1-1-2023

Patterns of utilization and clinical adoption of 0.35 Tesla MR-guided radiation therapy in the United States - Understanding the transition to adaptive, ultra-hypofractionated treatments

Michael D Chuong
Miami Cancer Institute

Lauren E Henke
Washington University School of Medicine in St. Louis

et al.

Recommended Citation

Patterns of utilization and clinical adoption of 0.35 Tesla MR-guided radiation therapy in the United States – Understanding the transition to adaptive, ultra-hypofractionated treatments

Michael D. Chuong [a], Mary Ann Clark [b,*], Lauren E. Henke [c], Amar U. Kishan [d], Lorraine Portelance [e], Parag J. Parikh [f], Michael F. Bassetti [g], Himanshu Nagar [h], Stephen A. Rosenberg [i], Minesh P. Mehta [a], Tamer Refaat [j], Justin M. Rineer [k], Adam Smith [l], Steven Seung [m], Bassem I. Zaki [n], Martin Fuss [b], Raymond H. Mak [o]

[a] Miami Cancer Institute, Miami, FL, United States
[b] ViewRay, Inc., Denver, CO, United States
[c] Washington University, School of Medicine, St. Louis, MO, United States
[d] University of California, Los Angeles Medical Center, Los Angeles, CA, United States
[e] University of Miami, Miami, FL, United States
[f] Henry Ford Health System, Grosse Pointe Farms, MI, United States
[g] University of Wisconsin, Madison, WI, United States
[h] Weill Cornell Medicine, New York, NY, United States
[i] H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, United States
[j] Loyola University Chicago, Stritch School of Medicine, Department of Radiation Oncology, Cardinal Bernardin Cancer Center, Maywood, IL, United States
[k] Orlando Health, Orlando, FL, United States
[l] McGlinn Cancer Institute at Reading Hospital, Tower Health, Reading, PA, United States
[m] Providence Cancer Institute, Portland, OR, United States
[n] Dartmouth-Hitchcock Norris Cotton Cancer Center, Lebanon, NH, United States
[o] Dana Farber/Brigham and Women's Cancer Center, Boston, MA, United States

ARTICLE INFO

ABSTRACT

Purpose/Objective: Magnetic resonance-guided radiation therapy (MRgRT) utilization is rapidly expanding worldwide, driven by advanced capabilities including continuous intrafraction visualization, automatic triggered beam delivery, and on-table adaptive replanning (oART). Our objective was to describe patterns of 0.35Tesla(T)-MRgRT (MRIdian) utilization in the United States (US) among early adopters of this novel technology.

Materials/Methods: Anonymized administrative data from all US MRIdian treatment systems were extracted for patients completing treatment from 2014 to 2020. Detailed treatment information was available for all MRIdian linear accelerator (linac) systems and some cobalt systems.

Results: Seventeen systems at 16 centers delivered 5736 courses and 36,389 fractions (fraction details unavailable for 1223 cobalt courses), of which 21.1% were adapted. Ultra-hypofractionation (UHfx) (1–5 fractions) was used in 70.3% of all courses. At least one adaptive fraction was used for 38.5% of courses (average 1.7 adapted fractions/course), with higher oART use in UHfx dose schedules (47.7% of courses, average 1.9 adapted fractions per course). The most commonly treated organ sites were pancreas (20.7%), liver (16.5%), prostate (12.5%), breast (11.5%), and lung (9.4%). Temporal trends show a compounded annual growth rate (CAGR) of 59.6% in

treatment courses delivered, with a dramatic increase in use of UHfx to 84.9% of courses in 2020 and similar increase in use of oART to 51.0% of courses.

Conclusions: This is the first comprehensive study reporting patterns of utilization among early adopters of MRIdian in the US. Intrafraction MR image-guidance, advanced motion management, and increasing adoption of adaptive radiation therapy has led to a substantial transition to ultra-hypofractionated regimens. 0.35 *T*-MRgRT has been predominantly used to treat abdominal and pelvic tumors with increasing use of on-table adaptive replanning, which represents a paradigm shift in radiation therapy.

Introduction

Radiation therapy (RT) has been fundamentally shaped by image-guidance, which provides critical information about patient and tumor anatomy on the day of treatment [1]. As image-guided radiation therapy (IGRT) has evolved, there has been increasing opportunity to optimize treatment regimens in an effort to reduce toxicity and improve efficacy [2]. Widespread adoption of cone-beam computerized tomography (CBCT) has facilitated stereotactic body radiation therapy (SBRT) delivery. However, CBCT causes additional radiation exposure. In addition, CBCT's low soft tissue contrast limits the opportunity to safely prescribe higher doses and use ultra-hypofractionation (UHfx), defined herein as the use of five or fewer fractions [3].

Magnetic resonance imaging (MRI) provides superior soft tissue contrast over CT, which can be of significant benefit to RT planning and delivery [4]. MRI-guided radiation therapy (MRgRT) has been introduced into the field of radiation oncology in the last decade and potentially represents a paradigm shift in the treatment of some cancers [5,6].

In 2014, the ViewRay MRIdian became the first clinically operational MRgRT system, combining a 0.35 T MRI scanner and a cobalt-60 treatment delivery unit. The second generation MRIdian, combining the same MR-imaging system with a linear accelerator (MRIdian-linac), began treating patients with high-energy X-rays in mid 2017. MRIdian uniquely combines excellent soft tissue contrast, continuous intra-fraction cine-MRI, soft tissue tracking, and automatic beam gating [6]. Additionally, it enables daily on-table adaptive planning to account for interfraction anatomic changes, ensuring organ-at-risk (OAR) constraints are met while optimizing target volume coverage. This functionality obviates the need for fiducial markers, eliminates radiation dose from daily and repeated CBCTs, permits planning target volume (PTV) margin reduction, target dose escalation, and shorter fractionation regimens, with potential cost- and time-savings implications.

Because the adoption of MRIdian in the United States (US) is still in the relatively early phase, clinical applications of this technology continue to expand and evolve. Clinical outcomes for some difficult-to-treat cancers have been encouraging, and ongoing clinical trials such as the MRIdian SMART trial, NCT03621644 have completed enrollment and data analysis is underway to produce more definitive data. [7–10] The number of institutions in the US that have adopted MRIdian has increased significantly, especially in the last three years. However, overall patterns of utilization across multiple centers have not been reported. We therefore performed a retrospective analysis of patients treated on MRIdian systems in the US since 2014, describing patterns of utilization focused on disease site, total dose prescribed, fractionation, and use of on-table adaptive replanning.

Materials and methods

For this retrospective analysis, we extracted treatment data from a structured query language (SQL) machine database that includes all patients treated on all MRIdian treatment systems globally. This database contains information on each center's treatments from the first clinical patient's treatment through the end of 2020, the data extraction date. Key MRIdian system data available includes number of courses, fractionation, number of on-table adaptive radiation therapy (oART)

fractions, organ site treated, planned dose, and year of treatment. The database does not include Protected Health Information (PHI), and none of the extracted data fields allow identification of individual patients. All data comply with applicable law governing data privacy, including but not limited to Health Insurance Portability and Accountability Act of 1996 ("HIPAA") and the General Data Protection Regulation 2016/679 ("GDPR"). This study did not include human subjects as it was retrospective machine data without any patient identifiers. Informed consent and Institutional Review Board (IRB) approval were not necessary.

We analyzed treatment records for all MRIdian treatment systems installed at US institutions and included all treatment courses from 2014 to the end of 2020. We excluded treatment courses from the primary analysis (n = 41) if they had prescriptions with clinically unreasonably high doses (prescribed total dose >100 Gy) and number of fractions (n > 45). Given the extreme deviation from standard clinical practice, these were thought to represent QA datasets or datasets used during machine commissioning. Additionally, detailed fraction-level data was unavailable for 1223 courses treated on cobalt-60 machines.

We used the raw data from fractions delivered to calculate treatment course-level summary data. A patient could have undergone more than one treatment course in the assessed timeframe, and each would be counted separately. We defined on-table adaptive radiation therapy (oART) fractions as fractions where the plan delivered during the fraction was a reoptimized plan rather than the original plan. We classified courses as oART courses, if at least one fraction was delivered using an adapted plan. Since treatment concept (e.g., SBRT) is not captured in the database, we defined a course of UHfx RT as five (5) fractions or fewer, except those defined as accelerated partial breast irradiation (APBI). We defined APBI treatments as: 1) 10 planned fractions and a planned dose of 38.5 Gy; 2) 5 planned fractions and a planned dose of 30 Gy; 3) 3 planned fractions and a planned dose of 25.5 Gy; or, 4) 1 planned fraction and a planned dose of 20 Gy [11–13]. We further identified subsets of patients receiving dose escalated or ablative therapy using commonly reported biologically equivalent dose (BED) thresholds.

Ablative RT dose was defined as prescriptions of greater than or equal to 100 Gy/BED$_{10}$. Dose escalated courses were defined as between 72 and 99 BED$_{10}$. These calculations exclude treatment prescriptions for prostate, reflecting the evidence of lower alpha/beta ratios needed to achieve prostate tumor control [14–18].

When detailed treatment data were not available for certain cobalt-60 system patients, the total number of missing courses (1223) was added back to the overall totals for course-level analyses and reporting as further described in Table 1 and Fig. 1 in the results section. Additionally, the fraction-level analysis counted total fractions delivered over the assessed timeframe. One center was excluded from the oART calculations due to inability to identify oART fractions (number of courses = 176) due to a unique workflow at the institution that prevented accurate data capture on oART fractions.

Total numbers of oART and UHfx courses were calculated using their respective ratios calculated from the detailed data multiplied by the total, including the cobalt courses. We counted total and average fractions and adapted fractions for all treatment courses. These analyses were stratified by tumor site and UHfx vs non-UHfx fractionation schemes. Growth rates were calculated using compounded annual growth rates (CAGR) methodology [19]. Data analysis was performed using Tableau Desktop 2021 (Seattle, WA) and Excel Office 365

Table 1
0.35 *T*-MRgRT utilization in the United States, 2014–2020.

Measure	Total (2014–2020)	2014	2018	2020
# Centers (systems)	16 (17)	1 (1)	9 (10)	16 (17)
# Total treatment courses*	5736	111	835	1832
% Courses treated with UHfx**	70.3 %	31.8 %	60.2 %	84.9 %
% Courses treated with APBI**	9.7 %	16.5 %	15.8 %	2.5 %
% Courses with ≥1 adaptive fraction***	38.5 %	0.0 %	27.3 %	51.0 %
Adaptive Courses***	38.5 %	0.0 %	27.3 %	51.0 %
% oART – UHfx	47.7 %	0.0 %	36.6 %	54.9 %
% oART – APBI	0.2 %	0.0 %	0.0 %	0.0 %
% oART – Non-UHfx/Non-APBI	24.9 %	0.0 %	18.7 %	30.0 %
# Fractions**	36,389	1185	5208	11,823
% oART Fractions***	21.2 %	0.0 %	14.8 %	32.8 %
Organ Site – Distribution**				
Breast	11.5 %	20.0 %	16.1 %	3.4 %
Liver	16.5 %	10.6 %	17.9 %	15.4 %
Lung	9.4 %	15.3 %	9.9 %	9.7 %
Pancreas	20.7 %	3.5 %	20.0 %	23.2 %
Prostate	12.5 %	3.5 %	12.2 %	18.2 %
Other****	29.4 %	47.1 %	23.9 %	30.2 %

* 3461 linac courses (all linac courses with detailed data available), 2275 total cobalt courses (1052 cobalt courses with detailed data available). Total n = 5736.

** for 4513 courses (excludes 1223 cobalt courses).

*** for 4337 courses (excludes 1223 cobalt courses and 176 courses without oART information).

**** other organ sites and undefined organ site.

(Microsoft Corporation, Redmond, WA).

Results

Seventeen systems at 16 centers delivered 5736 treatment courses from 2014 through 2020 (3461 MR-linac, 2275 cobalt, of which 1052 cobalt courses had detailed data and 1223 did not have detailed data) (Table 1). Total courses (including 1223 cobalt courses without detailed data) grew at a CAGR of 59.6 %, growing from 111 in 2014 to 1832 in 2020. A total of 36,389 fractions were delivered in 4513 courses on MRIdian systems with detailed data. The overall growth (CAGR) in the number of fractions delivered over this period was 46.7 % (1185 fractions to 11,823 fractions). Thirteen of 16 centers (81.2 %) had treated for at least 365 days, of which 9 delivered ≥100 courses per year in either 2019 or 2020 and 5 delivered >150 courses per year in either 2019 or 2020.

Across all years, 80.0 % of courses with detailed data available were treated with either UHfx (70.3 %) or APBI (9.7 %). (Fig. 1) The CAGR in UHfx courses over the assessed period was 87.9 %. UHfx increased from 31.8 % to 84.9 % over the 7-year period. The overall proportion of APBI courses decreased from 16.5 % in 2014 to 2.5 % in 2020, primarily driven by an overall decrease in the proportion of breast tumors treated in favor of other tumor sites.

In the assessed period, 38.5 % of 4337 courses with available oART data had at least one oART fraction delivered (Fig. 1). No course was

delivered with adaptive treatment in 2014 but adaptive replanning has been steadily increasing over time, with the percentage of oART courses reaching 51.0 % by the end of 2020. The CAGR for oART courses was 65.6 %.

When oART use was analyzed by treatment concept, we found that 47.7 %, 0.2 %, and 24.9 % of UHfx, APBI, and all other dose and fractionation schedules, respectively used oART at least once during the treatment course. (Table 1).

Over twenty-one percent (21.1 %) of all fractions with available oART data were adapted by the end of 2020. The proportion of adapted fractions increased from 12.0 % in 2016 (the first full year of use) to 32.8 % by the end of 2020. The number of oART fractions grew at a CAGR of 88.5 %.

The overall average number of fractions per treatment course was 8.1, whereas the average number of oART fractions was 1.7. By the end of 2020, the overall average number of fractions decreased to 6.5 and the number of oART fractions increased to 2.1. When stratified by treatment concept, we found an average of 4.8, 7.9, and 19.6 fractions for courses delivered using UHfx, APBI, and all other dose and fractionation schedules, respectively. When the same treatment concepts were analyzed for the frequency of oART use, we found an average of 1.9, 0.0, and 1.9 adapted fractions per course, respectively. The proportion of oART fractions in a course varied by treatment concept with 39.1 %, 0.0 %, and 10.0 % of fractions adapted, respectively. By 2020, the proportion of oART fractions in UHfx courses had increased to 45.3 % while oART use in all other course concepts was largely unchanged (Fig. 2).

From 2014 to 2020, the most commonly treated organ sites, based on 4513 courses with detailed data, were pancreas (20.7 %), liver (16.5 %), prostate (12.5 %), breast (11.5 %), and lung (9.4 %) (Table 1). Organ sites classified as "other" (10.4 %) included anus, bone, brain, cervix, colon, esophagus, gall bladder, head and neck, kidney, larynx, oral cavity, ovary, penis, pharynx, rectum, skin, small intestine, stomach, tongue, ureter, urinary bladder, uterus, and vagina. In addition, there were 19 % of courses with undefined organ sites that were also included in the "other" category, for a total of 29.4 %.

The proportion of pancreatic cancers treated increased from 3.5 % in 2014 to 23.2 % in 2020 with prostate increasing from 3.5 % to 18.2 %, and liver from 10.6 % to 15.4 %. The percentage of courses for lung cancer remained stable at between 9.5 % and 9.9 % over the last three years (2018–2020) (Fig. 3). The absolute numbers of courses increased over the 7-year time-period with CAGRs of 118.3 % (pancreas), 109.7 % (prostate), 69.8 % (liver), 47.8 % (lung).

The use of UHfx varied by organ site with overall proportions of 91.0 %, 86.8 %, 75.1 %, 72.0 % for liver, pancreas, lung, and prostate, respectively. The rates of UHfx by organ site were more variable in the earlier years of clinical use ranging from 11.1 % in prostate cancer to 83.9 % in liver in 2017 (Fig. 4). More recently, the percent of UHfx was less variable by tumor site ranging from 83.9 % in prostate to 95.2 % in pancreas cancer tumors in 2020.

In comparing 2018 vs 2020, the proportion of oART fractions was highest for pancreas (62.5 % vs 79.8 %), liver (11.9 % vs 25.4 %), and lung (0 % vs 22.4 %) cancers. The proportion of oART fractions in prostate tumors was low but increased from 0.3 % in 2018 to 4.2 % in 2020. However, oART use for APBI was very infrequent (0.2 %).

The percentage of treatment courses for breast cancer initially increased from 20.0 % in 2014, peaked at 30.4 % in 2016, before dramatically decreasing to 3.4 % by the end of 2020. Although 10 out of the 16 institutions included in this analysis treated breast tumors on MRIdian, the majority (71.2 %) were treated at a single institution. A series of prospective clinical trials on breast cancer conducted early in the assessed timeframe might explain the change in proportion. [NCT #03612648 and NCT#02076074].

The overall proportion of APBI treatment courses for breast cancer was 84.4 % with an additional 12.9 % of courses treated in five or fewer fractions to other dose schedules. The proportion of courses delivered

using conventional fractionation was low at 2.7 %. In 2018, the percent of breast treatments delivered using APBI reached its highest level at 97.9 % and then decreased to 74.2 % in 2020 because of an increase in the use of other dose schedules that did not meet the previously stated definitions for APBI.

The proportion of courses receiving ablative doses or dose escalation on MRIdian systems was 65.5 % over all years and 77.4 % for all UHfx patients. Additionally, 53.9 % of all UHfx courses were delivered with ablative doses of 100 Gy BED_{10} or greater. Liver (79.3 %), lung (88.7 %), and pancreas (74.3 %) courses treated with UHfx had the highest percentages of courses with ablative doses (Table 2). We note that in addition to prostate tumors, breast tumors also have a low alpha beta ratio ranging from 2.5 to 4.6, making a conversion into a BED_{10} meaningless [11–13].

Discussion

This is the first comprehensive study on the patterns of care among early adopters of MRIdian systems in the US and it provides important insights into the evolution of the use of this technology toward increasing UHfx and oART. The authors consider this analysis of almost 6000 treatment courses comprising over 36,000 fractions as meaningful because it is the largest study published to date describing clinical adoption of MRIdian in the US. This number represents roughly 50 % of all patients treated on MRIdian systems worldwide with a similar report detailing use of the technology under preparation for sites located in Europe and Asia.

Temporal trends from 2014 to 2020 on 17 systems at 16 centers showed a CAGR of 59.6 % in treatment courses delivered, with a dramatic increase in use of UHfx to 84.9 % of courses in 2020 and similar increase in use of oART to 51.0 % of courses. MRIdian's unique imaging capabilities may facilitate greater adoption of UHfx by reducing OAR dose through smaller margins (soft tissue tracking, automatic beam gating) and online adaptive replanning while delivering ablative dose to the target, even those in challenging anatomic locations not suitable for

dose escalation using CBCT guidance. Additionally, 53.9 % of these UHfx courses met our BED threshold for ablative dosing ($\geq$100 Gy_{10}) and an additional 15.8 % were considered definitive dosing ($\geq$72 Gy_{10}; EQD2 = 60).

Overall, 84.4 % of breast cancer tumors were treated in APBI treatment courses. By the end of 2020, there was a decrease in the proportion of APBI courses to 74.2 % and an increase in breast cancer patients receiving other UHfx courses; most likely due to pandemic-related recommendations to consider hypofractionation more aggressively as well as publication of 10-year data from the FLORENCE study. [20,13]. However, there was a decrease by one-half in the number of breast cancer patients treated in 2020 from the previous year (a drop from 124 to 62), which could have influenced this rate.

Examining disease site trends in the US, there has been increase in utilization of MRIdian to treat abdominopelvic tumors, predominantly pancreas, prostate, and liver, and with increasing utilization of UHfx and adaptive replanning. These disease sites share common challenges with mobile soft tissue targets and surrounding gastrointestinal organs at risk that can change daily, where the advantages of MRgRT and oART may provide the technical ability for clinicians to dose-escalate and/or ultra-hypofractionate. Similarly, another highly mobile anatomic disease site, the lung, has been frequently treated on the MRIdian system.

However, numerous other tumor sites have also been treated using the MRIdian system including other difficult to treat tumors, such as those near critical structures and those subject to significant breathing motion including oligometastases, kidney, bladder, adrenals, retroperitoneal, head and neck, and brain among others. Earlier studies reporting MRIdian clinical practice patterns are generally single institution reports which are limited in terms of understanding national trends. A 2018 US study reported on 666 treatment courses delivered at a single institution over the first 4.5 years of clinical use (2014–2018). [21] The most common disease sites treated at this institution were pancreas (15.2 %), liver (13.1 %), breast (31.4 %), lung (10.1 %), prostate (5.3 %), with 39.9 % SBRT and 13.3 % of all fractions adapted. These distributions are somewhat different from our reported more recent data which found

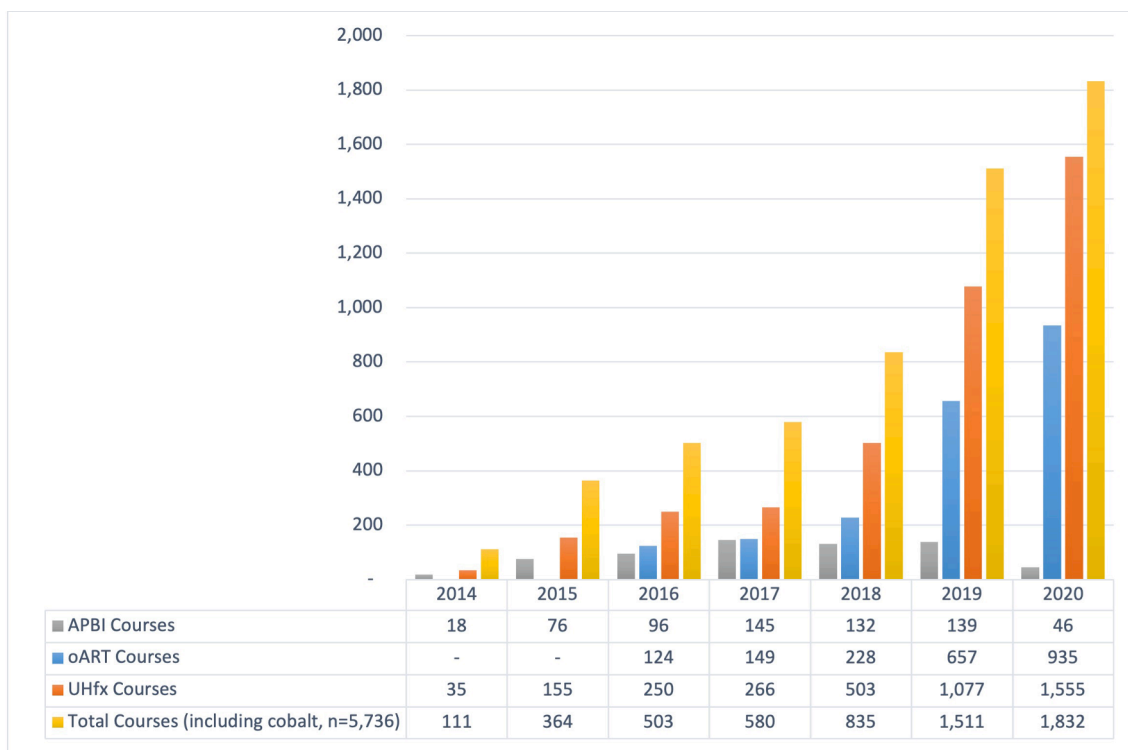|	2014	2015	2016	2017	2018	2019	2020
■ APBI Courses	18	76	96	145	132	139	46
■ oART Courses	-	-	124	149	228	657	935
■ UHfx Courses	35	155	250	266	503	1,077	1,555
■ Total Courses (including cobalt, n=5,736)	111	364	503	580	835	1,511	1,832

Fig. 1. MRIdian Treatment Courses Delivered in the US – 2014–2020. Total patient denominator over timeframe including all cobalt patients = 5736, APBI = Accelerated Partial Breast Irradiation, oART = on-table Adaptive Radiation Therapy, UHfx = ultra-hypofractionation.
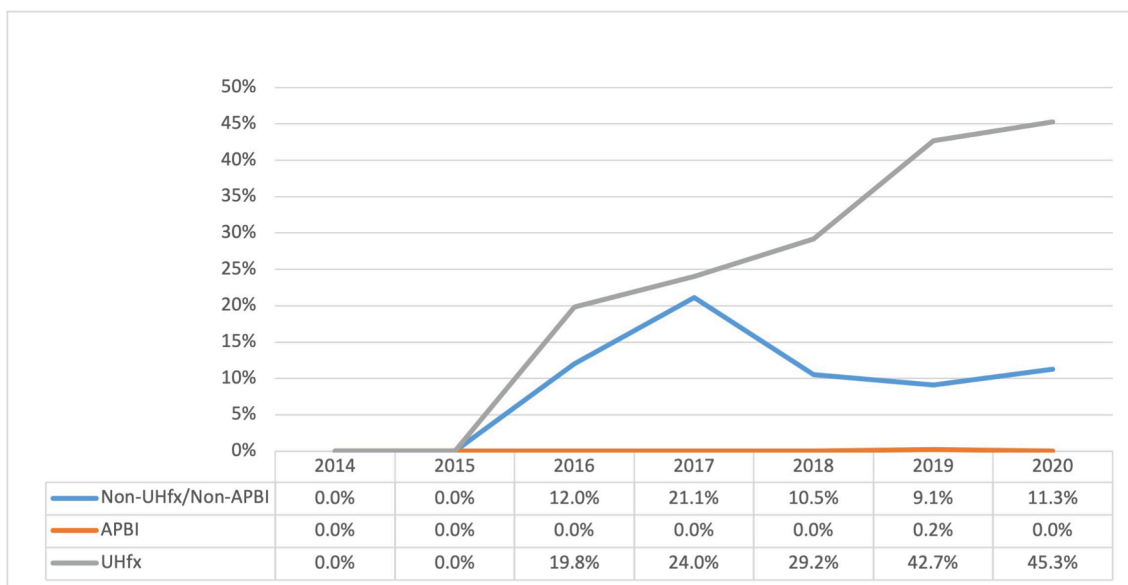
Fig. 2. MRIdian Percentage of Adapted Fractions by Treatment Concept in the US – 2014–2020. Total patient denominator = 4337, UHfx = ultra-hypofractionation, APBI = Accelerated Partial Breast Irradiation.
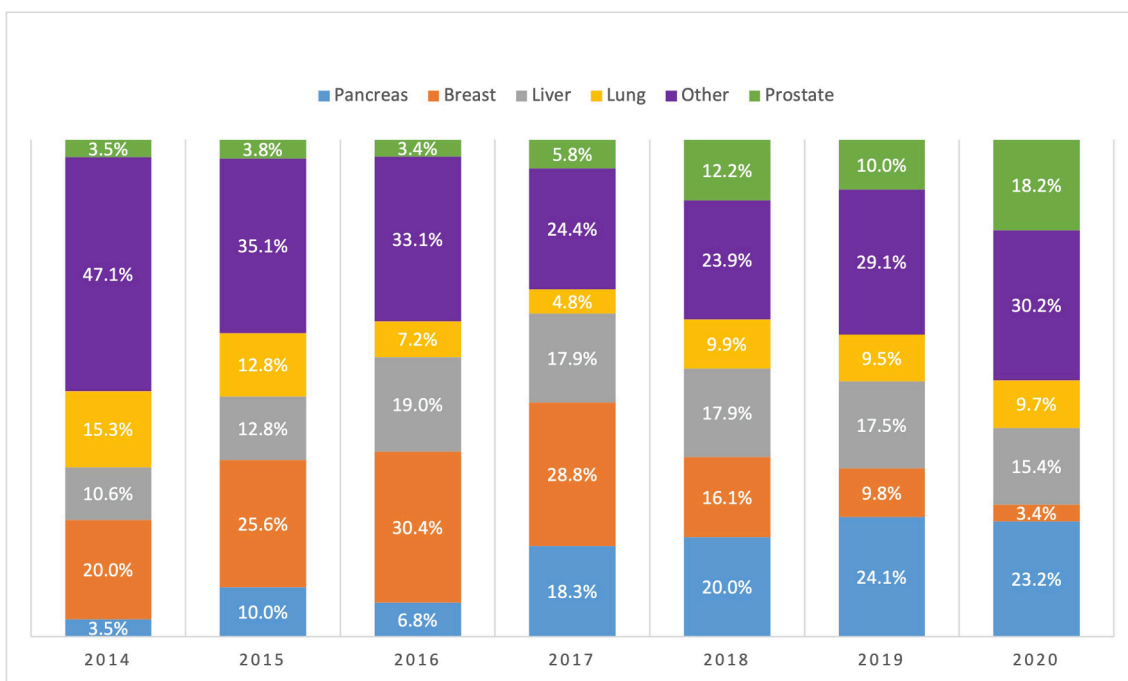

Fig. 3. MRIdian Organ Site Distribution in the US – 2014–2020. Total patient denominator = 4513.

lower overall breast tumor treatments and greater SBRT utilization. We note that most treatments for breast tumors in our study were driven by a single institution (the first to adopt the technology in the US) in the earlier years, although an increasing number of centers have clinically adopted MRIdian for treating breast tumors recently, reaching a total of 10 out of 16 sites by the end of 2020. Another potential reason for the lower proportion of breast tumors observed in more recent years may be due to the need for some institutions to prioritize other tumor sites over breast cancer in utilizing these machines that are still relatively scarce and may reach full capacity at each center.

A Turkish study reporting MRIdian utilization for the first 500 fractions found that 84 different tumor sites were treated, with the most treated diagnoses being prostate (33 %) and lung tumors (21 %) and

90.2 % of patients were treated with SBRT [22]. A second Turkish study published in 2020 reported on an additional 462 fractions (962 total) and found 19.9 % lung, 36.7 % pelvis, 43.3 % abdomen with 80.4 % using oART [23].

In 2021, authors of the MOMENTUM study published patterns of care results on 943 patients treated on the 1.5 T MR-linac [24]. Even though the types of tumor sites treated are similar to the 0.35 T MRgRT systems, the distribution in numbers of patients by tumor site was different with 40 % (vs 23.5 %) prostate, 5 % (vs 14.5 %) liver, 4 % (vs 11.2 %) pancreas and 1 % (vs 12.3 %) lung tumors treated. The MOMENTUM study also reported 17 % of treatments for lymph nodes, 12 % for brain and 10 % for rectum, out of the 39 different tumor sites treated on the 1.5 T MR-linac. We were unable to specifically define lymph node
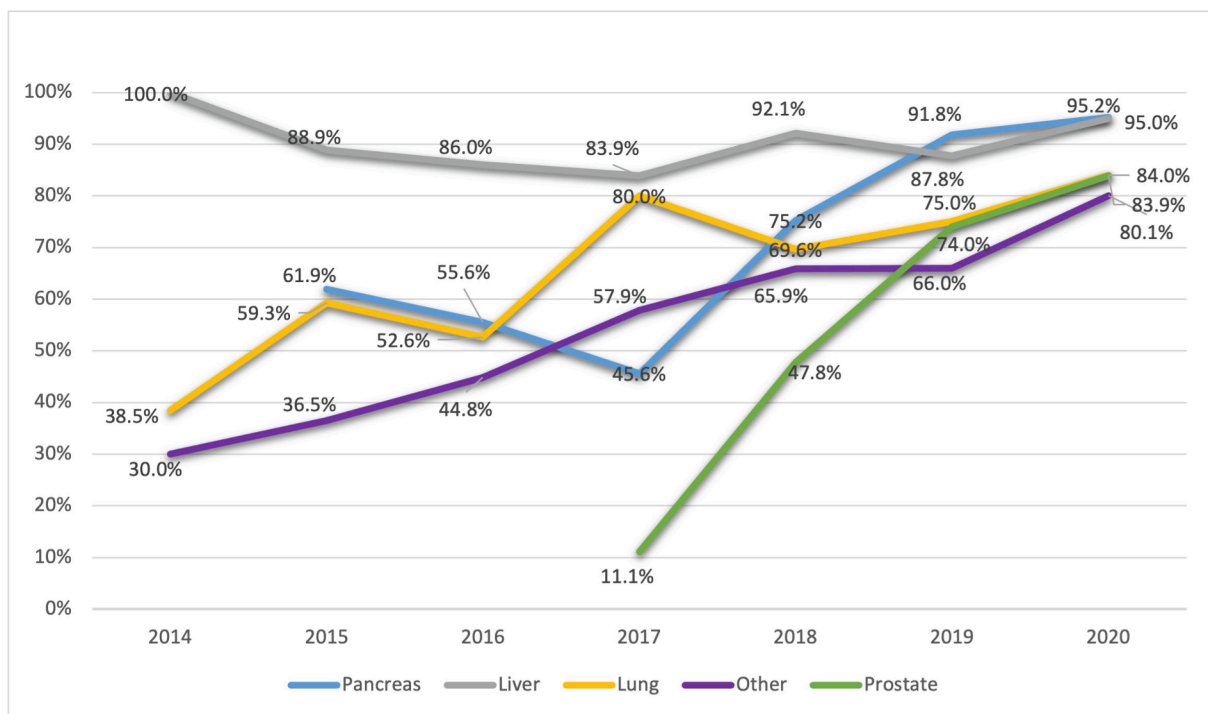
Fig. 4. MRIdian Ultra-hypofractionation By Organ Site in the US – 2014–2020. Total patient denominator = 4513, UHfx = ultra-hypofractionation.

Table 2
Percentage of UHfx Courses by Dose Level Calculated as a BED_{10}.

Organ Site	$BED_{10} \geq 100$ Gy	BED_{10} 72 to 99 Gy	Other* BED_{10}
Liver	79.3 %	12.6 %	8.2 %
Lung	88.7 %	6.3 %	5.0 %
Pancreas	74.3 %	15.4 %	10.3 %
Other	36.7 %	21.6 %	41.6 %

* Other is exclusive of APBI and prostate.

treatments in our data. However, it is likely that lymph node treatments are included in the "Other" tumor site category. This category represented 29.4 % overall. However, that category summarized all the remaining tumor sites. The actual undefined "Other" category represented 19.0 %, while brain and rectum tumors represented 0.7 % and 1.3 %.

The trends toward increasing UHfx with or without dose escalation using SBRT techniques have been ongoing in radiation oncology [25–28], driven by 1) growing clinical evidence for excellent treatment outcomes with low toxicity and high patient satisfaction [29], 2) reimbursement pressures with bundled payments such as the Centers for Medicare & Medicaid Services (CMS) proposed Radiation Oncology Alternative Payment Model (RO-APM) 3) novel technologies that increase the number of disease sites that may be safely treated, and 4) emphasis on shorter courses for patient safety during the COVID pandemic [20,30]. Despite increasing trends favoring the use of UHfx and SBRT, the percent of patients treated with SBRT in the US is still rather low in most tumor sites such as prostate [25–28] and pancreatic cancers [31], with the exception being early-stage lung tumors with a utilization rate of 60 % [32]. The patterns of care data from the MRIdian systems in the US suggest that these trends in UHfx have rapidly occurred for patients treated with these systems and potentially accelerated by the underlying technological capabilities of MR-guidance, advanced motion management and oART.

Notably, even in patients who received more than five fractions of treatments, the average number of fractions was 18.2 in 2020, fewer than conventionally fractionated courses of RT using existing RT

technologies, which usually range from 20 to 45 fractions per treatment course, according to tumor site [33–36]. Greater use of UHfx and hypofractionation could lower overall costs to the healthcare system, patients, and payers by reducing the number of fractions delivered, as well as improving access to RT in areas with limited availability and offer better patients' convenience [37,38].

An important aspect of this study is the recognition that the delivery of UHfx doses by its very nature requires very careful attention to OAR constraints and cognizance of day-to-day changes, which necessitates more frequent on-table adaptation of the original treatment plans by physicians as we observed in our data, relative to the situation commonly seen with standard fractionated radiotherapy with larger PTV margins. This additional effort and work by physicians and the clinical team are clearly necessary for safe delivery of such large doses per fraction near critical OAR. The combination of large doses per fraction, intra-fraction beam guidance, and the need for on-table replanning influence the throughput of this modality, relative to conventional linear accelerators.

We were not able to collect data on fraction time and as such can not report on time per fraction for dose deliveries using MR-image-guidance only, fractions that are delivered with additional real-time imaging-based beam gating or fractions that were delivered after oART dose replanning. Data detailing the additional oART work and related time have been published by a number of institutions, generally finding that additional 20 to 30 min of time are spent in the oART workflow [22,23,39,40,41,42,43]. Similar reports have also been published for the 1.5 T MR-linac system, finding comparable additional times needed for oART [44–47].

This study must be interpreted in the context of its limitations. First, treatment concept and organ site data were not fully complete and thus did not allow us to directly capture the effects of adaptive and MR-guidance on SBRT adoption and the exact treatment site. However, we were able to estimate SBRT utilization on the MRIdian systems using a combination of dose prescribed, number of fractions, and calculations of a BED_{10}. There were additional limitations in distinguishing between treatment of primary disease by site vs secondary metastasis to the same organ site (e.g., liver site likely includes both primary hepatocellular

carcinoma and secondary liver metastases). We theorize that "Other" treatment site likely represents oligo-metastatic lesions to non-organ locations such as abdominal-pelvic lymph nodes or soft tissue metastases given ongoing trends in treatment of oligometastatic disease [48] and institutional reports from MRIdian systems users, but nevertheless we are limited by the available data and cannot provide a more comprehensive analysis of trends by these disease entities. We also recognize that data for some treatment courses delivered on MRIdian cobalt systems lacked granularity. Lastly, while the patterns of care provide insights into how end users are applying this technology in the real world, we are limited by the lack of outcomes data directly tied to this dataset and the identified trends in UHfx and adaptive therapy usage. However, reports on clinical outcomes for MRIdian with or without adaptive therapy in both prospective and retrospective series continue to grow [13,39,40,49,50,51,52,53,54,55,56,57], and completed and ongoing prospective trials will provide additional insights. (NCT03621644, NCT04331041, NCT04247165, NCT04162665, NCT04242342, NCT04020276, NCT04915508, NCT04384770, NCT04402151, NCT04422132, NCT03541850, NCT03916419, NCT03936478, NCT03612648, NCT03878485, NCT03972072, NCT04376502, NCT04115254, NCT04368702).

Conclusions

This study reports the largest and most comprehensive analysis of MR-guided radiation therapy courses delivered in the US. The ability to clearly delineate soft tissues during treatment, deliver radiation dose while automatically controlling for organ motion, and adapt treatment plans with the patient on-table have accelerated a transition to UHfx in the US. Additionally, this technology has allowed dose escalation and delivery of ablative dose in a greater proportion of patients. Safer delivery of ablative doses, the ability to treat more complex tumors, and to reduce the number of fractions delivered could lead to improved clinical outcomes, lower overall healthcare costs, and offer better quality of life, patient satisfaction, and convenience.

Data statement

Original machine data for this study is not available due to the need to respect institution confidentiality.

Declaration of Competing Interest

Michael Chuong reports grants and personal fees from ViewRay; personal fees and non-financial support from Accuray and Sirtex; participates on an advisory board for ViewRay. Mary Ann Clark and Martin Fuss are employees and shareholders of ViewRay, Inc. Lauren E. Henke reports consulting fees from ViewRay, Inc. and Radialogica and grants and other from Varian Medical Systems. Amar Kishan has a grant with ASTRO-PCF, consulting fees and honoraria paid by Varian Medical Systems, Inc. and ViewRay, Inc., shareholder of ViewRay, Inc. Lorraine Portelance has a consulting contract with ViewRay, Inc.Parag J. Parikh reports stock and other ownership of Nuvaira, honoraria, speakers' bureau from ViewRay, and research funding from ViewRay. Michael F. Bassetti has a research grant from Astra Zeneca and royalties or licenses from National Jewish Hospital (Bcl3 antibody and Spi2A antibody). Himanshu Nagar participates on advisory boards for Bristol Meyers Squibb and ViewRay, Inc. Stephen A. Rosenberg participates on ViewRay medical advisory boards, Lung Research Consortium (both non-compensated), and has research grants from ViewRay; consulting fees paid by Novocure. Minesh Mehta has consulting fees from Karyopharm, Sapience, Zap, Mevion, Xoft, Tocagen; he is on the Board of Directors of Oncoceutics and owns stock in Oncoceutics and Chimerix. Bassem I. Zaki received manuscript support from ViewRay, Inc. and is a member of the ASTRO guideline subcommittee. Tamer Refaat reports nothing to disclose. Justin Rineer reports nothing to disclose. Adam Smith reports

nothing to disclose. Steven Seung reports nothing to disclose. Bassem I. Zaki reports leadership role on ASTRO's Guidelines Committee. Raymond H. Mak reports grants from ViewRay; consulting fees from ViewRay and Astra Zeneca.

Acknowledgements

References:

[1] Verellen D, De Ridder M, Storme G. A (short) history of image-guided radiotherapy. Radiother Oncol 2008;86:4–13.

[2] Zou W, Dong L, Kevin Teo BK. Current state of image guidance in radiation oncology: Implications for ptv margin expansion and adaptive therapy. Semin Radiat Oncol 2018;28:238–47.

[3] Srinivasan K, Mohammadi M, Shepherd J. Applications of linac-mounted kilovoltage cone-beam computed tomography in modern radiation therapy: A review. Pol J Radiol 2014;79:181–93.

[4] Lagendijk JJ, Raaymakers BW, Van den Berg CA, et al. Mr guidance in radiotherapy. Phys Med Biol 2014;59:R349–69.

[5] Liney GP, Whelan B, Oborn B, et al. Mri-linear accelerator radiotherapy systems. Clin Oncol (R Coll Radiol) 2018;30:686-691.

[6] Hall WA, Paulson ES, van der Heide UA, et al. The transformation of radiation oncology using real-time magnetic resonance guidance: A review. Eur J Cancer 2019;122:42–52.

[7] Henke L, Kashani R, Robinson C, et al. Phase i trial of stereotactic mr-guided online adaptive radiation therapy (smart) for the treatment of oligometastatic or unresectable primary malignancies of the abdomen. Radiother Oncol 2018;126: 519–26.

[8] Henke LE, Olsen JR, Contreras JA, et al. Stereotactic mr-guided online adaptive radiation therapy (smart) for ultracentral thorax malignancies: Results of a phase 1 trial. Adv Radiat Oncol 2019;4:201–9.

[9] Chuong MD, Bryant J, Mittauer KE, et al. Ablative 5-fraction stereotactic magnetic resonance-guided radiation therapy with on-table adaptive replanning and elective nodal irradiation for inoperable pancreas cancer. Pract Radiat Oncol 2021;11: 134–47.

[10] Bruynzeel AME, Tetar SU, Oei SS, et al. A prospective single-arm phase 2 study of stereotactic magnetic resonance guided adaptive radiation therapy for prostate cancer: early toxicity results. Int J Radiat Oncol Biol Phys 2019;105:1086–94.

[11] Vicini FA, Cecchini RS, White JR, et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. Lancet 2019;394(10215): 2155–64. https://doi.org/10.1016/S0140-6736(19)32514-0. Epub 2019 Dec 5.

[12] Meattini I, Marrazzo L, Saieva C, et al. Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: long-term results of the randomized Phase III APBI-IMRT-Florence trial. J Clin Oncol 2020;38(35): 4175–83. https://doi.org/10.1200/JCO.20.00650. Epub 2020 Aug 24.

[13] Kennedy WR, Thomas MA, Stanley JA, Luo J, Ochoa LL, Clifton KK, et al. Single-institution phase 1/2 prospective clinical trial of single-fraction, high-gradient adjuvant partial-breast irradiation for hormone sensitive stage 0-i breast cancer. Int J Radiat Oncol Biol Phys 2020;107(2):344–52.

[14] Kishan AU, Dang A, Katz AJ, et al. Long-term Outcomes of Stereotactic Body Radiotherapy for Low-Risk and Intermediate-Risk Prostate Cancer JAMA Network Open. 2019;2(2):e188006. doi:10.1001/jamanetworkopen.2018.8006.

[15] Miralbell R, Roberts SA, Zubizarreta E, Hendry JH. Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: alpha/beta = 1.4 (0.9-2.2) Gy. Int J Radiat Oncol Biol Phys 2012;82(1):e17–24.

[16] Van Leeuwen CM, Oei AL, Bel A, et al. The alfa and beta of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies. Radiat Oncol 2018;13:96.

[17] Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. Int J Radiat Oncol Biol Phys 1999;43(5):1095–101.

[18] Ray KJ, Sibson NR, Kiltie AE. Treatment of breast and prostate cancer by hypofractionated radiation therapy: Potential risks and benefits. Clin Oncol (R Coll Radiol) 2016;28(2):161.

[19] last accessed on December 30, 2021.

[20] Guckenberger M, Belka C, Bezjak A, et al. Practice recommendations for lung cancer radiotherapy during the COVID-19 pandemic: An ESTRO-ASTRO consensus statement. Radioth Oncol 2020;146:223–9.

[21] Henke LE, Contreras JA, Green OL, Cai B, Kim H, Roach MC, et al. Magnetic resonance image-guided radiotherapy (MRIgRT): a 4.5-year clinical experience. The Royal College of Radiologists. Clin Oncol 2018;30(11):720–7.

[22] Sahin B, Zoto Mustafayev T, Gungor G, Aydin G, Yapici B, Atalar B, et al. First 500 fractions delivered with a magnetic resonance-guided radiotherapy system: initial experience. Cureus 2019;11(12).

[23] Güngör G, Serbez İ, Temur B, Gür G, Kayalılar N, Mustafayev TZ, et al. Time analysis of online adaptive magnetic resonance-guided radiation therapy workflow according to anatomical sites. Pract Radiat Oncol, Adv online publication 2020. https://doi.org/10.1016/j.prro.2020.07.003.

[24] de Mol van Otterloo SR, Christodouleas JP, Blezer ELA,, et al. First cohort of patients treated on a novel high-field MR-linac within the MOMENTUM Study: Initial results from a prospective multi-institutional registry. Int J Radiation Oncol Biol Phys 2021;000(00):1–9.

[25] Baker BR, Basak R, Mohiuddin JJ, et al. Use of stereotactic body radiotherapy for prostate cancer in the United States from 2004 to 2012. Cancer 2016;122:2234–41.

[26] Mahal BA, Chen YW, Sethi RV, et al. Travel distance and stereotactic body radiotherapy for localized prostate cancer. Cancer 2018;124:1141–9.

[27] Stokes WA, Kavanagh BD, Raben D, et al. Implementation of hypofractionated prostate radiation therapy in the United States: A National Cancer Database analysis. Pract Radiat Oncol 2017;7:270–8.

[28] Mahase SS, D'Angelo D, Kang J, et al. Trends in the use of stereotactic body radiotherapy for treatment of prostate cancer in the United States. JAMA Netw Open 2020;3(2).

[29] Tetar S, Bruynzeel A, Bakker R, Jeulink M, Slotman BJ, Oei S, et al. Patient-reported outcome measurements on the tolerance of magnetic resonance imaging-guided radiation therapy. Cureus 2018;10(2).

[30] Spencer K, Jones CM, Girdler R, Roe C, et al. The impact of the COVID-19 pandemic on radiotherapy services in England, UK: a population-based study. Lancet Oncol 2021;22.

[31] De Geus SWL, Eskander M, Kasumova GG, et al. Stereotactic body. Radiotherapy for unresected pancreatic cancer: A nationwide review. Cancer 2017;123:4158–67.

[32] Holmes JA, Zagar TM, Chen R. Adoption of stereotactic body radiotherapy for stage IA non-small cell lung cancer across the United States. JNCI Cancer. Spectrum 2017;1(1):pkx003.

[33] Lievens Y, Defourny N, Corral J, et al. How public health services pay for radiotherapy in Europe: an ESTRO-HERO analysis of reimbursement. Lancet Oncol 2020;21:e42–54.

[34] Borras JM, Grau C, Corral J, Wong K, Barton MB, Ferlay J, et al. Estimating the number of fractions by tumour site for European countries in 2012 and 2021: an ESTRO-HERO analysis. Radiother Oncol 2018;126(2):198–204.

[35] Royce TJ, Qureshi MM, Truong MT. Radiotherapy utilization and fractionation patterns during the first course of cancer treatment in the United States from 2004–2014. J Am Coll Radiol 2018.

[36] Wong K, Delaney GP, Barton MB. Evidence-based optimal number of radiotherapy fractions for cancer: A useful tool to estimate radiotherapy demand. Radioth Oncol 2016;119:145–9.

[37] Atun R, Jaffray D, Barton M, et al. Expanding global access to radiotherapy. Lancet Oncol 2015;16.

[38] Irabor OC, Swanson W, Shaukat F, et al. Can the adoption of hypofractionation guidelines expand global radiotherapy access? An analysis for breast and prostate radiotherapy. JCO Global Oncol 2020;6:667–8.

[39] Finazzi T, Haasbeek CJA, Spoelstra FOB, Palacios MA, Admiraal MA, Bruynzeel AME, et al. Clinical outcomes of stereotactic MR-guided adaptive radiation therapy for high-risk lung tumors. Int J Radiat oncol Biol Phys 2020;107(2):270–8.

[40] Finazzi T, van Sörnsen de Koste JR, Palacios MA, Spoelstra FOB, Slotman BJ, Haasbeek CJA, Senan S, "Delivery of magnetic resonance-guided single-fraction stereotactic lung radiotherapy," Phys Imaging Radiat Oncol, vol. 14, pp. 17-23, 2020.

[41] Tetar S, et al. Clinical implementation of magnetic resonance imaging guided adaptive radiotherapy for localized prostate cancer. Phys Imaging Radiat Oncol 2019;9:69–76.

[42] Parikh NR, et al. Time-driven activity-based costing comparison of CT-guided versus MR-guided SBRT. JCO Oncol Pract, Adv online publication 2020. https://doi.org/10.1200/JOP.19.00605.

[43] Placidi L, et al. On-line adaptive MR guided radiotherapy for locally advanced pancreatic cancer: clinical and dosimetric considerations. Tech Innov Patient Support Radiat Oncol 2020;15:15–21.

[44] Intven MPW, de Mol van Otterloo SR, Mook S, Doornaert PAH, de Groot-van Breugel EN, Sikkes GG, et al. Online adaptive MR-guided radiotherapy for rectal cancer; feasibility of the workflow on a 1.5T MR-linac: clinical implementation and initial experience. Radiother Oncol. 2021 Jan;154:172-178. doi: 10.1016/j.radonc.2020.09.024. Epub 2020 Sep 22. PMID: 32976875.

[45] McDonald BA, Vedam S, Yang J, Wang J, Castillo P, Lee B, et al. MR-Linac Consortium Head and Neck Tumor Site Group. Initial Feasibility and Clinical Implementation of Daily MR-Guided Adaptive Head and Neck Cancer Radiation Therapy on a 1.5T MR-Linac System: Prospective R-IDEAL 2a/2b Systematic Clinical Evaluation of Technical Innovation. Int J Radiat Oncol Biol Phys. 2021 Apr 1;109(5):1606-1618. doi: 10.1016/j.ijrobp.2020.12.015. Epub 2020 Dec 16. PMID: 33340604; PMCID: PMC7965360.

[46] Daamen LA, de Mol van Otterloo SR, van Goor IWJM, Eijkelenkamp H, Erickson BA, Hall WA, et al. Online adaptive MR-guided stereotactic radiotherapy for unresectable malignancies in the upper abdomen using a 1.5T MR-linac. Acta Oncol 2022 Jan;61(1):111–5. https://doi.org/10.1080/0284186X.2021.2012593. Epub 2021 Dec 8. PMID: 34879792.

[47] Alongi F, Rigo M, Figlia V, Cuccia F, Giaj-Levra N, Nicosia L, et al.. 1.5 T MR-guided and daily adapted SBRT for prostate cancer: feasibility, preliminary clinical tolerability, quality of life and patient-reported outcomes during treatment. Radiat Oncol. 2020 Mar 23;15(1):69. doi: 10.1186/s13014-020-01510-w. PMID: 32248826; PMCID: PMC7092497.

[48] Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. J Clin Oncol 2020 Sep 1;38(25):2830–8.

[49] Rosenberg SA, Henke LE, Shaverdian N, Mittauer K, Wojcieszynski AP, Hullett CR. A multi-institutional experience of mr-guided liver stereotactic body radiation therapy. Adv Radiat Oncol 2018;4(1):142–9.

[50] Rudra S, Jiang N, Rosenberg SA, Olsen JR, Roach MC, Wan L, et al. Using adaptive magnetic resonance image-guided radiation therapy for treatment of inoperable pancreatic cancer. Cancer Med 2019;8(5):2123–32.

[51] Hassanzadeh C, Rudra S, Bommireddy A, Hawkins WG, Wang-Gillam A, Fields RC, et al. Ablative five-fraction stereotactic body radiotherapy for inoperable pancreatic cancer using online MR-guided adaptation. Adv Radiat Oncol 2020;6(1).

[52] Luterstein E, Cao M, Lamb JM, Raldow A, Low D, Steinberg ML, Lee P. Clinical outcomes using magnetic resonance-guided stereotactic body radiation therapy in patients with locally advanced cholangiocarcinoma. Adv Radiat Oncol 2019;5(2):189–95.

[53] Tetar SU, Bruynzeel AME, Oei SS, Senan S, Fraikin T, Slotman BJ, et al, Magnetic Resonance-guided Stereotactic Radiotherapy for Localized Prostate Cancer: Final Results on Patient-reported Outcomes of a Prospective Phase 2 Study, *Eur Urol Oncol,* 2020.

[54] Ugurluer G, Mustafayev TZ, Gunfor G, Atalar B, Abacioglu U, Sengoz M, et al. Stereotactic MR-guided online adaptive radiation therapy (SMART) for the treatment of liver metastases in oligometastatic patients: initial experience. Radiat Oncol J 2021;39(1):33–40.

[55] Ugurluer G, Atalar B, Mustafayev TZ, Gungor G, Aydin G, Sengoz M, et al. Magnetic resonance image-guided adaptive stereotactic body radiotherapy for prostate cancer: preliminary results of outcome and toxicity. Br J Radiol 2021;94.

[56] van Dams R, Wu TC, Kishan AU, et al. Ablative radiotherapy for liver tumors using stereotactic MRI-guidance: A prospective phase I trial. Radioth Oncol 2021;21. S0167-8140(21)06577-4.

[57] Weykamp F, Hoegen P, Klüter S, et al. Magnetic resonance-guided stereotactic body radiotherapy of liver tumors: initial clinical experience and patient-reported outcomes. Front Oncol 2021;11:610637.