment, with the death thought to be unconnected to SBRT. The four-fraction arm had a patient fatality 319 d after treatment due to respiratory failure thought to be related to SBRT. No difference in toxicity was reported between the single fraction *vs* multi-fraction arms in either RTOG 0915 or I-124407[22].

Rates of toxicities did appear to increase with greater follow-up. For example, 9 patients (16%) with a median follow up of 34 mo were initially reported to have grade 3-4 toxicities in RTOG 0236, but updated results at 4 years found 17 patients (31%) treated with 54 Gy in 3 fractions reporting grade 3-4 toxicities[18,21]. Rib fractures were recorded in 0-18% of patients in the included studies[26]. Late toxicities such as esophageal perforation and fatal pulmonary hemorrhage were documented in the 5 fraction arm of the NRG/RTOG 0813 dose escalation trial for centrally located lung tumors[24].

In the pooled analysis of the STARS and ROSEL studies, Chang *et al*[15] recorded treatment-related grade 3 toxicities in 10% of patients who underwent SBRT, contrasted with 44% of patients treated surgically who suffered grade 3-4 toxicities,

Table 1 Study characteristics and tumor control results

Study	No.	F/u (median)	Age (median)	Loc	Stage	Dose/fx	OS	LC	RC	DC
Miyakawa *et al*[20], 2017	71	44	77	C + P	T1-2N0M0	48-52 Gy/ 4 fx	5-yr 65%	5-yr 85%	NA	NA
Sun *et al*[80], 2017	65	86	71	C + P	T1-2N0M0	50 Gy/4 fx	7-yr 48%	7-yr 92%	7-yr 86%	7-yr 86%
Singh *et al*[22], 2017, I-124407	98	27	NA	P	T1-2N0M0	30 Gy/1 fx and 60 Gy/3fx	2-yr 71% (30 Gy) 2-yr 61% (60 Gy)	NA	NA	NA
Bezjak *et al*[24], 2016, RTOG 0813	71	33 (57.5 Gy) 30 (60 Gy)	NA	C	T1-2N0M0	57.5-60 Gy/5 fx	2-yr 70% (57.5 Gy) 2-yr 88% (60 Gy)	2-yr 90% (57.5 Gy) 2-yr 88% (60 Gy)	2-yr 95% (57.5 Gy) 2-yr 88% (60 Gy)	2-yr 84% (57.5 Gy) 2-yr 85% (60 Gy)
Navarro-Martin *et al*[11], 2016	38	42	74	P	T1-3N0M0	54 Gy/3 fx	3-yr 66%	3-yr 94%	3-yr 79%	3-yr 87%
Nyman *et al*[14], 2016, SPACE	102	37	74 (mean)	P	T1-2N0M0	66 Gy/3 fx	3-yr 54%	3-yr 86%	3-yr 93%	3-yr 76%
Chang *et al*[15], 2015, STARS and ROSEL	31	40	67	C + P	T1-2N0M0	54 Gy/3 fx, 50 Gy/4 fx, 60 Gy/5 fx	3-yr 95%	3-yr 96%	3-yr 90%	3-yr 97%
Lindberg *et al*[19], 2015	57	42	75 (mean)	P	T1-2N0M0	45 Gy/3 fx	5-yr 30%	5-yr 79%	3-yr 81% for regional/distant control	NA
Nagata *et al*[12], 2015, JCOG 0403	169	47 (inop) 67 (op)	78	NA	T1N0M0	48 Gy/4 fx	3-yr 60% 5-yr 43% (inop) 3-yr 77% 5-yr 54% (op)	3-yr 87% (inop) 3-yr 85% (op)	3-yr 92% (inop) 3-yr 75% (op)	3-yr 78% (inop) 3-yr 67% (op)
Shibamoto *et al*[6], 2015	180	53	77	C + P	T1-2N0M0	44-52 Gy /4 fx	5-yr 52%	5-y 83%	5-yr 84%	5-yr 76%
Videtic *et al*[13], 2015, RTOG 0915	94	30	75	P	T1-2N0M0	34 Gy/1 fx and 48 Gy/4 fx	3-yr 56%	3-yr 98%	NA	NA
Timmerman *et al*[18], 2014, RTOG 0236	55	48	72	P	T1-2N0M0	54 Gy/3 fx	5-yr 40%	5-yr 80%	5-yr 62% (local-regional control)	5-yr 79%
Taremi *et al*[26], 2012	108	19	73 (mean)	C + P	T1-2N0M0	48 Gy/4 fx or 54-60 Gy/3 fx (P) 50-60 Gy /8-10 fx (C)	4-yr 30%	4-yr 89%	4-yr 87%	4-yr 83%
Bral *et al*[46], 2011	40	16	73 (mean)	C + P	T1-3N0M0	60 Gy/3-4 fx	2-yr 52%	2-yr 84%	2 nodal recurrences	6 distant recurrences
Ricardi *et al*[16], 2010	62	28	74	P	Stage I	45 Gy/3 fx	3-yr 57%	3-yr 88%	3-yr 94%	3-yr 76%
Fakiris *et al*[17], 2009	70	50	70	C + P	T1-2N0M0	60-66 Gy/ 3 fx	3-yr 43%	3-yr 88%	3-yr 91%	3-yr 87%
Koto *et al*[10], 2007	31	32	77	C + P	T1-2N0M0	45 Gy/3 fx or 60 Gy/8 fx	3-yr 72%	3-yr 78% (T1) 3-yr 40% (T2)	3-yr 94%	3-yr 81%
McGarry *et al*[7], 2005	47	27 (Stage IA) 19 (Stage IB)	71 (Stage IA) 74 (Stage IB)	C + P	T1-2N0M0	24-72 Gy/ 3 fx	NA	2-yr 81%	2-yr 81%	2-yr 79%
Nagata *et al*[8], 2005	45	30 (Stage IA)	77 (Stage IA)	C + P	T1-2N0M0	48 Gy/4 fx	2-yr 90% (Stage IA)	1-yr 100%	2-yr 91%	2-yr 88% (Stage IA)

	22 (Stage IB) 73 (Stage IB)	2-yr 72% (Stage IB)	2-yr 77% (Stage IB)

No.: Number of patients treated with SBRT; F/u: Follow up in months; Loc: Tumor location; P: Peripheral; C: Central; Dose/fx: Total dose/fraction; OS: Overall survival; LC: Local control; RC: Regional control; DC: Distant control; Inop: Medically inoperable; Op: Medically operable; NA: Not available; RTOG: Radiation therapy oncology group; JCOG: Japan clinical oncology group.

including bleeding, fistula, hernia, anemia, weight loss, and cardiac arrhythmias. One patient died of surgical complications.

When compared to conventionally fractionated radiotherapy, toxicity was shown to be less prevalent in the SBRT arm of the SPACE trial, including rates of esophagitis (8% *vs* 30%), borderline significant pneumonitis (19% *vs* 34%) and dyspnea (67% *vs* 81%)[14]. Additionally, patient-reported quality of life data showed significantly worse dyspnea and chest pain in the three dimensional conformal radiation therapy arm compared to SBRT[14].

DISCUSSION

Despite the widely varying dose fractionation regimens, patient populations, and primary outcomes included in these prospective trials, results were similarly favorable. High rates of local control and overall survival have been reported, along with favorable toxicity outcomes. These included studies comparing fractionation schemes, operable *vs* non-operable candidates, and tumor location have paved the way for additional questions to be addressed in future studies.

We acknowledge the limitations of this review. The included studies treated patients over a large time frame with multiple inclusion criteria, differing tumor location, dose fractionation regimens, and prescription methods. Techniques of SBRT delivery were also inconsistent. Different versions of Common terminology criteria for adverse events were used to assess toxicities due to various publication years. Notably, a validity assessment of included studies to evaluate the risk of bias and confidence of results was not undertaken. Unpublished studies are unable to be adequately assessed, and this, too, may lead to an important bias leaning toward the effectiveness of treatment or the under-estimation of toxicities. Despite these limitations, published outcomes with SBRT are consistently promising. Because of this promise, increased attention should be paid to delivering regimens that can improve patients' quality of life.

Survival and tumor control

Survival and tumor control results were excellent in the included prospective studies, compared to historic controls in this patient population. As radiation techniques have evolved, the delivery of high dose radiation in fewer fractions has also become more precise. The use of intra-fraction volumetric imaging with cone beam CT can reduce target error compared to use of patient setup or bony anatomy alone[27,28]. Intra-fraction imaging is recommended as best practice per ESTRO ACROP guidelines[29]. Because a faster treatment delivery time is likely associated with less patient movement and therefore more accurate treatment delivery, the use of a flattening-filter free setting can help to optimize treatment delivery as well[30-32]. The use of heterogeneity corrections has also been shown in RTOG 0236 to have a significant effect on prescription dose and tumor coverage, and should be considered standard in SBRT treatments[33]. Taken together, these technological advances may also be contributing to improved outcomes in this patient population.

Using an α/β ratio of 10, the vast majority of patients were treated with total BED > 100 Gy_{10}, which has been shown to improve outcomes in NSCLC patients treated with SBRT[34]. Others have argued that biologically effective dose calculations, and the linear quadratic model on which they are constructed, may not be applicable for high fractional doses of radiation[35]. The radiobiological principles upon which the linear quadratic model is based, however, do not account for differences in re-oxygenation, the effects on tumor vasculature and the enhanced host immunity that hypofractionation can produce. Nevertheless, the use of BED > 100 Gy_{10} has been adopted as a recommendation for SBRT delivery by the National Comprehensive Cancer Network guidelines and American College of Radiology appropriateness criteria[36,37].

Fractionation for peripheral tumors

Better staging and delivery techniques have helped improve outcomes compared to historical data with conventionally fractionated radiation therapy. The SPACE trial

Table 2 Toxicity results

Study	Grade 3 + toxicity	Reported adverse events
Miyakawa *et al*[20], 2017	Grade 3-5, 5.6%	Radiation pneumonitis
Sun *et al*[80], 2017	Grade 3, 5%	Dermatitis, radiation pneumonitis, chest wall pain
Singh *et al*[22], 2017, I-124407	Grade 3, 30%	NA
Bezjak *et al*[24], 2016, RTOG 0813	Grade 3-5, 16%-21%	Respiratory and cardiac toxicities, esophageal perforation, pulmonary hemorrhage
Navarro-Martin *et al*[11], 2016	Grade 3, 10%	Cough, dyspnea, dermatitis
Nyman *et al*[14], 2016, SPACE	Grade 3, 14%	Dyspnea, cough, skin reactions
Chang *et al*[15], 2015, STARS and ROSEL	Grade 3, 10%	Chest wall pain, cough, fatigue, rib fracture
Lindberg *et al*[19], 2015	Grade 3-4, 30%	Rib fracture, dyspnea, ventricle tachycardia, cough, fatigue, fibrosis, lung infection, pain, pericardial effusion
		Inop: Dyspnea, hypoxia, pneumonitis, chest pain, cough
Nagata *et al*[12], 2015, JCOG 0403	Grade 3-4, 13% (inop) Grade 3, 6% (op)	Op: Dyspnea, hypoxia, pneumonitis, chest pain
Shibamoto *et al*[6], 2015	Grade 3, < 10%	Radiation pneumonitis, pleural effusion, esophagitis, rib fracture, dermatitis
Videtic *et al*[13], 2015, RTOG 0915	Grade 3-5, 12%	DLCO changes, pneumonitis, PFT changes, 2 treatment-related deaths
Timmerman *et al*[18], 2014, RTOG 0236	Grade 3-4, 31%	Hypocalcemia, hypoxia, pneumonitis, PFT decreased
Taremi *et al*[26], 2012	Grade 3, 11%	Fatigue, cough, chest wall pain, rib fracture
Bral *et al*[46], 2011	Grade 3, 20%	Pneumonitis, cough
Ricardi *et al*[16], 2010	Grade 3-4, 3%	Radiation pneumonitis
Fakiris *et al*[17], 2009	Grade 3-5, 16%	Apnea, pneumonia, pleural effusion, hemoptysis, respiratory failure, skin erythema
Koto *et al*[10], 2007	Grade 3, 3%	Pneumonitis
McGarry *et al*[7], 2005	Grade 3-4, 15%	Pneumonitis, hypoxia, dermatitis, pericardial effusion, tracheal necrosis
Nagata *et al*[8], 2005	None	None

RTOG: Radiation therapy oncology group; JCOG: Japan clinical oncology group; Inop: Medically inoperable; Op: Medically operable; DLCO: Diffusing capacity of the lungs for carbon monoxide; PFT: Pulmonary function test.

recently demonstrated equivalent survival outcomes compared with SBRT[14]. Although patients treated with SBRT reported better quality of life and decreased toxicity profiles, the improvement of survival and local control seen in conventionally fractionated radiation therapy during the past several decades is still notable[14]. Other trials, such as CHISEL study (NCT01014130) and LUSTRE trial (NCT01968941) are currently ongoing and will further investigate the role of conventionally fractionated radiation therapy.

Given the decreased number of visits and favorable toxicity profiles, SBRT offers increased patient convenience and improved quality of life outcomes compared to conventionally fractionated radiation therapy. It would seem that this advantage would be even greater with a decreasing number of SBRT fractions. Amongst the prospective studies included in this review, widely varying dose fractionations have been studied, with only a few comparisons evaluated. Of note, the 5-fraction regimen, which is a commonly used fractionation schema nationwide[38], has very limited prospective data, and no prospective, comparative data showing superiority. On the other hand, single-fraction dosing, which has been tested in both RTOG 0915 and I-124407, did not show a difference in toxicity or survival outcomes compared to multi-fraction regimens[13,22].

A follow-up study to RTOG 0915 was not funded because the issue of fractionation was not deemed to be of high enough priority by the National Cancer Institute. In the absence of federal funding for further prospective trials of fractionation, retrospective reviews will have to suffice. Our retrospective review of all patients treated with single- *vs* three-fraction regimens for peripheral early-stage NSCLC at our institution was concordant with the results from our prospective trial[22] and did not show any significant difference in overall survival, progression-free survival, local failure, nodal failure, or distant failure at 24 mo, despite including patients with lower performance status in the single-fraction cohort[39]. A propensity matched cohort analysis of the 3-

fraction SBRT regimen used at our institution and a 5-fraction regimen used at another academic institution showed comparable overall survival, progression-free survival, local control and distant control rates[40]. This is consistent with other retrospective analyses[41]. Most recently, we expanded the two-institution analysis to include 163 patients comparing single-fraction *vs* five-fraction SBRT and again found no difference in survival outcomes or local control[42].

Overall, with robust prospective and retrospective evidence showing high rates of local control and comparable safety outcomes to multi-fraction regimens, our institution has adopted the single-fraction radiation schedule for peripheral, early-stage NSCLCs.

Central tumors

Since the definition of a "No Fly Zone" in the 2006 publication by Timmerman *et al*[23] the spatial proximity of organs at risk, such as main airways, large blood vessels, the heart and esophagus has been the basis of the distinction between centrally and peripherally located NSCLC. Although updated results 3 years later by Fakiris *et al*[17] showed there was no difference in survival and toxicity between central and peripheral tumors, several subsequent trials have investigated central or peripheral tumors separately. Overall survival outcomes reported from NRG/RTOG 0813 were noted to be comparable to elderly, medically inoperable patients with peripheral early stage tumors. Despite the safety concerns for the treatment of central tumors, this trial also demonstrated reasonable toxicities, though we await the published manuscript.

A literature review of 20 publications reporting outcomes for 563 central lung tumors treated with SBRT included a majority of single-institution retrospective analyses, with only four prospective studies including 68 patients. Tumor location did not appear to impact overall survival, with overall treatment-related mortality reported as 2.7%. As might be expected, Grade 3 and 4 toxicities were more prevalent for central tumors, but occurred in < 9% of patients[43].

We have previously reported a case of single-fraction SBRT for a solitary metastasis of squamous cell carcinoma in the right hilum which resulted in complete response of the tumor, but sudden grade 4 bronchopulmonary hemorrhage 13 mo after treatment[44]. Given their location near critical organs, treatment of central tumors is inherently risky, with any fractionation schema predisposing to increased toxicity rates compared to tumors located peripherally.

The recently reported Nordic HILUS-Trial was a prospective, multi-center, non-randomized phase II trial of SBRT for central lung tumors (either primary NSCLC or metastasis), which treated patients with 8 fractions of 7 Gy/fraction, and stratified patients based on tumor location near a mainstem bronchus *vs* a lobar bronchus. Initial results have been published in abstract form. Twenty-one of the 74 included patients developed grade 3 or higher toxicities, with seven patients suffering fatal effects of hemoptysis (n = 6) or pneumonitis (n = 1)[45]. The LungTech trial (EORTC 22113-08113), which aims to evaluate efficiency and toxicity of SBRT in patients with centrally located tumors, is ongoing.

SBRT for operable candidates

In our review, despite widely varying inclusion criteria, dose fractionation schemas, and institutional protocols, most trials demonstrated excellent local and regional control for early stage NSCLC[6-8,10-19,22,24,26,46]. Among operable patients treated with SBRT, 3-year overall survival was 77%-95%. Grade 3-4 toxicity rates were 10%-30% with a few treatment-related deaths, most notably observed in treatment of central lung tumors[6-8,10-19,22,24,26,46]. These findings are comparable to perioperative complication rates of 15%-25% and the 30-d postoperative mortality rate of 1.7% seen in video-assisted thoracic surgery and open lobectomy in recent trials[47,48].

In the JCOG 0403 trial, the lower median overall survival reported for the patients deemed medically inoperable was likely complicated by the increased number of comorbidities and decreased performance status of that group, making any direct comparison problematic[12]. It would be similarly challenging to draw conclusions about SBRT as a viable alternative to lobectomy from the results of the STARS and ROSELS pooled analysis due to the small sample size and short follow up time[15]. More recently, a brief report was issued regarding results from the single-arm, phase 2 NRG Oncology RTOG 0618 trial, which evaluated SBRT for operable, peripheral T1-2 NSCLC. Of the 26 patients evaluated, only 1 patient had a primary tumor recurrence, and there were no lobular failures at a median follow-up of 48.1 mo. Four-year overall survival was reported as 56%, and median overall survival 55.2 mo[49].

Regardless, distant failure rates of up to 34% are common for both SBRT and surgery[6-8,10-19,22,24,26,46,47]. This is likely due to the fact that despite negative findings in initial nodal sampling, nearly 20% of patients are upstaged pathologically from clinical Stage I[47]. Additional studies have reported up to 30%-35% pathologic

upstaging at the time of surgery[50,51]. The incidence of occult mediastinal lymph node metastasis in patients with negative uptake on positron emission tomographic/computed tomographic (PET/CT) imaging was as high as 22%, especially in centrally located NSCLC tumors[52,53]. These findings are unsurprising since PET/CT, mediastinoscopy, and minimally invasive biopsy techniques such as endobronchial ultrasound transbronchial needle aspiration are less sensitive for nodal metastasis compared to nodal dissection[54-57].

A randomized trial of lung resection combined with nodal dissection published results showing improved survival among early stage NSCLC[58]. Despite including three-quarters of patients with stage II-III disease, the distant failure rate for patients undergoing systematic nodal dissection was a promising 22.5% without adjuvant chemotherapy *vs* 30.7% of patients who had mediastinal lymph node sampling[58]. However, if lymph nodes are sampled extensively prior to surgery to rule out nodal metastasis, systematic nodal dissection does not improve survival or reduce distant failure[59]. At this time, there is no evidence that clinically early stage NSCLC will benefit from intensive lymph node staging prior to SBRT[60], and several trials are currently investigating the potential role of invasive lymph node staging (NCT01786590, NCT02719847).

Our institution has undertaken a pilot study to evaluate the role of trans-cervical extended mediastinal lymphadenectomy (TEMLA) in combination with SBRT for Stage III NSCLC. The methodology of this study has been previously described[61]. TEMLA was completed and then followed by either surgical resection or single-fraction SBRT to the primary site, followed by 10 Gy SBRT directed to the mediastinum and/or positive surgical margin. Ten patients completed the study with preliminary results suggesting that the regimen is both well tolerated and provides good regional control[62]. These findings further suggest that SBRT may be potentially expanded for use in regionally advanced disease.

Toxicity

The SBRT technique allows for a high radiation dose to be delivered to a tumor target while maintaining a rapid drop-off gradient. Since it is assumed that an ablative dose delivered to the target alone should be safe, the toxicity associated with treatment must be related to dose inadvertently deposited in surrounding tissues[63]. These include toxicities such as chest wall pain and rib fractures in treatment of peripheral tumors, and decline in pulmonary function tests, pneumonia, and pleural or pericardial effusions in treatment of tumors in the central chest region[23,46,64,65]. These studies collectively show that toxicity is similar between varied fractionation schema. As mentioned above, toxicity may be increased in central tumors despite the use of prolonged fractionation courses.

Future directions

The use of chemotherapy has been retrospectively assessed in patients with T1-3N0M0 NSCLC who underwent SBRT, and was found to reduce distant failure and improve overall survival. However, only 26% of the patients (n = 17) received adjuvant chemotherapy[66]. Subsequently, the STEREO trial was opened to investigate the use of adjuvant chemotherapy in medically inoperable patients with early stage NSCLC treated with SBRT (NCT01300299), but given the difficulty in accruing participants (likely due to significant underlying comorbidities of this population), the study was discontinued. Improved overall survival after surgery and adjuvant chemotherapy for stage IB T2N0M0 has been demonstrated in several studies[67-69], but this finding has not been reproduced in larger prospective trials[70-74]. Even when patients were staged clinically and had potential occult nodal metastasis[47,50,51], neoadjuvant or adjuvant chemotherapy with surgery for early stage NSCLC did not improve survival[75]. However, adjuvant chemotherapy may be beneficial in select patients with resected early stage NSCLC, such as the tumor size > 4 cm and solid or micropapillary subtypes of adenocarcinoma[70,76]. Chemotherapy may reduce the risk of distant failure observed in patients treated with either surgery or SBRT alone, but its survival benefits for early stage NSCLC remain unclear.

In addition, other ongoing studies for early stage NSCLC evaluating other treatment regimens and modalities include: immunotherapy with SBRT (NCT02581787, NCT03050554), neoadjuvant SBRT and surgery[77,78], SBRT dose escalation specifically for T2N0M0 large tumors[79], radiofrequency ablation[37], and proton therapy (NCT00875901).

In conclusion, this review shows that SBRT remains the standard of care for medically inoperable patients with early stage NSCLC. While survival and local control outcomes of conventionally fractionated radiation therapy have been shown to be comparable, SBRT still offers better toxicity and quality of life outcomes. Prospective trials evaluating fractionation schema have not shown a clear benefit to

multi-fraction regimens for peripheral, early stage NSCLC, and as such, our institution has adopted a single-fraction SBRT scheme. Additionally, further work is being done to evaluate the role of SBRT for regional nodal disease in stage III NSCLC patients. Additional studies are underway to evaluate various modalities and therapy schedules in this challenging patient population.

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