Single-fraction high-dose-rate brachytherapy: a scoping review on outcomes and toxicities for all disease sites

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Abstract

Purpose: Brachytherapy is well positioned to safely deliver highly conformal single-fraction doses of radiation, which can lower costs and improve efficiency. Traditionally, high-dose-rate brachytherapy (HDR-BT) has been delivered over multiple treatments. A scoping literature review was conducted to better understand the available literature on single-fraction HDR-BT for all disease sites.

Material and methods: According to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, PubMed database was queried from 1994-2021 using the following search terms: ‘brachytherapy’, ‘high-dose-rate’, and ‘single-fraction’. A total of 53 studies met our exclusion criteria.

Results: Liver had the highest number of studies, with a total of 618 patients treated with doses ranging from 8 to 25 Gy. Median follow-up ranged from 11-33 months. Local control (LC) rates ranged from 37% to 98%. G3 acute/late toxicities or higher were reported in 3 patients. Prostate cancer included a total of 1,474 patients treated with doses ranging from 19 to 21 Gy. Median follow-up ranged from 20 to 72 months. Prostate specific antigen (PSA) control outcomes after definitive treatment ranged from 65% to 94%, and salvage treatments from 5% to 84%. G3 acute/late toxicities or higher ranged from 0 to 6%. Breast cancer included a total of 268 patients treated with doses ranging from 16 to 20 Gy. Median follow-up ranged from 24 to 72 months. LC rates were 100%. G3 acute toxicities or higher ranged from 0 to 6%. Regarding other cancers, conclusions were limited given the small number of patients within each respective site.

Conclusions: Currently used regimens appear safe, but efficacy vary by different disease sites. Outcomes are more promising for breast and liver, while are less encouraging for prostate. Additional prospective evaluation of single-fraction HDR-BT regimens are warranted.

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Key words: brachytherapy, high-dose-rate, single-fraction.
generated 26,899 results, ‘high-dose-rate’, which generated 5,356 results, and ‘single-fraction’, which generated 56,908 results. A combined search of ‘brachytherapy AND high-dose-rate AND single-fraction’, yielded 454 results.

The results were reviewed by three authors for inclusion/exclusion (MK, SN, and MK). From the initial 454 records for review, 357 were excluded as they were irrelevant, they were dosimetry studies, or multi-fraction treatments. As a result, 97 reports were sought for retrieval, of which one was not retrieved as the full article was not available on PubMed. From the 96 reports that were assessed for eligibility, 43 papers were excluded for the following reasons: 9 had the same cohort, 11 with follow-up less than 1 year, 4 with sample size less than 10 patients, 5 reports with combination of both follow-up less than 1 year and sample size less than 10 patients, 4 case reports, 6 review articles, and 4 studies that were not applicable. Therefore, 53 studies were included in the final scoping review (Figure 1).

Prostate

Clinical outcomes

Seventeen studies (14 definitive, 1 focal definitive, and 2 focal salvage) with 1,474 patients reported on single-fraction treatment between 2016-2021 (Table 1). Six studies were from the UK, 3 from the USA, 3 from Spain, 3 from Canada, 1 from the Netherlands, and 1 from Italy. Single-fraction dose delivered ranged from 19 to 21 Gy. Eight studies treated patients with androgen deprivation therapy treatment over a range between 3 and 36 months. In the definitive therapy series, median follow-up ranged from 20 to 72 months, while in the salvage series it ranged from 25 to 26 months [1-17].

Of the 14 studies that treated patients with definitive intent, prostate specific antigen (PSA) control rates ranged from 65 to 94% (Figure 2). Seven studies stratified PSA control based on risk groups. PSA control rates for low-risk patients ranged from 79% to 100%, for intermediate-risk patients ranged from 75% to 86%, and for high-risk patients ranged from 75% to 76% (Figure 3).

The most significant study reported was a randomized controlled trial of single-fraction 19 Gy vs. two fractions of 13.5 Gy [18]. This study included 170 patients with either low- or intermediate-risk, with no prior androgen deprivation therapy. Median follow-up was 60 months. The study resulted in a significantly higher rate of PSA biochemical failure in the single-fraction arm. G3 genitourinary (GU) toxicity was only seen in 3% in the single-fraction arm and no reported cases in the two-fraction arm; however, this was statistically insignificant between both groups.

When reviewing patterns of failures after single-fraction treatment, high rates of local failures were reported in a dominant intra-prostatic lesion. Studies that reported on local failure rates reported that this occurred in 4-78% of cases. Attempts to reduce failures in the dominant intra-prostatic lesion by increasing the single-fraction dose have not been successful to date. Prada et al. increased the whole gland single-fraction dose to 20.5 Gy [9], and Armstrong et al. performed a focal boost of 21 Gy to the dominant intra-prostatic lesion [2], but there were still higher than expected failures compared with a multi-fraction regimen. For patients treated with salvage treatment, two studies reported on outcomes with 2-year PSA control rates ranging from 42% to 59%. These results, similar to the definitive setting, demonstrated less than ideal outcomes with single-fraction treatment [12, 16].

![Fig. 1. PRISMA diagram. Identification of studies via databases and registers](image-url)
| Author(s), year | Study type | Def/salvage | No. of patients | Patient risk group | ADT | Dose (Gy) | Median follow-up (months) | Biochemical control | Freedom from local failure | Toxicity (CTCAE) |
|---------------|------------|-------------|----------------|-------------------|-----|-----------|---------------------------|-------------------|-----------------------|-----------------|
| Armstrong et al., 2021 | Pros | Def | Group 1: 25, Group 2: 25 | Group 1: L: 0%, I: 44%, H: 56%, Group 2: L: 4%, I: 40%, H: 56% | 6 months | 21 to DIL with SIB | Group 1: 70 Gy, Group 2: 70 Gy | Group 1: 5 y. – 88%, Group 2: 5 y. – 76% | Group 1: 5 y. – 96%, Group 2: 5 y. – 84% | Acute: 12% G2 GU, 0% ≥ G3 GU, Late: 0% ≥ G2 GI, 3 pts. G3 urethral strictures |
| Tsang et al., 2021 | Pros | Def | 78 | L: 4%, I: 96% | 6 months | T2c and either PSA > 10 or GS 7 | 19 | 48.5 | 5 y. – 69% | N.R. | 5 y. ≥ G2 GU 30%, 5 y. ≥ G2 GI 0% |
| Tharmalingam et al., 2020 | Pros | Def | 441 | L: 10%, I: 65%, H: 25% | 38% median: 6 months | 19 | 26 | 3 y. – 88% (L: 100%, I: 86%, H: 75%) | 15 local with 11 isolated local failures | Acute G2 GU/GI: 12%/3%, 2 pts. late G3 GU, 2 pts. late G3 GI |
| Hoskin et al., 2017 | Pros | Def | 49 | L: 57%, I: 43% | 74% median duration 7 months | 19-20 | 49 | 4 y. – 94% | N.R. | Late 4 y. G3 GU/GI G3 2%/0% |
| Soatti et al., 2020 | Retro | Def | 87 | – | – | 19-20 | 72 | 6 y. – 65% (L: 90%, I: 90%, H: 76%) | – | – |
| Barnes et al., 2019 | Retro | Def | 28 | L: 50%, I: 50% | 1 pt. (short-term) | 19-20 (2 pts. 20) | 28 | 3 y. – 81% (in 19 Gy group) (L: 86%, I: 79%) | 3 y. – 86% | 18% late G2 GU, No late ≥ G3 GI or GU |
| Xu et al., 2019 | Retro | Def | 124 | L: 21%, I: 79% | None | 19 | 26 | 4 y. – 78% (I: 86%) | 12 pts. with recurrence 10 with imaging had local recurrence 8 had biopsy-proved local recurrence | Late GU/GI: 22%/60%, No acute/late ≥ G3 GU/GI |
| Author(s), year | Study type | Def/salvage | No. of patients | Patient risk group | ADT | Dose (Gy) | Median follow-up (months) | Biochemical control | Freedom from local failure | Toxicity (CTCAE) |
|----------------|------------|-------------|----------------|--------------------|-----|-----------|---------------------------|--------------------|--------------------------|-----------------|
| Siddiqui et al., 2019 | Pros | Def | 68 | L: 59% I: 41% | None | 19 | 47 | 5 y. – 77% (L: 79%, I: 75%) | 5 y. – 81% | Late ≥ G2 GU: 15% Late ≥ G2 GI: 6% |
| Peters et al., 2019, Maenhout et al., 2018 | Pros | Def | 30 | L: 13% I: 87% | None | Focal: 19 | 48 | 4 y. – 70% | Local recurrence in 9/10 pts. with biochemical failure; 7/9 out-of-field | No late ≥ G2 GI 1 late G2 GU |
| Gomez-Iiturriaga et al., 2017 | Pros | Def | 43 | L: 44% I: 56% | None | 19 | 20 | N.R. | N.R. | 2 y. – GI ≥ G1: 0% 2 y. GU G1/2/3: 14%/2%/0% |
| Reynaud et al., 2021 | Pros | Def | 16 | N.R. for this arm | None | 19 | 45 | 81% | N.R. | 0 G2 GU 1 G2 GI |
| Prada et al., 2016 | – | Def | 60 | L: 73% I: 27% | 3 m: 3 m | 19 | 72 | 6 y. – 66% (L: 82%, I: 79%) | 88% free of local recurrence | Late G3 GI/GU: 0%/0% |
| Prada et al., 2018 | – | Def | 60 | L: 37% I: 57% | 3 m: 43% | 20.5 | 51 | 6 y. – 82% | 92% | Late GI: none 0 late ≥ G2 GU |
| Slevin et al., 2020 | Retro | Salvage | 43 | Prim tumor risk category: L: 30% I: 40% H: 30% | 3 m: 6 m 21%: 2-3 y | Focal: 19 | 26 | 3 y. – 42% | Local recurrence in 16% | Late G3 GI/GU: 2%/0% |
| Willigenburg et al., 2021 | Pros | Salvage | 150 | Prim tumor risk category: L: 18% I: 37% H: 39% | – | Focal: 19 | 25 | Model 1: 5 y.: L: 84% I: 70% H: 31% Model 2: 5 y.: L: 100% I: 71% H: 5% | N.R. | N.R. |
| Alayed et al., 2021 | Pros | Def | Trial 1: 87 Trial 2: 60 | Trial 1: L: 23% I: 75% Trial 2: L: 8% I: 90% | Trial 1: None | Trial 1: 19 whole gland, Trial 2: 19 whole gland/23 focal boost | Trial 1: 62 Trial 2: 50 | Trial 1: 5 y. – 67% Trial 2: 5 y. – 69% Trial 1 and 2 combined: (L: 91%, I: 76%) | 78% of failures local | Trial 1: Late G3 GI/GU: 2%/0% Trial 2: Late G3 GI/GU: 0%/0% |

*Study included 4, 2, and 1 fraction HDR BT monotherapy, but did not stratify the outcomes separately, except for PSA control for the 19-20 Gy group*
Toxicities

Acute G1-G2 GU toxicities were reported in 0-12%, while acute G1-G2 gastrointestinal (GI) toxicities were reported in 0-3% of patients. Late G1-G2 GU toxicities were reported in 0-60%, while late G1-G2 GI toxicities were reported in 0-6%. Types of late G3 toxicities reported were urethral strictures [2], rectal fistulae [14], chronic diarrhea [11] that was medically managed, and obstruction of the urinary tract that necessitated TURP [1].

Breast

Seven studies (all definitive after lumpectomy) with 268 patients were reporting on receiving single-fraction treatment between 2008-2021 (Table 2). Five studies were from France, 1 from Spain, and 1 from the USA. Single-fraction high-dose brachytherapy dose delivered ranged between 16 and 21 Gy. Median ages of patients treated ranged from 64 to 77 years, and included patients with early-stage breast cancer [18-24].

Median reported follow-up ranged from 24 to 72 months. At 6 years, freedom from local recurrence (LR) was 100%, disease-free survival (DFS) ranged from 82% to 100%, and median overall survival (OS) ranged from 82% to 100%.

Toxicities

Single-fraction treatment appeared to be well-tolerated in acute and late term settings. Amongst the doses used, Sacchini’s paper initially assessed a single-fraction dose of 20 Gy. However, due to increased acute toxicity rates, the dose was lowered to 18 Gy [24]. This is also a unique series that used an HDR applicator intra-operatively, and the dose distribution with this approach was very different from that of the other papers, which used an interstitial technique. For papers that used doses in the 16-18 Gy range, serious acute toxicities were seen in < 5% of patients. No grade 3 or higher late toxicities have been reported to date. Excellent to good cosmesis outcomes were reported in 76-98% of patients. These early to mid-term results of single-fraction brachytherapy appear promising for this highly selected group of favorable patients. Longer term data is needed to confirm the favorable oncologic and cosmetic results.

Liver

Eighteen studies (7 primary, 11 metastasis) with 618 patients have been reported on receiving single-fraction treatment between 2004-2021 (Table 3). Seventeen studies were from Germany, and one was from Poland [25-42]. Single-fraction high-dose brachytherapy dose delivered ranged from 8 to 25 Gy. Median follow-up range for series that treated a primary liver cancer was 12-23 months, and median follow-up range for series that treated liver metastasis ranged from 11 to 28 months. Local control range for primary disease ranged from 37% to 93%, and local control range for metastasis ranged from 40% to 94% (Figure 4). Furthermore, Denecke et al. focused on comparing single-fraction brachytherapy as a bridge to liver transplant compared with the standard modality of transarterial chemoembolization (TACE). This study showed that for patients who are not candidates for TACE, single-fraction treatment may be an acceptable alternative modality [28]. There are large variations in the local control rates reported. Much of this seems to be related to the dose given as well as the size of the tumor treated. Ricke et al. showed in a dose escalation trial, for example, improved local control rates when increasing the dosage from 15 Gy to 25 Gy in a single-fraction [33].

Toxicities

G3 toxicity was reported in 3 patients with liver abscesses post-interstitial brachytherapy in a study done by Drewes et al. [29]. Other serious complications were noted, including post-interventional abdominal hemorrhage, pneumothorax, biliary abscess [41], and Gram-negative septicemia [38]; however, only a few cases were reported.
### Table 2. Single-fraction breast high-dose-rate brachytherapy (HDR-BT) studies

| Study (year)       | No. of patients | Median age (years) | Median lesion size (cm) | Single-fraction dose (Gy) | Median follow-up (months) | LR (months) | DFS (months) | Median OS (months) | Acute toxicities | Chronic toxicities | Cosmesis (excellent or good) |
|--------------------|-----------------|--------------------|-------------------------|---------------------------|---------------------------|-------------|--------------|-------------------|------------------|-------------------|---------------------|
| Sacchini (2008)    | 52              | 76                 | < 2                     | 20<sup>1</sup>, 18<sup>2</sup> | 31.4                      | 0%          | –            | –                 | 4% re-operation for poor wound healing | –                | Better cosmesis scores in patients treated with 18 Gy than 20 Gy |
| Latorre (2018)     | 20              | 63.5               | < 3                     | 18                         | 24                        | 0% (24)     | 95% (24)     | 100% (24)         | No G3 toxicities or higher observed | No G3 toxicities or higher observed | No differences in cosmetic results pre or post therapy |
| Kinj (2018)        | 48              | 77.7               | 1.2                     | 16                         | 40                        | 0% (40)     | 100% (36)    | 93.1% (36)        | 2 patients had G3 breast hematomas 1 patient had G3 breast abscess | No G3 toxicities or higher observed | 76% |
| Kinj (2019)        | 48              | 77.7               | 1.2                     | 16                         | 64                        | 0% (64)     | 100% (60)    | 87.3% (60)        | Previously reported in Kinj 2018 | No G3 toxicities or higher observed | Excellent: 76.4% Good: 25.6% |
| Hannoun-Lévi (2020)| 26              | 76.6               | 1.04                    | 16                         | 63                        | 0% (60)     | 100% (60)    | 88.5% (60)        | G3 events: 4.5% | No G3 toxicities or higher observed | Excellent: 80.8% Good: 19.2% |
| Hannoun-Lévi (2021)| 48              | 75                 | 1                       | 16                         | 72                        | 0% (72)     | 82.2% (72)   | 82.2% (72)        | G3 events: 4.5%<sup>1</sup> | No G3 toxicities or higher observed | 98% |
| Boulahssass (2021) | 26              | 77                 | < 2                     | 16                         | 63                        | –           | –            | –                 | –                | –                | 88% |

<sup>1</sup>the first 18 patients were treated with a single-fraction dose of 20 Gy. <sup>2</sup>given high rates of acute toxicities with 20 Gy, the remaining 34 were treated with a single-fraction dose of 18 Gy. <sup>3</sup>the paper did not distinguish between the G3 events in the hyper-fractionated and single-fraction group.
### Table 3. Single-fraction liver high-dose-rate (HDR) studies

| Entity | Study (year) | No. of patients | Median age (years) | Median lesion size (cm) | Single-fraction dose (Gy) | Median follow-up (months) | LTC (months) | PFS (months) | Median OS (months) | Toxicities |
|--------|--------------|-----------------|-------------------|------------------------|--------------------------|--------------------------|-------------|-------------|-------------------|------------|
| Primary hepatic malignancies | Collettini (2012) | 35 | 68 | 7.1 | 15 | 12.8 | – | 8.75 | – | Distant tumor progression: 30% | No major complications |
| | Collettini (2015) | 98 | 70 | – | 16.5 | 23.1 | 21.1 | 15.2 | 29.2 | 80.2% (12) 62.0% (24) 46.0% (36) | Mortality 43.9% 12 patients lost to follow-up |
| | Denecke (2015) | 12 | 59 | 1 | 18.9 (15-25) | – | 10% (12) 10% (36) | – | – | 1 patient had arterial bleeding post-removal of brachytherapy catheters requiring embolization |
| | Schnapauff (2015) | 19 | – | – | 20 | 33 | 32.1 | 20 | 50 | Mortality: 42% 3 patients lost to follow-up 1 patient had post-interventional hepatic hemorrhage that spontaneously tamponated |
| | Walter (2021) | 38 | 67 | 2.9 | 15 | – | – | – | – | – |
| | Tselis (2013) | 22 | 64 | 84 | 8 (7-14) | 12.4 | 90% (6) 81% (12) 50% (18) | – | 13.2 | Mortality: 80% No procedure-related deaths Major complications: 5% |
| | Schnapauff (2012) | 15 | 66 | 5.25 | 20 | 14 | 10 | 13 | 14 | Mortality: 60% |
| | Jonczyk (2018) | 35 | 66 | A: 2.04 B: 6.92 | A: 20 Gy B: > 12 Gy | A: (8) 98% (6) 87% (12) 72% (24) 72% (36) 72% (60) 89% (6) 78% (12) 37% (24) 37% (36) 37% (60) | – | A: (5) 41% (6) 35% (12) 24% (24) 24% (36) 16% (60) 39% (6) 25% (12) 17% (24) 17% (36) 17% (60) | A: (15.5) 94% (6) 68% (12) 61% (24) 46% (36) 36% (60) 75% (6) 63% (12) 36% (24) 16% (36) 12% (60) | Mortality: 57.3% |
| Secondary hepatic malignancies | Ricke (2004) | 21 | 66 | 4.8 | 10-20 | 14 | 87% (6) 87% (9) | 59% (6) 34% (12) | 86% (6) 69% (12) | 1 patient had post-intervention symptomatic liver dysfunction 1 patient had mechanical occlusion of central bile duct requiring endoscopic stenting |
### Table 3. Cont.

| Entity | Study (year) | No. of patients | Median age (years) | Median lesion size (cm) | Single-fraction dose (Gy) | Median follow-up (months) | LTC (months) | PFS (months) | Median OS (months) | Toxicities |
|--------|--------------|-----------------|--------------------|-------------------------|--------------------------|---------------------------|--------------|--------------|-------------------|------------|
| Ricke (2004) | 20 | 66 | A: 7.4 | B: 3.4 | 17 (12-25) | 13 | A: 74% (6) | 30% (12) | B: 100% (6) | 71% (12) | 89% (6) | 83% (12) | 1 patient had post-interventional intra-abdominal bleeding 1 patient had mechanical occlusion of central bile duct requiring endoscopic stenting 4 patients lost to follow-up. 3:4 patients died |
| Kieszko (2018) | 61 | – | – | 20 (13-29) | 11 | 88.7% (6) | 70.7% (12) | 78.1% (6) | 53.8% (12) | 96.7% (6) | 79.6% (12) | 15 patients succumbed to cancer (24.6%) No G2 events or greater were observed |
| Wieners (2009) | 33 | 64 | 4.6 | 18 Gy (15-25) | 28 | 87% (6) | 76% (12) | 76% (18) | 69% (24) | 10.5% | No progression (6%) Intra-hepatic (57.5%) Extra-hepatic (27.2%) Intra- and extra-hepatic (9%) |
| Ricke (2010) | 73 | | 3.1 | 15, 20, and 25 | 15.2 | 25.1% | 6 | 10.5 (exclude tumor recurrences) | 23.4 (first ablation) | 46.7 (first diagnosis of liver metastases) | 56.2 (first diagnosis of primary tumor) | 2 patients had occult blood requiring transfusion 2 patients had symptomatic gastric ulcer 1 patient had pleural effusion treated by pleurodesis 1 patient had anaphylactic reaction to iodide contrast media |
| Coletti (2014) | 37 | 66 | 2.85 | 19.1 (15-20) | 16.9 | 10.7 | 88.3% (12) | 81.2% (24) | 68.4% (36) | | Local progression (12.9%) | 18 | 87.6% (12) | 57.3% (24) | 41.6% (36) | 43% died from colorectal cancer |
| Entity        | Study (year) | No. of patients | Median age (years) | Median lesion size (cm) | Single-fraction dose (Gy) | Median follow-up (months) | LTC (months) | PFS (months) | Median OS (months) | Toxicities                                                                 |
|---------------|--------------|-----------------|-------------------|-------------------------|---------------------------|---------------------------|---------------|---------------|-------------------|---------------------------------------------------------------------------|
| Wieners       | (2015)       | 16              | –                 | 2.9                     | 19 (15-20)                | 13.7                      | –             | 4.9           | 8.6               | No progression (20%)<br>Intra-hepatic progression (40%)<br>Extra-hepatic progression (20%)<br>Intra- and extra-hepatic progression (20%)<br>3 post-interventional abscesses (20%)<br>80% (6)<br>45% (12) |
| Drewes        | (2019)       | 16              | 62                | 2.2                     | 21 (5-29.1)               | –                         | 86.7% (3.3)   | 3.4           | 8.9               | 3 patients had G3 liver abscesses post interstitial brachytherapy<br>30 day mortality (0%)<br>Symptomatic post-interventional blood loss through puncture site (1.4%) |
| Wieners       | (2011)       | 41              | 55                | 4.4                     | 15-25                     | 18                        | 97% (6)       | 8.1           | 97% (6)          | Intra-hepatic progression (58.5%)<br>Extra-hepatic (7.3%)<br>Intra- and extra-hepatic progression (19.5%)<br>Local progression (11.5%)<br>No post-interventional mortality<br>Hepatic abscess (11.1%)<br>8 of 10 patients with local tumor progression died from poor liver function<br>93% (12)<br>93.5% (18)<br>40% (12)<br>27% (18)<br>88.9% (9) |
| Schippers     | (2017)       | 27              | 63                | 2.1                     | –                         | 96.3% (3)                 | No progression (88.9%)<br>Local progression (11.1%)<br>No post-interventional mortality<br>Hepatic abscess (11.1%)<br>10 of 3 patients with biliodigestive anastomosis developed hepatic abscess 4.9 months post-ablation |
with such complications (Table 3). Overall single-fraction HDR-BT appeared to be a safe modality given a low number of serious toxicities reported to date.

Other cancers

Eleven published studies met the inclusion criteria in assessing the efficacy of single-fraction high-dose brachytherapy for cancers other than prostate, breast, and liver. The studies were published by groups in the following locations: 4 from the USA, 3 from Germany, 1 from Italy, 1 from the United Kingdom, 1 from China, and 1 from Spain [43-53]. Table 4 summarizes the oncological outcomes and toxicities for these eleven publications. There were 3 studies for gastrointestinal, 2 studies for head and neck, 3 studies for lung, 1 study for gastrointestinal stromal tumor, 1 study for glioma, and 1 study for endometrial carcinoma. Amongst these studies, lung appears to have promising data. Yoon et al. reported on 23 patients treated with 21.5 Gy single-fraction HDR brachytherapy, with local control of 96% at 2 years for centrally located primary and metastatic lung cancer, and no G3 or higher toxicities were reported [52]. Xiang et al. also reported on single-fraction HDR lung brachytherapy in a phase I clinical trial. A single-fraction of 30 Gy brachytherapy to the primary in combination with intensity-modulated radiation therapy (IMRT) to nodal regions while receiving concurrent chemotherapy resulted in 82% local tumor control at 2 years [51]. It is difficult to make any definitive conclusions regarding the efficacy of single-fraction brachytherapy for lung or these other less common sites, given the limited data for each type of cancer.

Discussion

There is interest in single-fraction treatment both from a patient and hospital system perspectives. Increasing studies are being conducted using single-fraction external beam treatments [54], including randomized clinical trials. Brachytherapy is uniquely positioned to deliver very high doses of radiation in single treatments with rapid fall-off, and may provide various advantages over external beam approaches. Delivering a single-fraction HDR brachytherapy is technically feasible, but there are unanswered questions regarding the safety and efficacy of delivering very high doses of radiation in a single treatment. Determining whether pursuit of such an effort is worthwhile requires an understanding of the current published literature on this topic.

Our literature search identified 53 papers, which were included in this review. A large number of prostate cancer patients have been treated with single-fraction treatment and mostly in the definitive setting. There has even been a randomized controlled trial on two versus single-fraction HDR-BT demonstrating inferior biochemical control in the single-fraction arm [55]. Multiple studies also demonstrate high rates of locally persistent disease predominantly in the dominant intra-prostatic lesion [56]. Further attempts at single-fraction dose escalation has also not significantly improved outcomes [1]. In addition, in reviewing the biochemical control outcomes by risk group, it does not appear that there is a risk group that has acceptable control with single-fraction treatment. Based on the current literature, it does not appear that single-fraction HDR-BT for definitive prostate cancer treatment is an acceptable standard of care. Any future work in this area should be conducted as part of a clinical trial.

The published work on single-fraction treatment in the salvage setting is limited to just two studies, but the overall trends are similar as that seen in the definitive setting, with worse than expected biochemical control compared with multi-fractionated regimens. It seems likely that single-fraction treatment in the salvage setting will also not be ideal regarding long-term oncologic control. The reasons for these less than promising results is not entirely clear. It likely includes an incomplete understanding of radiation biology and accurate conversions of dose using α/β ratio and linear quadratic modelling as well has cell re-assortment and hypoxia. These limitations should be balanced with the possible lower toxicities seen in the short-term with a single-fraction treatment, which is a more pertinent consideration in the re-irradiation setting. However, longer follow-up is needed with single-fraction regimens in this setting. As in the definitive setting, worse GU toxicities have been reported with single- vs. multi-fraction regimens [4].

Single-fraction breast literature appears promising both in terms of early oncologic control and limited toxicities. It is difficult to know whether the high local control rates confirm that single-fraction treatments are truly effective, or whether the relatively low-risk population would not have recurred even without adjuvant radiation. The experience with single-fraction treatment is also mostly limited to one group in France that has used an interstitial technique. There is an ongoing clinical trial with a balloon-based single-fraction technique, which has not reported oncologic outcomes yet [57], but has reported limited severe toxicities to date. Single-fraction external beam treatments are also being developed both in the pre-operative and post-operative spaces [58]. Continued work in this space is needed to determine the ideal single-fraction dose, and long-term oncologic...
| Entity | Study (year) | No. of patients | Median age (years) | Mean lesion size (cm) | Single-fraction dose (Gy) | Median follow-up (months) | LTC (months) | PFS (months) | Median OS (months, %) | Definitive or salvage | Toxicities |
|--------|-------------|----------------|-------------------|-----------------------|--------------------------|--------------------------|-------------|-------------|------------------------|------------------------|------------|
| GI     | Kolotas (2003) | 38  | 631 | – | 10-15 | 23.4 | – | Local progression: 10.5%  
Partial remission: 15.7% | 15 | Salvage | Mortality: 65.7%  
1 patient developed a fistula6  
1 patient developed an abscess7 |
| Hoskin (2004) | 22  | 82 | – | 10 | 110 | – | – | 7.2 | Salvage | No significant acute toxicity  
9 deaths due to causes other than progression of malignancy with 3 cases unknown |
| Omari (2019) | 12  | 63 | 2 | 19.9 (5.4-22) | 8.34 | 89% | 6.5 | 11.4 | Salvage | 1 patient had G3-infected hepatic hematomaa |
| GIST   | Omari (2019) | 10  | 58 | 2.4 | 15 (6.7-22) | 24.6 | 97.5% (25) | 6.8 | 37.3 | Definitive | Mortality: 60%  
1 patient had G3 hepatic hemorrhage9  
1 patient had G3 pneumothorax10 |
| Glioma | Fabrini (2009) | 21  | 60 | – | 18 | 32.3 | – | 8.6 | 42% (6) | 21.7 | Definitive | Mortality: 71%  
1 patient had G5 fatal post-operative hemorrhage (day 1)  
1 patient had G3 CSF leak |
| Head and neck | Nag (2005) | 18  | 611 | – | 101 (7.5-20) | 65 | 77% (12) | 69% (36) | 59% (60) | 72% (12) | 65% (36) | 53% (60) | 50 | 12 (83%) | 36 (63%) | 60 (42%) | Definitive and salvage | No major intra-operative or acute post-operative complications  
3 deaths from post-operative complications  
1 death from septicemia due to chemotherapy  
6 deaths from unrelated causes |
| Teckie (2013) | 57  | 54 | – | 15 (12-20) | 16 | – | 67% (12) | 57% (36) | 6% (36) | 12 (75%) | 36 (43%) | Definitive | Mortality: 70%  
G3 late events: 16%  
No G4-5 events observed |
| Lung   | Chan (2010) | 17  | 74 | 32 | 18 (14.4-20) | 22 | 83% (24) | 76% (24) | 21 (53%) | Salvage | Mortality: 64.7%  
1 patient died from pneumonia  
1 patient died from second primary cancer  
No treatment-related deaths |
and toxicity outcomes. It is important for future studies to include prospective collection of quality-of-life data, as these would be necessary to understand the place of brachytherapy compared with alternative external beam methods for delivering single-fraction doses.

Single-fraction liver treatments have been published in retrospective, single-arm prospective, and even in randomized controlled trials [59]. Liver single-fraction literature is unique in that dose escalation trials have been performed to find the ideal dose, as previously mentioned in a study by Ricke et al. [33]. Significant work has also been done to determine organ at risk dose constraints, and understanding of the limitations of treating perihilar disease. Local control rates for appropriately sized lesions treated with appropriate single-fraction doses demonstrate local control ranges comparable to stereotactic body radiation therapy or other ablative techniques. Toxicities also seem limited. According to the 2018 ESMO guidelines for hepatocellular cancer, single-fraction liver brachytherapy is now included as a treatment option. These encouraging results in the liver are despite the fact that many patients were heavily pretreated, and had failed other prior local therapy regimens.

Additional single-fraction studies have been done outside of the prostate, breast, and liver, but are very limited. There is some promising data in the lung, but overall conclusions are limited given the small numbers of patients who have been treated to date. Our study has some limitations. PubMed was the only queried database, and if we had conducted a systematic review and included additional databases, we may have found more studies. Also, not all studies provided the same categories of data, such as prostate risk groups, which made it more challenging to evaluate certain patients’ sub-groups.

Conclusions

The medium-sized body of literature published on single-fraction HDR brachytherapy shows this modality as safe, but its’ efficacy varies amongst different disease sites. Breast and liver have the most promising data, while prostate has the least encouraging, and conclusions are limited with respect to other cancers. Additional prospective evaluation of single-fraction HDR-BT studies is warranted.

Disclosure

Dr. Mitchell Kamrava, MD, MHDS have conflicts of interest. ABS board of directors’ member at large, ADROP board of directors’ member at large, advisory board fees Theragenics Corp., DSMB GammaTile, Alessa, and Book Royalties Springer.

The other authors report no conflict of interest.

References

1. Alayed Y, Loblaw A, McGuffin M et al. Single-fraction HDR brachytherapy as monotherapy in low and intermediate risk prostate cancer: Outcomes from two clinical trials with and without an MRI-guided boost. *Radiother Oncol* 2021; 154: 29-35.
2. Armstrong S, Brown S, Stancliffe M et al. Single dose high-dose-rate brachytherapy with focal dose escalation for prostate cancer: Mature results of a phase 2 clinical trial. Radiother Oncol 2019; 135: 67-74.

3. Barnes JM, Gabani P, Sanders M et al. Single fraction high-dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: toxicities and early outcomes from a single institutional experience. J Contemp Brachytherapy 2019; 11: 399-408.

4. Corkum M, Loblaw A, Hasan Y et al. Prostate high dose rate brachytherapy as monotherapy for prostate cancer: Late toxicity and patient reported outcomes from a randomized phase II clinical trial. Radiother Oncol 2021; 156: 160-165.

5. Gomez-Irurriaga A, Casquero F, Pijoan JJ et al. Health-related-quality-of-life and toxicity after single fraction 19 Gy high-dose-rate prostate brachytherapy: Phase II trial. Radiother Oncol 2018; 126: 278-282.

6. Hoskin P, Rojas A, Ostler P et al. Single-dose high-dose-rate brachytherapy compared to two and three fractions for locally advanced prostate cancer. Radiother Oncol 2017; 124: 56-60.

7. Peters M, van Son MJ, Moerland MA et al. MRI-guided ultra-focal HDR brachytherapy for localized prostate cancer: median 4-year results of a feasibility study. Int J Radiat Oncol Biol Phys 2019; 104: 1045-1053.

8. Prada PJ, Cardenal J, Blanco AG et al. High-dose-rate interstitial brachytherapy as monotherapy in one fraction for the treatment of favorable stage prostate cancer: Toxicity and long-term biochemical results. Radiother Oncol 2016; 119: 411-416.

9. Prada PJ, Ferri M, Cardenal J et al. High-dose-rate interstitial brachytherapy as monotherapy in one fraction of 20.5 Gy for the treatment of localized prostate cancer: Toxicity and 6-year biochemical results. Brachytherapy 2018; 17: 845-851.

10. Reynaud T, Hathout L, Carignan D et al. PSA outcomes and late toxicity of single-fraction HDR brachytherapy and LDR brachytherapy as monotherapy in localized prostate cancer: a phase 2 randomized pilot study. Brachytherapy 2021; 20: 1090-1098.

11. Siddiqui ZA, Gustafson GS, Ye H et al. Five-year outcomes of a single-institution prospective trial of 19-Gy single-fraction high-dose-rate brachytherapy for low- and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2019; 104: 1038-1044.

12. Slevin F, Hodgson S, Radda SL et al. Efficacy and toxicity outcomes for patients treated with focal salvage high dose rate brachytherapy for locally recurrent prostate cancer. Clin Transl Radiat Oncol 2020; 23: 20-26.

13. Scattì CP, Delishaj D, D’Amico R et al. High-dose-rate brachytherapy as monotherapy for localized prostate cancer using three different doses – 14 years of a single-centre experience. J Contemp Brachytherapy 2020; 12: 533-539.

14. Tharmalingam H, Tsang Y, Ostler P et al.; National UK HDR Prostate Brachytherapy Database. Single dose high-dose-rate (HDR) brachytherapy (BT) as monotherapy for localised prostate cancer: Early results of a UK national cohort study. Radiother Oncol 2020; 143: 95-100.

15. Tsang YM, Tharmalingam H, Belessiotis-Richards K et al. Ultra-hypofractionated radiotherapy for low- and intermediate risk prostate cancer: high-dose-rate brachytherapy vs stereotactic ablative radiotherapy. Radiother Oncol 2015; 158: 184-190.

16. Willingenburg T, van Son MJ, van de Poll SMG et al. Development and internal validation of multivariable prediction models for biochemical failure after MRI-guided focal salvage high-dose-rate brachytherapy for radiorecurrent prostate cancer. Clin Transl Radiat Oncol 2021; 30: 7-14.

17. Xu MJ, Chen KS, Chang AJ et al. Single-fraction brachytherapy as monotherapy for early-stage prostate cancer: The UCSF experience. Brachytherapy 2019; 18: 470-476.

18. Boulahebsas R, Chand ME, Gal J et al. Quality of life and comprehensive geriatric assessment (CGA) in older adults receiving accelerated partial breast irradiation (APBI) using a single fraction of multi-carrier interstitial high-dose-rate brachytherapy (MIB). The SiFEBI phase I/II trial. J Geriatr Oncol 2021; 12: 1085-1091.

19. Hannoun-Lévi JM, Lam Cham Kee D, Gal J et al. Accelerated partial breast irradiation in the elderly: 5-year results of the single fraction elderly breast irradiation (SiFEBI) phase I/II trial. Brachytherapy 2020; 19: 90-96.

20. Hannoun-Lévi JM, Montagne L, Sumodhee S et al. APBI versus ultra-APBI in the elderly with low-risk breast cancer: a comparative analysis of oncological outcome and late toxicity. Int J Radiat Oncol Biol Phys 2021; 111: 56-67.

21. Kinj R, Chand ME, Gal J et al. Five-year oncological outcome after a single fraction of accelerated partial breast irradiation in the elderly. Radiother Oncol 2019; 14: 234.

22. Kinj R, Chand ME, Gal J et al. Single fraction of accelerated partial breast irradiation in the elderly: early clinical outcome. Radiat Oncol 2018; 13: 174.

23. Latore JA, Galdós P, Buznego LA et al. Accelerated partial breast irradiation in a single 18 Gy fraction with high-dose-rate brachytherapy: preliminary results. J Contemp Brachytherapy 2018; 10: 58-63.

24. Sacchini V, Beal K, Goldberg J et al. Study of quadrant high-dose intraoperative radiation therapy for early-stage breast cancer. Br J Surg 2008; 95: 1105-1110.

25. Colletti F, Lutter A, Schnapauff D et al. Unresectable colorectal liver metastases: percutaneous ablation using CT-guided high-dose-rate brachytherapy (CT-HDBRT). Rofo 2014; 186: 606-612.

26. Colletti F, Schnapauff D, Poellinger A et al. Hepatocellular carcinoma: computed-tomography-guided high-dose-rate brachytherapy (CT-HDBRT) ablation of large (>7 cm) and very large (>7 cm) tumours. Eur Radiol 2012; 22: 1101-1109.

27. Colletti F, Schreiber N, Schnapauff D et al. CT-guided high-dose-rate brachytherapy of unresectable hepatocellular carcinoma. Strahlenther Onkol 2015; 191: 405-412.

28. Denecke T, Stelter L, Schnapauff D et al. CT-guided interstitial brachytherapy of hepatocellular carcinoma before liver transplantation: an equivalent alternative to transarterial chemoembolization? Eur Radiol 2015; 25: 2608-2616.

29. Dreves R, Omani J, Manig M et al. Treatment of hepatic pancreatic ductal adenocarcinoma metastases with high-dose-rate image-guided interstitial brachytherapy: a single center experience. J Contemp Brachytherapy 2019; 11: 329-336.

30. Jonczyk M, Colletti F, Schnapauff D et al. Cholangiocarcinoma: CT-guided high-dose rate brachytherapy (CT-HDBRT) for limited (<4 cm) and large (>4 cm) tumors. Anti-cancer Res 2018; 38: 5843-5852.

31. Kieszko D, Cisek P, Kordzińska-Cisek I, Grzybowska-Szatkowska L. Treatment of hepatic metastases with computed tomography-guided interstitial brachytherapy. Oncol Lett 2018; 15: 8717-8722.

32. Ricke J, Mohnike K, Pech M et al. Local response and impact on survival after local ablation of liver metastases from colorectal carcinoma by computed tomography-guided high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 2010; 78: 479-485.

33. Ricke J, Wust P, Stohlmann A et al. CT-guided interstitial brachytherapy of liver malignancies alone or in combination with thermal ablation for colorectal carcinoma: results of a novel technique. Int J Radiat Oncol Biol Phys 2004; 58: 1496-1505.

34. Ricke J, Wust P, Wieners G et al. Liver malignancies: CT-guided interstitial brachytherapy in patients with unfavorable lesions for thermal ablation. J Vasc Interv Radiol 2004; 15: 1279-1286.
Teckie S, Scala LM, Ho F et al. High-dose-rate intraoperative brachytherapy as salvage therapy for intrahepatic recurrence of HCC after surgical resection. *Anticancer Res* 2015; 35: 319-323.

Hoskin PJ, de Canha SM, Bownes P et al. High dose rate afterloading intraluminal brachytherapy for advanced inoperable gastric adenocarcinoma. *Brachytherapy* 2005; 4: 217-223.

Nag S, Koc M, Schuller DE et al. Intraoperative single fraction high-dose-rate brachytherapy in the multidisciplinary treatment of neuroendocrine tumor liver metastases. *J Vasc Interv Radiol* 2017; 28: 672-682.

Schnapauff D, Collettini F, Hartwig K et al. CT-guided brachytherapy for centrally located liver tumours: a single institution study. *Eur Radiol* 2013; 23: 2264-2270.

Walter F, Nierer L, Rottler M et al. Comparison of liver exposure in CT-guided high-dose rate (HDR) interstitial brachytherapy versus SBRT in hepatocellular carcinoma. *Radiother Oncol* 2021; 16: 86.

Wiener G, Mohrle K, Peters N et al. Treatment of hepatic metastases of breast cancer with CT-guided interstitial brachytherapy – a phase II-study. *Radiother Oncol* 2011; 100: 314-319.

Wiener G, Pech M, Hildebrandt B et al. Phase II feasibility study on the combination of two different regional treatment approaches in patients with colorectal “liver-only” metastases: hepatic interstitial brachytherapy plus regional chemotherapy. *Cardiovasc Intervent Radiol* 2009; 32: 937-945.

Wiener G, Schippers AC, Collettini F et al. CT-guided high-dose-rate brachytherapy in the interdisciplinat treatment of patients with liver metastases of pancreatic cancer. *Hepatobiliary Pancreat Dis Int* 2015; 14: 530-538.

Chan MD, Dupuy DE, Mayo-Smith WW et al. Combined radiofrequency ablation and high-dose rate brachytherapy for early-stage non-small-cell lung cancer. *Brachytherapy* 2011; 10: 253-259.

Fabrini MG, Perrone F, De Franco L et al. Perioperative high-dose-rate brachytherapy in the treatment of recurrent malignant gliomas. *Strahlenther Onkol* 2009; 185: 524-529. Erratum in: *Strahlenther Onkol* 2009; 185: 703.

Nag S, Koc M, Schuller DE et al. Intraoperative single fraction high-dose-rate brachytherapy for head and neck cancers. *Brachytherapy* 2005; 4: 217-223.

Hoskin PJ, de Canha SM, Bownes P et al. High dose rate afterloading intraluminal brachytherapy for advanced inoperable rectal carcinoma. *Radiother Oncol* 2004; 73: 195-198.

Kolotas C, Röddiger S, Strassmann G et al. Palliative interstitial HDR brachytherapy for recurrent rectal cancer. *Implantation techniques and results. Strahlenther Onkol* 2003; 179: 458-463.

Omari J, Drewes R, Matthias M et al. Treatment of metastatic, imatinib refractory, gastrointestinal stroma tumor with image-guided high-dose-rate interstitial brachytherapy. *Brachytherapy* 2019; 18: 63-70.

Omari J, Drewes R, Orthmer M et al. Treatment of metastatic gastric adenocarcinoma with image-guided high-dose rate, interstitial brachytherapy as second-line or salvage therapy. *Diagn Interv Radiol* 2019; 25: 360-367.

Teckie S, Scala LM, Ho F et al. High-dose-rate intraoperative brachytherapy and radical surgical resection in the management of recurrent head-and-neck cancer. *Brachytherapy* 2013; 12: 228-234.

Xiang L, Zhang JW, Lin S et al. Computed tomography-guided interstitial high-dose-rate brachytherapy in combination with regional positive lymph node intensity-modulated radiation therapy in locally advanced peripheral non-small cell lung cancer: a phase 1 clinical trial. *Int J Radiat Oncol Biol Phys* 2015; 92: 1027-1034.

Yoon SM, Suh R, Abtin F et al. Outcomes with multi-disciplinary management of central lung tumors with CT-guided percutaneous high dose rate brachyablation. *Radiother Oncol* 2021; 16: 99.

Zhang Y, Ascano C, Herrerons A et al. Is one brachytherapy fraction of 7 Gy similar to more fractions after external beam irradiation in postoperative endometrial carcinoma? *Clin Transl Oncol* 2020; 22: 1295-1302.

Bartl AJ, Mahoney M, Hennon MW et al. Systematic review of single-fraction stereotactic body radiation therapy for early stage non-small-cell lung cancer and lung oligometastases: how to stop worrying and love one and done. *Cancers (Basel)* 2022; 14: 790.