

Editor's note:

“Palliative Radiotherapy Column” features in articles emphasising the critical role of radiotherapy in palliative care. Chairs to the columns are Dr. Edward L.W. Chow from Odette Cancer Centre, Sunnybrook Health Sciences Centre in Toronto and Dr. Stephen Lutz from Blanchard Valley Regional Cancer Center in Findlay, gathering a group of promising researchers in the field to make it an excellent column. The column includes original research manuscripts and timely review articles relating to palliative radiotherapy, and editorials and commentaries on recently published trials and studies as well.

Palliative Radiotherapy Column

The role of hypofractionated radiation in the management of non-osseous metastatic or uncontrolled local cancer

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Abstract: Radiation therapy is often used to palliate symptoms caused by cancer. Short course, or “hypofractionated” palliative radiation therapy provides equivalent palliation in the setting of non-osseous metastasis or uncontrolled localized cancer while being more convenient and cost-effective than longer courses of radiation. Hypofractionated palliative radiation plays a role in the management of obstruction due to tumor, neurologic symptoms, pain caused by localized bulky disease, and bleeding in patients with primary tumors of the lung, head and neck, bladder, rectum, gynecologic malignancies, and metastasis to the liver, lung and brain. Hypofractionated palliative radiation is well tolerated with minimal and self-limited side effects. The side effects that do occur are generally limited to the body region treated and last from a few days to a few weeks.

Keywords: Hypofractionated radiation; palliative radiation

Submitted Sep 03, 2014. Accepted for publication Sep 12, 2014.

doi: [10.3978/j.issn.2224-5820.2014.10.01](https://doi.org/10.3978/j.issn.2224-5820.2014.10.01)

View this article at: <http://dx.doi.org/10.3978/j.issn.2224-5820.2014.10.01>

Introduction

Radiation therapy is often used to palliate symptoms caused by cancer. In this article, the authors will review the literature supporting short course, or “hypofractionated” palliative radiation therapy in the setting of non-osseous metastasis or uncontrolled localized cancer. A recent review summarizes the literature surrounding the use of radiotherapy (RT) in the palliation of osseous metastasis (1).

Hypofractionated palliative radiation plays a role in the management of obstruction due to tumor, neurologic symptoms, pain caused by localized bulky disease, and bleeding in patients with primary tumors of the lung, head and neck, bladder, rectum, gynecologic malignancies, and metastasis to the liver, lung and brain. It may provide equivalent palliation and relief while being time-efficient, cost effective and less toxic than longer courses of radiation therapy.

Hypofractionated radiation therapy

The earliest uses of radiation therapy employed a single treatment (or a small number of fractions) of large doses of radiation. Treatment was often limited by excessive skin reactions without meaningful effect on the underlying malignancy. Through experimentation, treatment evolved to a larger number of smaller doses (or fractions) of radiation delivered 5 days per week over several weeks. These smaller doses are on the order of 1.8-2 Gy per fraction, for a period of 5-8 weeks. The exact treatment schedule is based on the clinical circumstances and tumor histology (2).

Hypofractionated radiation therapy, or the use of a smaller number of larger size fractions (3-8 Gy) of radiation, is ideally suited for palliation of symptoms due to metastatic cancer. Treatment courses are shortened, which is important when the quantity of days remaining is short and quality of life (QOL) is the primary goal of treatment. Patients in this phase of life tend to be uncomfortable with transport. For these patients, the potential for increased risk of long-term side effects that are associated with larger doses per fraction related to late-responding tissues is less relevant. In addition, the lower biologic equivalent dose of these shorter courses can further minimize this risk of late side effects.

Many of the studies of hypofractionated radiation therapy in the palliation of uncontrolled local disease or metastatic cancer are retrospective, single-institution reviews that were performed in an era prior to widespread use of QOL questionnaires and metrics (3). The most robust data on the equivalence in efficacy, increased convenience, lower cost and less toxicity resides in the setting of single fraction RT for osseous metastasis. The same principles of efficacy, convenience, cost and toxicity apply to hypofractionated radiation therapy for treatment of non-osseous metastasis that is the focus of this review.

The perceived reluctance of radiation oncologists to offer short course palliation is cited by palliative care professionals as a reason that patients on hospice do not often get referred for palliative radiation, though those same physicians recognize the palliative benefit that radiation can provide for conditions such as painful bone metastases (4). Those same clinicians are less familiar with the potential benefits of palliative RT for tumor-related symptoms beyond painful bone metastases (4,5). Palliation of symptoms such as hemoptysis and bleeding due to tumors in various locations, obstruction of airways or other organs, pain or neurologic symptoms caused by local tumor growth and brain metastasis is the subject of this review. Key to the administration of

any palliative radiation is the expectation that a patient will live long enough to see a benefit from palliative radiation. Palliative effects of radiation can be seen within 24-48 hours for bleeding but can take several weeks for the full palliative effect in other settings.

Lung cancer/palliation of disease in the lung

Eleven randomized trials and one non-randomized trial have compared palliative radiation therapy schemes for patients with lung cancer (6-17) (Table 1). In addition, six single-arm prospective trials (18-23) and multiple retrospective reviews have looked at hypofractionated radiation therapy for this patient group. The vast majority of these studies were conducted outside the US without the routine use of chemotherapy. No consistent mechanism for scoring symptoms, QOL or degree of palliation was used.

Fractionation regimens

Seven of these trials compared a 2-fraction regimen with longer (5-25 fractions) courses of radiation therapy. The vast majority of these trials did not demonstrate any benefit to the longer courses of radiation therapy, with a few notable exceptions.

Two trials (9,10) did suggest a survival advantage to the longer courses of radiation, while one (13) demonstrated a survival benefit to the shorter course regimen. One study (10) noted shorter duration of esophagitis with the 2-fraction regimen while another (12) demonstrated a trend toward more esophagitis in the 2-fraction regimen. Two studies (10,12) noted better palliation with the 2-fraction regimens though one (9) demonstrated more prolonged palliation with 10 fractions.

Two trials (7,17) compared a single fraction of 10 Gy to either 2- or 5-fraction courses in patients with poor performance status (PS). Whereas the Medical Research Council (MRC) trial did not demonstrate any benefit to the 2-fraction regimen as compared to a single fraction, the National Cancer Institute of Canada (NCIC) trial noted a 2-month improvement in survival, better symptom relief and improved QOL with 5 vs. 2 fractions. One explanation for this difference may be the proportion of patients with poor PS; in the NCIC trial 40% of patients were Eastern Cooperative Oncology Group (ECOG) 0-1 compared to 0% in the MRC trial. One theme that emerges throughout the palliative literature is that PS is a strong predictor of survival (24).

Table 1 Randomized trials of fractionation in lung cancer

Reference	# Patients	Stage or selection criteria	Performance status % ECOG 0-1	Dose (Gy)	# Fractions	Median survival (months)	Response rate and/or comments
Macbeth (10)	509	Inoperable, non-metastatic	76%	17	2	7	More rapid palliation 17 Gy arm
				39	13	9	
Sundström (15)	421	Stage III-IV	60% *KPS 70-80	17	2	8.2	No differences in palliation or toxicity
				42	15	7	
				50	25	6.8	
Simpson (14)	409	Inoperable stage IIIB	60%	30	10	6	69% overall response No difference between 3 arms
				40	20	6	
				40	10 (split)	6	
MRC (6)	369	Inoperable	50%	17	2	6	65-81% 56-86%
				27 or 30	6 or 10	6	
Kramer (9)	297	Stage III-IV	36%	16	2	11% 1 year	P=0.03 Survival Palliation prolonged to week 22 in 30 Gy arm
				30	10	20%	
Teo (16)	291	Inoperable mostly stage IIIA/B	54%	45	18	5	71% (P=0.02) 54%
				31.2	4	5	
MRC (7)	235	Inoperable	0% 100% ECOG 2-4	17	2	3	48-75% 55-72%
				10	1	4	
Bezjak (17)	230	Mostly locally advanced	22%	10	1	4.2	Better palliation and QOL in 20 Gy arm
				20	5	6	
Rees (12)	216	Suitable for palliative RT	60%	17	2	6	No difference
				22.5	5	6	
Senkus-Konefka (13)	100	Inoperable	40%	20	5	5.3	No difference in symptom control Survival P=0.02
				16	2	8	
Abratt (8)	84	Unresectable stage III	57%	35	10	8.5	68% (P=0.7) 76% more esophagitis seen with 45 Gy
				45	15	8.5	

*, Grouped so that cannot discern truly ECOG 0-1; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; MRC, Medical Research Council; QOL, quality of life; RT, radiotherapy; #, number of.

Performance status (PS)

Seven of the randomized trials had more than 50% of patients with ECOG 0-1 (6,8,10,12,14-16). Of these seven trials, only one (10) suggested a survival benefit for the longer course of radiation therapy. Macbeth *et al.* randomized 509 patients to either 17 Gy in 2 fractions or 39 Gy in 13 fractions. More rapid palliation and a shorter duration of radiation-induced

esophagitis were seen in the 2-fraction regimen. There was a small survival advantage seen in the 13-fraction regimen with a hazard ratio of 0.82 [95% confidence interval (CI): 0.69-0.99, P=0.03]. One large caveat with applying this trial to patients treated with palliative intent in the US is that patients with locally advanced, non-metastatic lung cancer were eligible. Though not specifically stated, this designation presumably

correlates to stage IIIA and IIIB lung cancer, which in patients with ECOG 0-1, are typically treated curatively with concurrent chemoradiation in the US. Stage III lung cancer typically involves lymph nodes in the ipsilateral mediastinum (IIIA) or contralateral mediastinum, supraclavicular lymph nodes or multiple tumors in the same lung (IIIB). It remains to be seen whether the survival advantage would be seen in a similar population of stage IIIB/IV patients given that no significant differences in local recurrence rates were seen between the groups at 6, 12 or 24 months. Distant disease was seen as the site of first failure more commonly in those treated with the 2-fraction regimen.

In the five trials largely comprised of patients with ECOG ≥ 2 , only one (9) demonstrated a survival advantage for the longer fraction course. Kramer *et al.* enrolled patients with ECOG 3-4/stage III disease as well as ECOG 0-1/Stage IV lung cancer. In a subgroup analysis, the improved survival seen with the longer course of radiation was seen only in the patients with ECOG 0-1.

In an effort to decrease travel time for patients at the end of life, Plataniotis *et al.* (11) treated 92 patients with either 17 Gy in 2 fractions given 1 week apart *vs.* 4.25 Gy given TID on day 1 and BID on day 2 with a 4-hour inter-fraction interval. Patients were not randomized but were assigned to a treatment group based upon the distance they would have to travel to receive treatment. There was no clinically significant difference in toxicity, efficacy, or survival between the two different fractionation schemes; however, the sample size was small.

Fairchild *et al.* (25) performed a systematic review of 13 randomized trials of fractionation in the palliation of symptomatic lung cancer. No significant differences were seen with respect to symptom control. Their review suggested an improvement in survival that favored fractionation regimens with higher biologic effective dose [biologically effective dose (BED) ≥ 35 Gy₁₀]. One caveat to their conclusion is that only 28% of patients included in the analysis had extrathoracic metastatic disease, again leaving open the question of whether there truly is a survival benefit associated with a particular fractionation regimen for patients with metastatic disease.

American Society for Radiation Oncology (ASTRO)'s recent evidence-based clinical practice guideline on palliative thoracic RT (26) noted that despite a heterogeneity of data in 14 randomized controlled trials, there was a benefit to palliative radiation therapy without favoring a particular fractionation regimen. Toxicity was noted to be generally mild but increased with regimens that had a higher BED. No difference was found in response

rates (RRs). There was a suggestion of survival benefit seen for longer fractionation regimens in some of the trials for those patients with a good PS at the expense of higher toxicity, cost and decreased convenience. It suggested that 2-fraction regimens are more easily integrated between cycles of systemic therapy, though there is limited data in this setting. Patients treated on the studies of palliative fractionation regimens did not get systemic therapy. Further research is needed to determine how best to integrate systemic therapy with palliative radiation regimens.

Risk for radiation myelitis

The MRC (27) analyzed the data from their three trials of hypofractionated radiation therapy and reported five cases of spinal cord injury consistent with radiation myelopathy. Three of 524 patients treated with 17 Gy/2 regimens and 2/153 patients treated with 39 Gy/13 developed radiation myelopathy. None of the other radiation schemes had any myelitis noted. The 2-year cumulative rate of myelitis was approximately 2% for 17 Gy/2 and 39 Gy/13 and 0% for the other regimens. Symptoms began no earlier than 8 months after delivery of treatment, a time frame that is longer than most patients treated in this manner survive. Despite this being a rare complication, its severity can cause profound patient morbidity, and techniques to decrease the dose to the spinal cord, such as a posterior spinal cord block or an off-cord oblique beam, seem reasonable to minimize the risk of myelopathy.

Summary

The vast majority of trials of hypofractionated palliative radiation demonstrate equivalence in outcomes and toxicity for shorter courses of radiation therapy. These 2-fraction regimens can easily be integrated between cycles of systemic therapy. The increased convenience and decreased cost associated with 2-fraction regimens have established this regimen as an accepted standard of care for palliative lung radiation therapy in the setting of metastatic lung cancer that should be increasingly utilized in place of more protracted regimens.

Gynecologic (GYN), genitourinary (GU) or gastrointestinal (GI) cancer/palliation of disease in the pelvis

Uncontrolled tumor in the pelvis can cause bleeding,

discharge, pain, obstruction or hydronephrosis. Despite the fact that patients with advanced pelvic malignancies have relatively short life-expectancy, these symptoms can be very problematic during their remaining life. Various hypofractionated radiation regimens have been utilized in an attempt to maximally palliate these patients while minimizing uncomfortable travel, cost and time in the hospital.

One randomized trial (28), one non-randomized comparison (29) and at least 12 single-arm studies (28-42) have been conducted (Table 2).

Among the earliest hypofractionated palliative schedules used to treat advanced pelvic malignancies was a regimen of 10 Gy delivered to the whole pelvis and repeated monthly for 1-3 fractions (30). Field reductions were utilized for the second and third fractions and megavoltage photon beams were used in the vast majority of patients. A dose response curve was noted ranging from 45% palliation of bleeding with a single fraction to 100% with 3 fractions in the patients with cervical or vaginal primaries. Similar dose responses were noted for other symptoms and disease regression. The vast majority of these patients did not achieve local control for their remaining short (median survival 3-9 months) lifespan. Serious bowel complications were all related to uncontrolled local tumor. No significant palliation was noted for those treated for endometrial or ovarian primary tumors. In contrast, in a study of patients with endometrial and cervical primaries treated with a single 10 Gy fraction (32), approximately 50% of patients were palliated with this regimen for their remaining lifetime. Five of 42 patients suffered late GI toxicity, namely fistula, developing 10 months or longer after the completion of radiation.

Several themes emerge from the series that have used 10 Gy for 1-3 fractions. First, it is extremely effective at controlling bleeding from pelvic malignancies. Secondly, acute toxicity is generally mild and time-limited. Lastly, there is an increased rate of late grade 3-4 GI toxicity, predominantly fistulae, that occurs beginning 9 months from the completion of treatment. Limiting the use of the third fraction, reducing the field size for subsequent fractions and selecting patients with shorter life expectancies have been suggested as means to decrease the rate of late GI toxicity. In addition, many of the series reported local recurrences within patients' short remaining lifespan, though the short and incomplete follow-up in many of these series limits the ability to make firm conclusions about the duration of the palliative effect.

In response to the late GI toxicity seen in Radiation Therapy Oncology Group (RTOG) 79-05, a phase I trial of

10 Gy repeated monthly with misonidazole (40), the RTOG developed the "Quad Shot". This regimen consists of 3.7 Gy given twice per day times 4 over 2 days repeated at monthly intervals times 3, if patients did not progress or did not decline clinically. In the initial trial, there was one late grade 3 toxicity and a 32% RR. A randomized trial (39) was undertaken to determine if the RR would increase if the interval between repetitions of the Quad Shot was shortened to 2 vs. 4 weeks. No difference in hemostasis, pain relief, relief of tenesmus or tumor response was noted between arms but the shorter interval was associated with increased acute toxicity. When combined with paclitaxel (43) in a small single arm study, RRs increased to 95% with 90% of patients palliated.

Rectal cancer

In patients with locally advanced and metastatic rectal cancer (47), a hypofractionated radiation therapy course can limit the need for palliative colostomy to 33%. This regimen is associated with an 82% local control rate with less than 10% mild acute toxicity and no late toxicity. For those with pain due to recurrent, unresectable rectal cancer, pain relief can be achieved in 70-90% of patients receiving palliative radiation therapy (48).

Bladder cancer

Hypofractionated regimens have been successfully employed in the treatment of elderly patients with bladder cancer who are considered incurable due to age, comorbidities and PS (28,29,34,36,45). One trial utilized a hypofractionated approach, but their inclusion criteria allowed for patients that were treated for cure and thus is not discussed in this article (49). Palliation of hematuria (50-79% of patients) and pain (52-76% of patients) can be achieved in patients with metastatic bladder cancer. RRs vary from 52-64% in the series where it is reported. Most studies note equivalence in regimens in terms of palliation, response and toxicity, though many also report acute worsening of urinary symptoms due to treatment (34,41). In two of the series (29,45) the fractionation scheme was based on PS with worse PS patients receiving more hypofractionated, shorter courses of radiation. In both of those series the more hypofractionated arms achieved better palliation of pain and hemostasis. Pain relief and hemostasis was achieved in 73% and 59% in the 2-fraction arm compared to 37% and 16% with the longer course of radiation in the series by Srinivasan (29). Nearly 80% of patients had recurrence of hematuria if they survived

Table 2 Hypofractionated palliative radiation in advanced GYN/GU/GI malignancies						
Reference (Trial design or selection criteria)	# Patients	Dose per fraction (Gy)	# Fractions	Frequency	Response or palliation	Toxicity
Spanos (38)	142	3.7 BID ×4	3	Monthly	32% CR or PR.	One late grade 3 GI toxicity.
Spanos (39)	68	3.7 BID ×4	3	Monthly	No difference in hemostasis, pain	Increased acute toxicity with shorter rest interval. No difference in late toxicity but follow-up too short.
(Randomized)	68	3.7 BID ×4	3	Biweekly	relief, relief of tenesmus or RR.	
Carrascosa (43)	13 Pelvic*	3.7 BID ×4	3	Monthly with paclitaxel	95% RR. 90% palliation.	Two grade 3 acute toxicity. No late toxicity.
Caravatta (44)	27	3.5-4.5	4		89% RR.	No late toxicity.
Lacarrière (45)	13	3	10	Daily	54% hemostasis.	
(Selected by PS)	19	4	5	Daily	79% hemostasis.	
Kim (46)	17	5	4-5	Daily	94% hemostasis, 67% pain relief.	Mild acute toxicity. No grade 3-4 late toxicity.
Janjan (47)	87	5	6	Twice weekly	75% response or stability.	No late toxicity. <10% acute toxicity grade ≤3.
McLaren (36)	65	6	5-6	Weekly	64% CR or PR of symptoms, 92% hemostasis.	No grade 3 or higher late toxicity.
Jose (34)	65	6	5-6	Weekly	50% hemostasis, 62% CR.	Acute GU/GI 63%/36%. Late GU/GI 44%/6%.
Wijkström (41)	162	7	3	QOD	52% CR or PR.	42% acute toxicity. Late toxicity 7%.
Duchesne (28)	272	3.5	10	Daily	68% palliated.	
(Randomized)		7	3	QOD	No difference in efficacy or toxicity.	
Kynaston (35)	26	8	2-3	Day 0, 7, 21	92% palliated.	
Srinivasan (29)	22	8.5	2	QOD	59% hemostasis, 73% pain improved.	
(selected by PS)	19	3.75	12	Over 26 days	16% hemostasis, 37% pain improved.	
Yan (42)	51	6-8 (86% 7)	3	Day 0, 7, 21	93% hemostasis, 76% pain control.	58% grade 1-2 acute toxicity One grade 3-4 late toxicity
Boulware (30)	111	10	1-3	Q 3-4 weeks	Dose response, 100% hemostasis with 3 fx in 86 patients with cervical or vaginal primaries.	No GI toxicity attributable to RT
Chafe (31)	30	10	1	NA	100% hemostasis.	No acute toxicity
Hodson (33)	27	10	3	Monthly	100% hemostasis, relief of pain.	Bowel obstruction, fistula, RT proctitis
Halle (32)	42	10	1-3	Monthly	60% hemostasis, 22% pain relief.	~50% palliated for life; five late toxicity—3 fistula; 5% had 3 fx.
Spanos (40)	46	10	1-3	Monthly misonidazole	35% CR or PR (16/46).	80% had 3 fx; 24% grade 3-4 GI toxicity
Onsrud (37)	64	10	1-3	Monthly	90% hemostasis.	6% late grade 3-4 GI toxicity

*, this trial included seven patients with head and neck primaries and 13 with pelvic malignancies; GYN/GU/GI, gynecologic/genitourinary/gastrointestinal; CR, complete response; PR, partial response; RR, response rate; PS, performance status; RT, radiotherapy; fx, fractions; NA, not applicable; #, number of.

Table 3 Hypofractionated radiation therapy trials in head and neck cancer

Reference Trial design	# Patients	Dose/fx	# fx	Schedule	Efficacy	Toxicity
Chen (50) Retrospective review	83	3.7 BID	4	Repeated ×3 at 2-3 weeks	No difference	9% RTOG Quad Shot regimen vs. 37%
	77	2	35	Daily		
	67	3	10	Daily		
	86	2.5	15	Daily		
	60	4	5	Daily		
Corry (51) Single arm	30	3.7 BID	4	Monthly ×3	53% RR 44% improved QOL	No ≥ grade 3 toxicity
Paris (52) Single arm	37	3.7 BID	4	Monthly ×3	77% RR	No late toxicity
Carrascosa (43) Single arm	7 HN*	3.7 BID	4	Monthly ×3 with paclitaxel	95% RR 90% palliation	10% grade 3 acute No late toxicity
Monnier (53) Retrospective review	78	3 Gy	8	Day 1 & 3 Repeated weeks 1, 3, 5, 7 cisplatin	54% RR	31% needed break 4% acute grade 3-4 12% late grade 3-4
Das (54) Single arm	33	4	10	Twice/week	88% pain relief 60% improved PS	Grade 3 mucositis 18%, dermatitis 3%
Kancherla (55) Retrospective review	33	4	5	Repeated after 2 weeks	79% symptom relief 72% RR	18% grade 3 acute
Mohanti (56) Single arm	505	4	5	Addl RT for responders	37% RR 47-59% symptom relief	Not stated for palliative RT
Porceddu (57) Single arm	37	6	5-6	Twice weekly	80% RR 62% improved QOL 67% improved pain	Grade 3 mucositis 26% Grade 3 dysphagia 11%
Weissberg (58) Randomized	64	2 4	30-35 10-12	Daily Daily	No difference between arms	No difference between arms

*, this trial included 7 patients with head and neck primaries and 13 with pelvic malignancies; RR, response rate, including complete and partial response; fx, fractions; RTOG, Radiation Therapy Oncology Group; QOL, quality of life; HN, head & neck cancer patients; Addl, additional; PS, performance status; RT, radiotherapy; #, number of.

6 months after treatment (45). However, the only randomized trial of fractionation in bladder cancer by Duchesne *et al.* (28) did not demonstrate any difference in survival, efficacy or toxicity between the shorter and longer courses of radiation. Sixty-eight percent of patients were effectively palliated. Palliation of hematuria, frequency, dysuria and nocturia was achieved in 88%, 82%, 72% and 64%, respectively. The two radiation regimens studied in this trial were similar to the non-randomized series.

Summary

Multiple alternative hypofractionated regimens have been

studied in advanced pelvic malignancies with generally good palliative effects and reasonable toxicity. Many of these studies utilized 2-dimensional treatment; more conformal therapy should maintain the effective palliative response with decreased toxicity.

Head and neck cancer

Locally advanced tumors of the head and neck pose significant local problems for patients during their remaining lifespan. Multiple prospective and retrospective studies have reported reasonable RRs and palliation with reasonable morbidity (Table 3).

Only one randomized controlled trial of fractionation has been performed in the setting of surgically unresectable stage III and IV head and neck cancer (58). Weissberg *et al.* did not demonstrate any significant difference in efficacy or toxicity between 60-70 Gy in 30-35 fractions when compared with 40-48 Gy in 10-12 fractions.

A phase II prospective study of 3.7 Gy BID times 4 over 2 days (the "Quad Shot") was undertaken by Corry *et al.* (51). This Quad Shot was then repeated at monthly intervals times 3, if patients did not progress or decline clinically. The median survival was 5.7 months. No toxicity greater than or equal to grade 3 was noted. The tumor RR was 53% and 44% of patients experienced improvements in their QOL. The Quad Shot has been studied with concurrent paclitaxel (43) with an increase in the RR to 95% and 90% palliation of symptoms without any increase in late toxicity but with a 10% rate of acute grade 3 toxicity.

Chen *et al.* performed a retrospective review of five different fractionation regimens (50). No difference was seen in efficacy between the various regimens, but the RTOG Quad Shot regimen was associated with significantly less acute toxicity (9%) when compared to all of the other regimens (37%).

Mohanti *et al.* (56) studied patients with poor-prognosis, unresectable stage IV head and neck cancer. Patients were initially treated with a palliative regimen of 20 Gy in 5 fractions over 1 week. Those patients that had significant regression went on to receive conventionally fractionated radiation to the dose equivalent of 70 Gy₂. Those who received full dose RT survived for a median of 13 months when compared to 6 months for non-responders. Overall the RR for those receiving palliative radiation was 37% with 47-59% palliation of symptoms.

Though multiple regimens have been studied in the palliative treatment of locally advanced head and neck cancer, the RTOG "Quad Shot" offers the best combination of efficacy, safety and patient convenience. This regimen has been associated with RRs of 53-95% and has been successfully combined with chemotherapy. The monthly interval between repeats allows non-responders and those whose PS declines to discontinue treatment.

Palliation of hepatic metastasis

Many of the studies of liver radiation for metastatic disease give whole liver irradiation plus or minus a boost (59,60). Given advances in chemotherapeutic agents, this approach has limited relevance. In an effort to improve efficacy

and minimize the liver toxicity associated with whole liver radiation therapy, others have studied an accelerated hyperfractionated (more than 1 fraction per day at a dose lower than 1.8-2 Gy) approach (61). Palliative treatment of liver metastasis can be divided into purely palliative radiation (the scope of this article) *vs.* stereotactic body irradiation of oligometastatic disease, a discussion of which is beyond the scope of this article. Interested readers are directed to the following reference for further reading on that topic (62).

The Trans-Tasman Radiation Oncology Group looked at 2 fractions of 5 Gy given to the liver tumors plus a margin to relieve symptoms due to hepatic metastasis such as abdominal distention, hepatic pain, night sweats, nausea and/or vomiting. At 2 weeks, 50-66% improvement in individual symptoms was noted. Progressive relief of hepatic pain was noted through the 10 weeks follow-up period. There was a 7% grade 3 toxicity rate and 75% of patients perceived a benefit from treatment. A pain flare was noted in four patients (62,63).

Brain metastasis

The most extensive studies of fractionation, comprising ~2,000 patients treated with RT for brain metastasis, were conducted by the RTOG (64,65). Two studies enrolled patients to one of five different radiation regimens (40 Gy in 20 fractions, 40 Gy in 15 fractions, 30 Gy in 15 fractions, 30 Gy in 10 fractions, or 20 Gy in 5 fractions). Selected institutions also participated in ultra-hypofractionated randomization consisting of 1-2 fractions of radiation (10 Gy in 1 fraction or 12 Gy in 2 fractions) (65). There was no difference in any of the five radiation regimens in terms of the frequency of symptom improvement, the duration of symptom improvement, the time to progression of disease, overall survival or the palliative index. Both the patient's initial performance and neurologic status predicted response (64). *Table 4* provides a summary of the trials of fractionation in the treatment of brain metastasis.

There was some concern that patients considered to have a more favorable prognosis may benefit from the higher dose radiation fractionation regimens and were evaluated in a subgroup analysis (67). Though there was a subgroup of breast cancer patients that had a significantly longer median survival (37 weeks compared to 11 weeks), there was no difference in the time to progression or death without progression of neurologic symptoms between the various fractionation regimens. The same held true for those with

Table 4 Hypofractionated radiation trials in brain metastasis

Reference	# Patients	Dose/fractions (Gy)	# Fractions	Time (weeks)	Efficacy	Toxicity
Borgelt (64)	233	3	10	2	No difference in frequency of neurologic improvement, duration of improvement, time to progression, survival or palliative index	
First study	217	2	15	3		
	233	2.66	15	3		
	227	2	20	4		
Borgelt (64)	447	4	5	1		
Second study	228	3	10	2		
	227	2.66	15	3		
Borgelt (65)	26	10	1	1 day	1-2 day regimens had less complete response, shorter duration of improvement and time to progression of symptoms. No difference in symptomatic improvement or survival	No difference in toxicity.
	33	6	2	2 days		
	143	2-4	5-20	1-4		
Rades (66)	69	4	5	1	No difference in survival or local control	No difference in acute or late toxicity
	138	3	10	2		
		2	20	4		

#, number of.

lung cancer and other/unknown primaries. No significant benefit was seen to longer radiation therapy courses.

In a retrospective review of breast cancer patients treated with different fractionation regimens (20 Gy in 5 fractions, 30 Gy in 10 fractions or 40 Gy in 20 fractions, determined by the facility at which they were treated), no difference was seen between regimens in terms of progression of disease, neurologic symptoms or toxicity (66).

A phase I dose-escalated accelerated hypofractionated trial was conducted by Caravatta and colleagues (68). Four fractions, ranging in fraction size from 3-4.5 Gy in 0.5 Gy increments, were delivered BID over 2 days. Only one patient experienced grade 3 acute neurologic toxicity with a median follow-up of 5 months. By 3 weeks after treatment, 76% of patients had resolution or improvement of their symptoms.

Treatment of patients with brain metastasis has changed since the publication of these trials. The majority of patients in the series described above had symptomatic brain metastasis. Today, many patients present simply as a result of a screening magnetic resonance imaging (MRI) and aggressive approaches for oligometastatic disease may be warranted depending on other disease and patient related factors. Since many patients, even if asymptomatic, present with multiple metastatic foci, the data is still very

relevant. The majority of patients present with recursive partitioning analysis (RPA) class 2 and have a median survival of 4.5 months (69). For these patients 20 Gy in 5 fractions or supportive care alone are both reasonable options. There is currently no data to support less toxicity or better local control with longer courses of whole brain RT.

No data exists to support longer fractionated courses over shorter ones; however, there is value in adding surgery or stereotactic radiosurgery to whole brain radiation therapy in patients with good PS, single or oligometastatic (≤ 3) brain disease and controlled systemic disease. Post-operative radiosurgery or radiation boost can be considered in selected patients as can stereotactic radiosurgery alone. For patients whose expected survival is less than 3 months, either supportive care or whole brain radiation therapy are very reasonable approaches. The ASTRO brain metastasis guideline (70) reviews the indications and levels of evidence very well.

Discussion

Hypofractionated palliative radiation can dramatically improve QOL in patients with locally advanced or metastatic cancer. Due to the limited life span of such patients, and the potential difficulties that patients and their families have with transportation to treatment facilities,

every effort should be made to decrease the burden of lengthy multi-fraction courses of radiation. Many centers currently provide same-day consultation, simulation and dose planning, and manage to deliver the first fraction of radiation as well. The rapid response RT programme at the Toronto-Sunnybrook Regional Cancer Center is one such example (71). In the setting of osseous metastasis, this may be the only visit necessary to achieve effective palliation. Additional fractions are typically required for treatment of non-osseous metastasis as detailed in this review. In many of the clinical scenarios detailed here, 2-fraction regimens provide equivalent relief of symptoms with minimal inconvenience to patients. Discussion of survival is complicated by the inclusion criteria of the studies and the practice patterns of different countries. In many of the studies, patients were included for palliative radiation treatment, due to limited resources and philosophy of care, who would be treated with curative intent in the US.

Effective palliation typically begins to occur within 7-10 days of initiation of radiation therapy, with full-effect within 4-6 weeks. Typically palliation is achieved for much of, if not all of the patient's remaining lifespan. Given the timeframe to onset of relief, every effort should be made to avoid palliative radiation in those patients whose expected survival is less than 2 weeks. Physicians routinely overestimate life-expectancy which complicates the decision to begin palliative radiation. Palliative care professionals often cite lengthy multi-fraction radiation regimens as an impediment to referral for palliative radiation treatment. Radiation oncologists who consciously choose to offer shorter courses for appropriate end-of-life patients will certainly fit in with and better augment the efforts of their local hospice and palliative medicine teams.

Conclusions

Hypofractionated palliative radiation is well tolerated with minimal and self-limited side effects. The side effects that do occur are generally limited to the body region treated and last from a few days to a few weeks. Palliative RT is also generally cost-effective when compared to chemotherapy and bisphosphonates. Though the cost-effectiveness of palliative radiation therapy compares favorably to that of chemotherapy, it can still prove too costly for hospice programs. Many hospice programs limit or deny palliative radiation therapy, though it may benefit patients. Technologies designed to further reduce the incidence of rare but serious late effects have the potential to strain

already tight budgets. Limiting the use of expensive techniques such as image-guidance and intensity modulated radiation therapy as well as limiting the number of fractions may help more patients gain access to needed palliation.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Johnstone C, Lutz ST. The role of hypofractionated radiation in the management of non-osseous metastatic or uncontrolled local cancer. *Ann Palliat Med* 2014;3(4):291-303. doi: 10.3978/j.issn.2224-5820.2014.10.01