Brachytherapy

Techniques and Evidences

Yasuo Yoshioka
Jun Itami
Masahiko Oguchi
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Editors

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Foreword

Brachytherapy in Japan has a long tradition starting more than a century ago and taking a significant development with HDR afterloading brachytherapy since 50 years. Research and development by Japanese brachytherapy clinicians and scientists have contributed substantially to modern brachytherapy of today.

The introduction of the Japanese afterloading technique was one of the first outstanding features which opened the way also to HDR treatments where Japanese clinical researchers made a major contribution in particular for HDR brachytherapy in cervical cancer. Large patient cohorts for this successful technique were investigated and published in regard to dose, fractionation, and outcome—one of the first major clinical contributions to cervical cancer HDR brachytherapy in the early days of transition from LDR to HDR. Furthermore Japanese researchers were among the first to integrate CT and MRI into fractionated HDR brachytherapy treatment planning for cervical cancer. With the limited technology available at that time already important findings could be published. Of special interest is the traditional technique combining midline shielding for adapted external beam dose distributions with brachytherapy, resulting in favorable dose distributions for organs at risk. This technique has further potential using modern intensity-modulated techniques to further improve the relatively low incidence of late complications in rectum and bladder without compromising disease control. The use of image-guided interstitial techniques for advanced gynecological cancers is highly innovative, not only following standardized commercially available solutions, but setting a specific innovative path for the future. Based on growing clinical experience Japanese experts from various institutions are leading initiatives to spread the image-guided techniques all over Japan and beyond to Asia.

Prostate brachytherapy is nowadays performed in Japan with LDR seeds and HDR interstitial techniques. Since 2003 a very successful LDR seeds program has been established throughout Japan. A dedicated Prostate Permanent Seed Implantation Study Group ensures continuous updates and training. The leading benchmark study in HDR monotherapy in the world came from Japan. Beginning with 4- to 9-fraction regimens, HDR monotherapy has then been optimized and further developed to sophisticated single-fraction approaches. These developments will provide benchmark clinical data for international spread of HDR monotherapy.

Breast cancer brachytherapy has been adapted from the encouraging results presented in various clinical trials, mostly coming from Europe. The special situation of Japanese closed cavity breast surgery and small CTV volumes has been taken into account for translating this technique into clinical practice in Japan.

Esophageal brachytherapy has been an important activity in Japan throughout the last decades, in particular with developing HDR endoluminal brachytherapy in early superficial disease, in locally advanced disease, and in stenotic lesions within a palliative setting. Important recommendations for prescribing and reporting endoluminal brachytherapy were published supporting appropriate use of this important endoluminal technique.

Japanese researchers have provided during the last decades significant clinical evidence for bile duct endolumenal brachytherapy based on large multicenter clinical experience.

In addition, this comprehensive brachytherapy book covers many disease sites relevant for brachytherapy such as oral cancer, ocular melanoma, and lung cancer.

We wish this brachytherapy book a wide dissemination in the Japanese oncological community and in particular in radiation oncology. We hope that this book will further contribute to the growth of this important area of radiation oncology, which has a significant clinical impact. The application of well-established procedures with continuous improvement in techniques and high technology shows the increasing potential for this treatment technique. Brachytherapy enables very high tumor control rates with very limited radiotherapy-associated morbidity.

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Preface

Brachytherapy has a long history since the discovery of radium-226 by Marie Curie in 1898 and its introduction to the cancer treatment in France in 1901. Already in 1913, the clinical results of brachytherapy in cervical cancer surpassed the results obtained through Wertheim's operation. The era of "Strahl statt Stahl" (rays instead of iron knife) came. Brachytherapy was at that time a sole modality which can be curative in the deep-lying tumors. Additionally the wisdom of fractionated radiation therapy derived from the experience obtained through low-dose-rate brachytherapy using radium-226. However, with the advent of telecobalt and megavoltage radiation therapy, the indications of brachytherapy were quite narrowed and once seemed to be obsolete. In addition, radiation exposure to the medical personnel remained quite annoying. The introduction of the afterloading method by Henschke and a small radionuclide with a high specific radioactivity such as iridium-192 changed the scene of brachytherapy. Now the high-dose-rate irradiation in interstitial as well as intracavitary applications became possible. Provided that radionuclide placement is performed according to the planning, inverse square law guarantees very sharp dose distribution confined to the tumor. Additionally, implanted applicators move according to the physiological movement of the tumor and planning target volume can be reduced to a minimum. Even in comparison to the most modern external beam radiation like intensity-modulated proton therapy, brachytherapy can attain favorable physical dose distribution. Fame of brachytherapy as the utmost precision therapy remains impeccable.

In this book, radiation oncologists majoring in brachytherapy describe the present status of brachytherapy in oncology with their eagerness. This book is dedicated to young radiation oncologists and we wish many of them will be inspired to join the fascinating and stimulating world of brachytherapy.

Tokyo, Japan — Yasuo Yoshioka
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2018 Spring

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Part I

General

History of Brachytherapy in Japan

1

Tetsuo Nishimura

Abstract

In Japan, brachytherapy using radium source began in 1911. The Cancer Institute Hospital had been leading brachytherapy in Japan since purchasing 5 g of radium source in 1934. After the World War II, the number of facilities using radium sources had been increased. However, the problem of radiation exposure by medical staff of brachytherapy treatment hindered the development of brachytherapy. In 1966, the remote afterloading system (RALS) using high dose rate cobalt sources was developed to overcome the problem of radiation exposure to medical staffs.

Thereafter, the introduction of high dose rate iridium RALS in 1991 and the start of prostate seed therapy in 2003 have resulted in an increase in the number of patients in Japan. More than 7000 patients are now undergoing brachytherapy in a year.

In 1999, Japanese group of brachytherapy (JGB) was established as a subgroup of the Japanese Society for Radiation Oncology (JASTRO). Interest in not only academic activities but also education and quality assurance was raised. The academic activity is shown through the increased number of published articles written in English by Japanese authors.

Keywords

Afterloading · Brachytherapy · History · Radium · Remote afterloading system

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1.1 Start of Brachytherapy in Japan

Soon after the discovery in 1896, ^{226}Ra sources were brought into Japan by Professor Tanakadate, a physicist of the University of Tokyo in 1903. The treatment using ^{226}Ra sources began at University of Tokyo in 1911. The Cancer Institute Hospital (CIH) in Tokyo which began radium therapy in 1929 purchased 5 g of ^{226}Ra source from Belgium based on a donation of 1 million yen from Mitsui Foundation. As a result, CIH could become one of the world's leading radium holding facilities. Clinical experience for the initial 5 years was published by Yamakawa in 1940 [1]. According to this article, not only the intracavitary treatment of cervical cancer but also interstitial treatment of oral cancer was carried out. After the interruption during World War II, radium therapy was restarted by Tsukamoto. In the annual meeting of Japan Radiology Society in 1957, Tsukamoto presented a special report demonstrating excellent results of radium therapy in the era prior to megavoltage external beam radiotherapy [2]. In treatment for laryngeal cancer, the Harmer's method modified by Tsukamoto was carried out in which the radium sources were directly placed outside of the thyroid cartilage (Fig. 1.1). A 5-year survival rate of this method for early glottic cancer was shown to be 70%.

In the physics department of CIH, ^{222}Rn gas was collected from ^{226}Ra source to make seed sources since 1935. Thus, ^{222}Rn seeds had been supplied to other facilities until 1975 in Japan.After World War II, treatment using radium source became more popular since the 1950s, and the numbers of licensed facilities using radium source increased to 296 in 1967 and 404 in 1974, respectively [3].

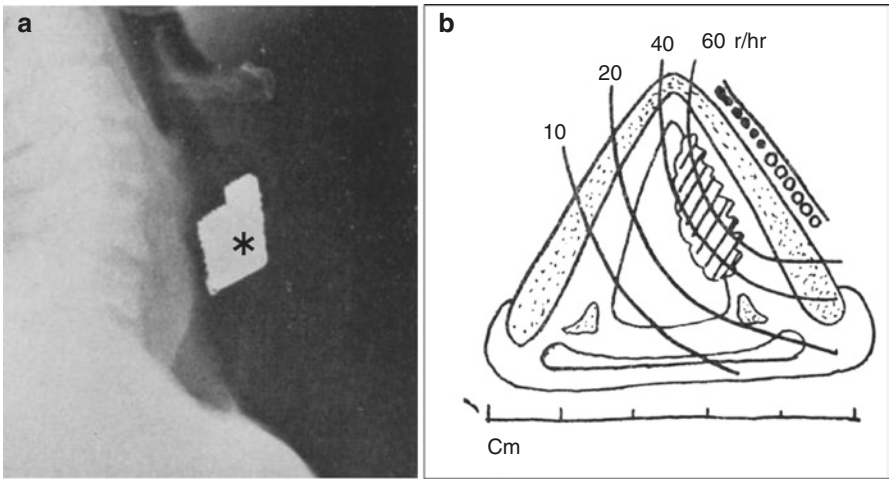

Fig. 1.1 Radium therapy for laryngeal cancer with the Harmer's method modified by Tsukamoto. (**a**) Radium sources (*) placed outside of the larynx are shown in lateral radiography. (**b**) Dose distribution of radium therapy

1.2 Shift from Radium to New Sources and Efforts to Reduce Radiation Exposure

In Japan, there were much concerns about radiation exposure in not only citizens but medical staffs because of a history of radiation exposure from atomic and hydrogen bomb. As a solution for reduction of exposure, conversion of brachytherapy sources from higher energy to lower was attempted. After the ICRP Recommendation 33 in 1981, the number of licensed facilities of radium gradually decreased to 252 in 1989, 118 in 1997, and 22 in 2005, respectively [4]. As an alternative to radium sources, ^{60}Co, ^{137}Cs, and ^{192}Ir sources were imported in 1954, 1961, and 1978, respectively. ^{198}Au and ^{192}Ir sources were domestically produced in 1975 and 1980, respectively. Supply of ^{222}Rn seed was replaced to ^{198}Au grain in 1975 [3]. In 1973, ^{253}Cf source emitting neutron was used in some facilities, but it was applied only in the research level.

Another way to reduce radiation exposure was to introduce an afterloading technique. In 1962 Tazaki developed an afterloading applicator (TAO applicator) for intracavitary brachytherapy for cervical cancer with ^{226}Ra sources [5]. Prior to introduction of this instrument, the position of ^{226}Ra sources was checked following direct insertion of radioactive sources. The use of this applicator could reduce the physician's average exposure dose in each session from 0.295 mSv in 1960–1962 to 0.022 mSv in 1963–1965. TAO applicators were widely used for many years as standard applicators and contributed to the standardization of radiation therapy for cervical cancer.

Recently, the number of facilities using low dose rate has been decreased except for ^{125}I (Fig. 1.2).

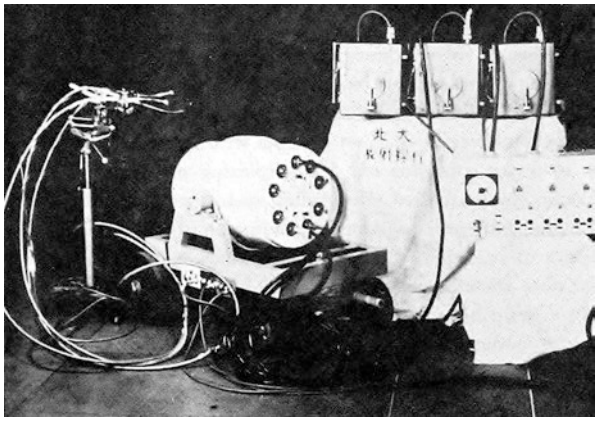

Fig. 1.2 The high dose rate remote afterloading system (RALSTRON) developed in Hokkaido University

1.3 Development of High Dose Rate Remote Afterloading System

As a fundamental solution to avoid radiation exposure in brachytherapy, a high dose rate remote afterloading system (HDR-RALS) was developed by Wakabayashi at the Hokkaido University in 1966 (Fig. 1.3) [6]. This equipment had three channels of HDR ^{60}Co sources of 3 mm in diameter. Two companies manufactured this equipment which was widely sold not only throughout Japan but also overseas, mainly to Asian countries.

Although HDR brachytherapy was accepted in radiotherapy for cervical cancer, optimal dose fractionation became a critical issue in the actual treatment. Arai et al. proposed that 29 Gy/4 fractions at point A in HDR brachytherapy was equivalent to 50 Gy in low dose rate (LDR) brachytherapy based on the data of facilities with large experience [7]. Their proposal became a basis of the present standard treatment (6 Gy/fraction) in Japan.

The HDR-RALS was originally designed for treatment of cervical cancer. It was also used for intracavitary treatment in the head and neck, esophagus, uterine body, rectum, and so on.

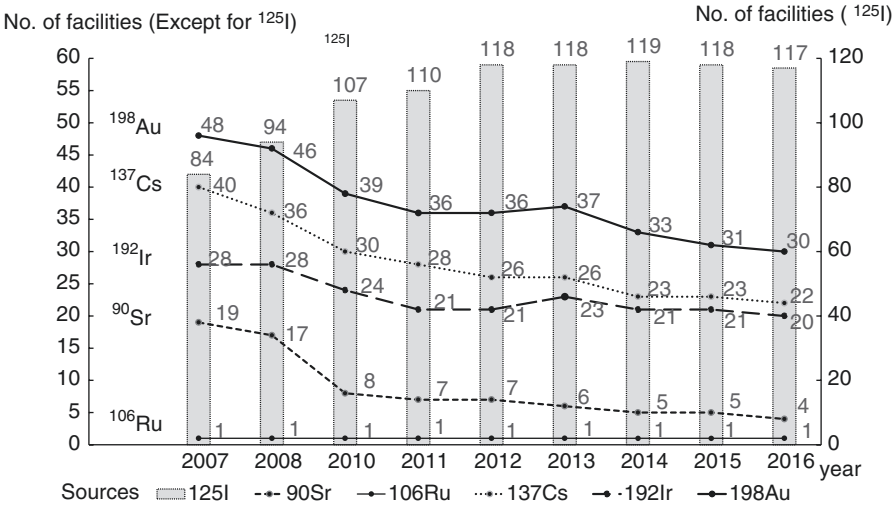

Fig. 1.3 Licensed facilities using low dose rate (LDR) sources in Japan by year. ^{125}I has been used for prostate cancer. ^{137}Cs, ^{192}Ir, and ^{198}Au have been used mainly for head and neck cancer. ^{90}Sr has been used for pterygium. ^{106}Ru has been used for ocular tumor in the National Cancer Center Central Hospital as only one facility

1.4 Introduction of the New Type of HDR-RALS

In 1991, the treatment with HDR ^{192}Ir RALS imported from Europe started in Osaka University. There were four types of equipment sold in Japan. Because of the small size of source and dose optimization program, these types of equipment were rapidly replaced from the old ^{60}Co RALS. In 2002, a new type of ^{60}Co RALS with equivalent source size to the ^{192}Ir RALS was introduced.

Because of smaller diameter of radiation source, the indication of brachytherapy spread to interstitial brachytherapy in various sites (head and neck, breast, soft tissue, pelvis, and so on) and intraluminal irradiation in the bronchus, bile duct, vessels, and so on.

On the other hand, the development of the applicator was essential to carry out safe and reliable treatment. Original applicators were developed by Japanese investigators. Among them, applicators for the esophagus and bronchus were approved to be covered by health insurance.

The number of facilities using old ^{60}Co HDR RALS gradually decreased, and the last facility disposed this equipment in 2015. There were 158 facilities of HDR brachytherapy in 2016 (Fig. 1.4).

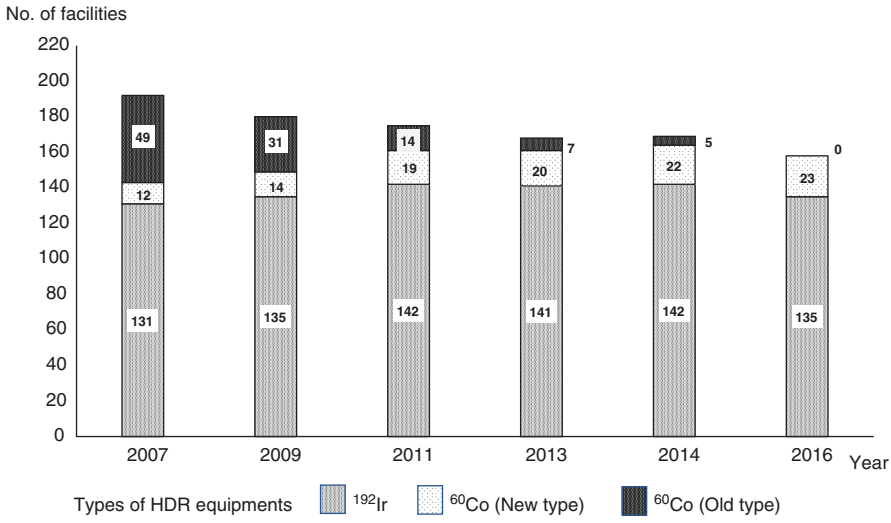

Fig. 1.4 Licensed facilities using high dose rate (HDR) remote afterloading system in Japan by year. There are two types of HDR equipment used in Japan. The old type ^{60}Co RALS has been disposed in 2015

1.5 Interstitial Brachytherapy for Prostate Cancer

One of the recent topics was the start of interstitial brachytherapy for prostate cancer in the history of brachytherapy in Japan. The first HDR brachytherapy for prostate cancer was carried out at Osaka University in 1994. On the other hand,, the first LDR ^{125}I seed brachytherapy was performed at Tokyo Medical Center in 2003 after a long preparation period including revision of law. There were more than 3000 patients each year in more than 100 facilities (Figs. 1.5 and 1.6).

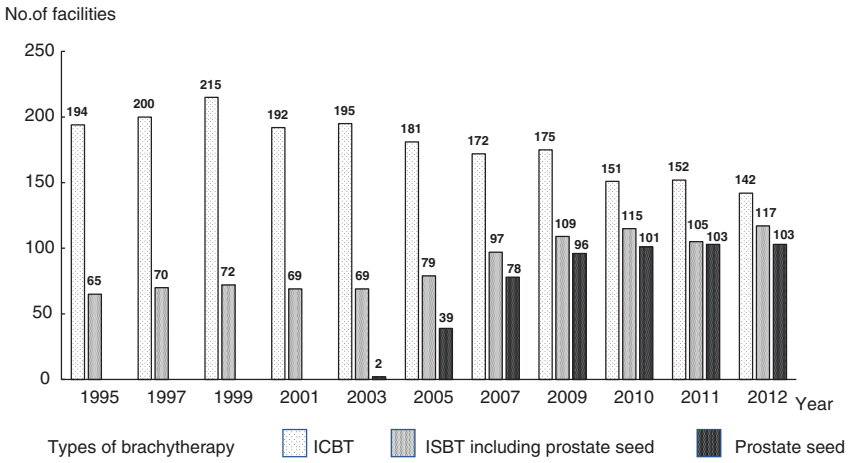

Fig. 1.5 Facilities of brachytherapy actually treating patients according to JASTRO structure survey. The number of intracavitary brachytherapy (ICBT) has been decreasing. In this figure, interstitial brachytherapy (ISBT) includes prostate seed treatment according to the original data. An increased number of ISBT facilities reflect an increase of prostatic treatment facilities

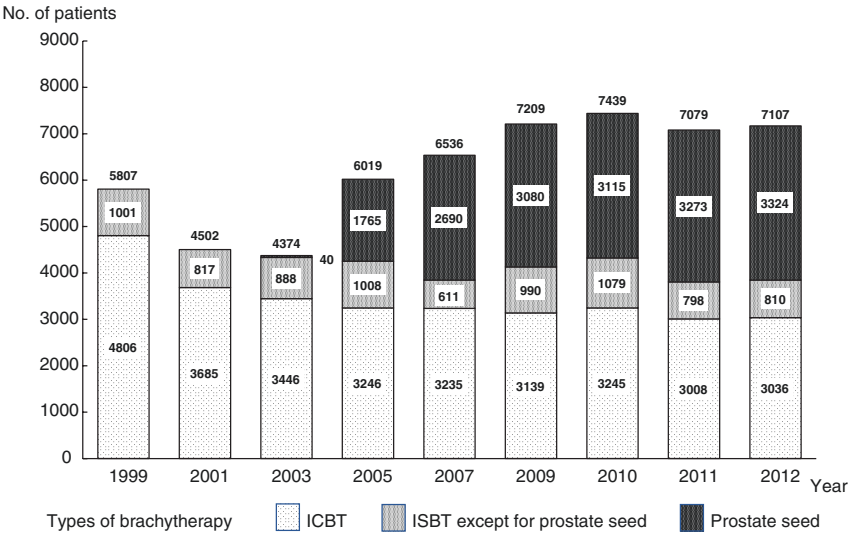

Fig. 1.6 The number of patients treated with brachytherapy to JASTRO structure survey. In this figure, interstitial brachytherapy (ISBT) does not include prostate seed treatment. The total number of patients treated with brachytherapy has been increasing

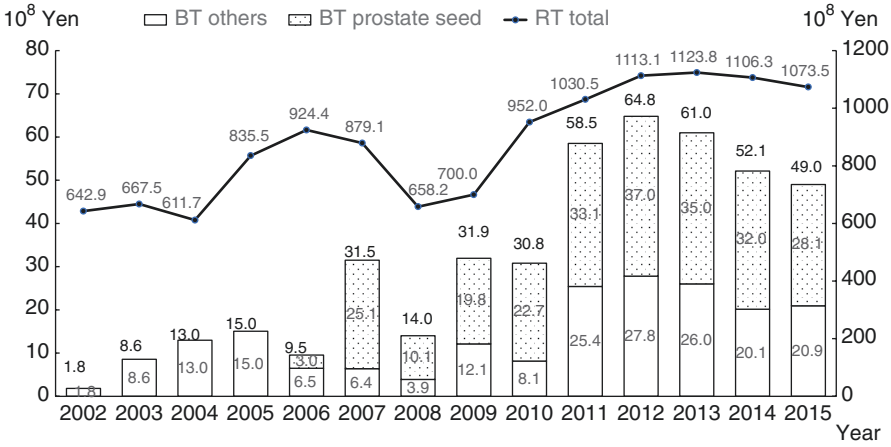

Fig. 1.7 Medical expense of total radiotherapy and brachytherapy by year. The data in this figure were calculated and estimated under the author's responsibility according to the opened data by the Ministry of Health, Labor, and Welfare regarding medical expense

1.6 The Trend of the Number of Patients and Medical Expenses of Brachytherapy

The Japanese Society for Radiation Oncology (JASTRO) has conducted biannual structural survey since 1990. According to the opened data up to 2012 [8], more than 7000 patients were annually treated with brachytherapy in Japan (Fig. 1.6). Especially, the number of brachytherapy patients has dramatically increased after the start of ^{125}I seed brachytherapy. On the other hand., the numbers of intracavitary brachytherapy and interstitial brachytherapy except for ^{125}I seed were kept in a constant level. In Japan, total medical expense of malignant neoplasms was reported

as 4.1 trillion yen in 2015 [9]. Although the proportion of radiation therapy was low in the total medical expense of cancer, it has gradually increased (Fig. 1.7). The expense of brachytherapy has been rapidly increased.

1.7 Educational and Academic Activities

From the late 1990s, interest in medical safety increased in Japan because of frequent occurrence of medical accident. There were several reports regarding dose misadministration in external beam radiotherapy. In the field of brachytherapy, there was an event of radiation exposure to a staff involved in HDR source exchange in 1998. Although this event caused no health injury, it became a social problem. In the field of brachytherapy, HDR-RALS and ^{125}II safety teaching courses had been held every year since 1998 and 2003, respectively.

In 1999, JGB (Japanese Group of Brachytherapy) was found as an activity of the Japanese Society for Radiation Oncology (JASTRO). Since 1999, the annual meeting has been held. In 2013, the JGB published the QA guidelines for brachytherapy.

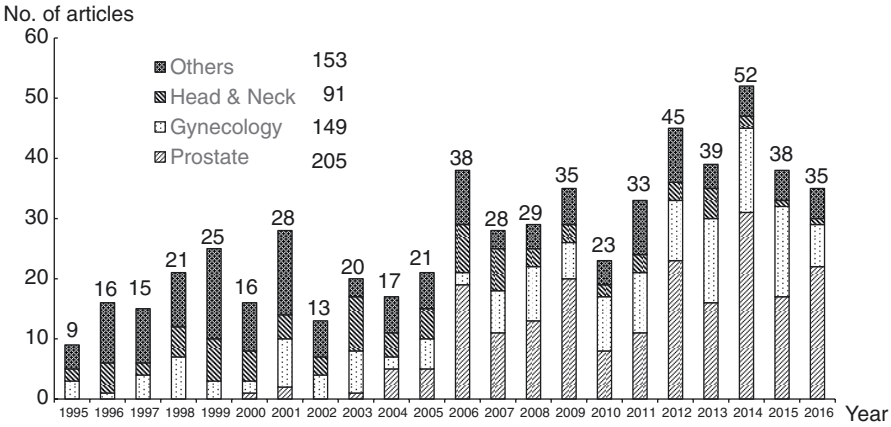

Fig. 1.8 Articles on brachytherapy written in English by Japanese authors

The academic activity is shown as the number of published articles written in English by Japanese researchers (Fig. 1.8). Scopus databases were searched using the terms "brachytherapy" and ("Japan" or "Japanese"). Totally, 598 articles were identified between 1995 and 2016.

Although articles on the head and neck had been a majority, the number has been decreased. On the other hand,, prostate and gynecological brachytherapy treatments are the two major topics. These data suggest that it is expected that more research activity will be presented in the future.

References

1. Yamakawa H. Results of radiotherapy for cancer patients during past 5 years (1934–1939). Nippon Acta Radiol. 1940;1:152–93. (In Japanese)
2. Tsukamoto K. My experience in the radiation treatment of malignant tumor. Nippon Acta Radiol. 1957;17:435–65. (In Japanese)
3. Onai Y. The story of radium: radiation and cancer treatment. Tokyo: Nippon Shuppan Service; 1998. (In Japanese)
4. Japan Radioisotope Association. Statics on the use of radiation in Japan. https://www.jrias.or.jp/report/cat/101.html. Retrieved date: Sep. 24, 2017
5. Wakabayashi M. High dose rate intracavitary radiotherapy using the RALSTRON, vol. 4. Sapporo: Hokkaido University Medical Library Series; 1971.
6. Tazaki E, Arai T, Oryu S, Tazaki E. An applicator for intracavitary radiation therapy of carcinoma of the uterine cervix. Jap J Clin Radiol. 1965;10(10):768–75. (In Japanese)
7. Arai T, Morita S, Iinuma T. Radiation treatment of cervix cancer using high dose rate remote after-loading intracavitary irradiation: an analysis of the correlation between optimal dose range and fractionation. Jpn J Cancer Clin. 1979;25:605–12. (In Japanese)
8. JASTRO data center. Japanese structure survey of radiation oncology. https://www.jastro.or.jp/medicalpersonnel/data_center/. Retrieved date: Nov. 3,2017
9. Ministry of Health, Labor and Welfare. http://www.mhlw.go.jp/toukei_hakusho/dl/05.pdf. Retrieved date: Jan. 31, 2018

Japanese Brachytherapy in the World

2

Jun Itami

Abstract

High-dose rate (HDR) afterloading brachytherapy was introduced in Japan in the late 1960s and replaced low-dose rate (LDR) brachytherapy very rapidly. Fractionated regimen of HDR intracavitary brachytherapy of cervical cancer was established in the 1970s based upon an extensive analysis of clinical findings of the patients undergoing HDR and LDR brachytherapies. It was the first report deriving HDR and LDR equivalent doses not from theoretical consideration of power law theories prevalent at that time. Various milestone reports of HDR brachytherapy have been published from Japanese groups.

Keywords

Brachytherapy · High-dose rate · Intracavitary · Interstitial · Japanese contribution

Japanese are mostly humble and dislike ones who insist their own accomplishment loudly. Many consider "Samurai-warrior does not talk much." Although Japan has contributed much to the development of brachytherapy, especially of the high-dose rate (HDR) brachytherapy, some milestone works remain largely ignored in English literature of brachytherapy because Japanese researchers do not request their righteous treatment from humbleness and some works were written in Japanese or non-English languages. The author intends to cast light onto such milestone works in HDR brachytherapy in Japan.

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2.1 Development of HDR Remote Afterloading Machine in Japan

Ulrich Henschke, who was trained as a gynecological radiation oncologist in Berlin and Munich, serviced in *Luftwaffe* during WW2, and emigrated to the USA after WW2, introduced afterloading method in brachytherapy as early as in the 1950s in the time of low-dose rate (LDR) brachytherapy [1]. With introduction of the afterloading method, radiation exposure to the medical staffs diminished markedly. However, LDR sources remained in the patient body for some time, and the patient must stay in a shielded ward, whose care inevitably caused radiation exposure to the caring staffs. Because of the radiation phobia of Japanese population evoked by the atomic bombs of Hiroshima and Nagasaki, and fisherman's death induced (partially) by radiation exposure of hydrogen bomb experiment in Bikini Islands, radiation exposure of medical staffs was so much feared, and LDR brachytherapy faced a danger of no more continuation. In such circumstances, Wakabayashi et al. succeeded in the development of remote afterloading machine in high-dose rate (HDR) using high activity Co-60 sources in 1966 [2], 5 years after report of the first HDR afterloading machine by Henschke [3]. The machine has been called popularly as remote afterloading system and specifically developed for intracavitary irradiation of the cervical cancer with six variable Co-60 sources, which were welded to the wire and remotely transported by the wire into the applicators. In intracavitary brachytherapy, one (nominal activity 2 Ci) of the sources will be used for each vaginal applicator and one (nominal activity 4 Ci) for an intrauterine applicator. Some machine has source retraction mechanism, with which a certain length of intrauterine applicator will be irradiated with multiple source dwell positions. Co-60 source pellet had a diameter of 3 mm and too big to be applied to the interstitial irradiation. RALSTRON was developed under cooperation with Shimadzu Co., and similar remote afterloading system, named "RALS," initially with Cs-137 sources and later with high activity Co-60 sources, was also produced and distributed by Toshiba. With the introduction of remote afterloading system, the intracavitary radiation could be performed in outpatient clinic without a need for admission, and applicators could be placed more precisely with fluoroscopic assistance. They very rapidly replaced LDR brachytherapy of cervical cancer. Already in 1980, about 100 remote afterloading systems were installed and used in Japan. The development of RALSTRON by Wakabayashi et al. really changed the scene of gynecological brachytherapy in Japan. Already in the late 1970s, knowledge of HDR intracavitary irradiation in the cervical cancer accumulated sufficiently to give an optimal dose ratio of HDR and LDR brachytherapy from clinical observations, not from power low equation radiobiological theory [4]. It was quite earlier than in most European and American countries, where the long tradition of LDR brachytherapy and its presumed biological superiority presumably disturbed the fast introduction of HDR brachytherapy except in Germany. Because of the big size of Co-60 sources in the RALS, its application to the interstitial irradiation must wait for the advent of a small source of Ir-192 with a

high specific radioactivity in the early 1980s. Concerning the world distribution of RALSTRON, some safety concerns were expressed, and only very limited countries had imported RALSTRON.

2.2 Ratio of Equivalent HDR and LDR Doses in Intracavitary Brachytherapy of Cervical Cancer

In Japan, remote afterloading system was commercially available from Shimadzu and Toshiba from 1967. Because of an over-exaggerated fear of radiation exposure to medical staffs, HDR remote afterloading system replaced very rapidly LDR intracavitary brachytherapy of cervical cancer. However how HDR intracavitary brachytherapy would be applied in the cervical cancer remained largely unknown. Many researchers referred to the work of Liversage [5] and Ellis [6], which was dealing with the comparison of equivalent doses of LDR and HDR brachytherapies. Joslin et al. were the first who reported the results of HDR intracavitary brachytherapy in the cervical cancer in 1972 [7]. They used a fractional dose of 10 Gy at the Manchester point A in the HDR intracavitary brachytherapy and suggested that the biological effect of the HDR treatment would be higher than LDR intracavitary irradiation by referring to the radiobiological modeling of Ellis [6]. However exploration of the optimal dose of HDR brachytherapy by analyzing the interrelationship of dose, dose rate, local control rate, and incidence of morbidities must await the publication of Arai et al. in 1979 [4]. They retrospectively analyzed treatment results of 1006 cervical cancer patients undergoing intracavitary brachytherapy in three Japanese institutions from 1961 to 1972. Five hundred seventeen and 489 patients were treated by HDR and LDR intracavitary brachytherapy, respectively. The applicators used in LDR and HDR brachytherapy produced almost the same dose distribution. In LDR brachytherapy, 5-year survivals of stages I, II, II, and IV were 87.0%, 75.2%, 49.0%, and 16.3%, respectively. In HDR brachytherapy, 5-year survivals of stages I, II, II, and IV were 82.6%, 70.5%, 51.4%, and 23.9%, respectively. There could not be seen any statistically significant differences between HDR and LDR brachytherapy. Three hundred eighteen patients irradiated by HDR brachytherapy and 171 patients by LDR brachytherapy were treated in the same time period (1966–1971) by the same school of radiation oncologists. The incidence of morbidities classified according to Kottmeier's proposal [8] was analyzed in these patients. Concerning rectal morbidity, grade 1 and grade 2 or greater was seen in 4.5% and 7.6%, respectively, in HDR. In contrast, in LDR, grade 1 and grade 2 or greater was seen in 8.9% and 7.7%, respectively. Concerning bladder morbidity, grade 1 and grade 2 or greater was seen in 3.3% and 8.2%, respectively, in HDR. In contrast, in LDR, grade 1 and grade 2 or greater was seen in 5.0% and 4.5%, respectively. Between HDR and LDR brachytherapy, there could not be seen any statistically significant differences in rectal as well as bladder morbidities. They further investigated the optimal dose of brachytherapy for local control without morbidity in the patients whose primary tumors were exclusively treated by brachytherapy (with external beam radiation therapy delivered with the central shielding). From

analysis of the scattergram of dose and number of fractions of brachytherapy, they concluded 29 Gy ± 3 Gy in 4–5 fractions of HDR brachytherapy and 50 Gy ± 5 Gy in 3–4 fractions of LDR brachytherapy are equal and optimal, and the resulting dose ratio of HDR and LDR is 0.58. It must be stressed that all the conclusions were derived from the clinical findings, not from theoretical consideration of survival curves or power law of equivalent doses. The accomplishment formed a fundamental knowledge of HDR brachytherapy in Japan. With their accomplishment, clinically safe HDR brachytherapy was realized, and the installment of remote afterloading machine was accelerated further.

2.3 Phase III Clinical Trials Comparing HDR Versus LDR in Cervical Cancer

There have been only four randomized clinical trials comparing HDR and LDR intracavitary brachytherapy in the cervical cancer, of which two were reported from Japan. Other two came from Thailand and India. With the introduction of concurrent chemoradiotherapy with CDDP and the abolishment of shielded wards for LDR brachytherapy, this kind of study could probably be performed no more. Concerning Japanese studies, one came from Osaka University group [9, 10] and the other from Sapporo Medical University group [11]. Osaka University group launched the phase III trial as early as 1975, and the final patients were entered in 1983. From 1979, a shortage of shielded wards made the precise randomization between HDR and LDR brachytherapy very difficult, and 259 patients were treated by HDR and 171 by LDR. In the patients treated by HDR, 5-year cause-specific survival was 85%, 73%, and 53% in stage I, II, and III, respectively. In the patients treated by LDR, 5-year cause-specific survival was 93%, 78%, and 47% in stage I, II, and III, respectively. There were no statistically significant differences between HDR and LDR brachytherapy. Although incidence of morbidities equal to or greater than grade 2 was higher in HDR (10% vs. 4% in LDR), they concluded the incidence is clinically acceptable and HDR intracavitary brachytherapy can be an important treatment option in the cervical cancer.

Phase III randomized trial of Sapporo Medical University group was performed from 1984 to 1997 in 132 patients with stage II and III cervical cancers. In HDR, 5-year cause-specific survival was 69% and 51% in stage II and III, respectively. In LDR, 5-year cause-specific survival was 87% and 60% in stage II and III, respectively. Between HDR and LDR, there could not be seen any statistically significant differences in the cause-specific survivals. Although the reported incidence of morbidities of grade 3 or greater was quite high (5-year incidence 10% in HDR vs. 13% in LDR), there were also no differences. Based upon these data, Cochrane Review concluded that HDR and LDR are equally effective treatment option in all stages of cervical cancers [12].

2.4 Initial Experience of HDR Interstitial Therapy in Japan

In 1982, HDR brachytherapy machine of German company Buchler using a high activity Ir-192 source was installed in Japan. That was the first machine of Ir-198 HDR source in Japan. Like Japan, Germany has a long history of using HDR brachytherapy. In 1966, HDR afterloading machine using even as high as 100 Ci of Ir-192 (GammaMed) was developed for treating brain tumor with interstitial brachytherapy by Mundinger of Freiburg University [13]. In contrast, other European countries and America with some exceptions continued to use LDR brachytherapy seemingly because of the long accumulated knowledge of LDR brachytherapy since the early 1900s and the confidence of radiobiological superiority of LDR brachytherapy. The afterloading machine of Buchler at that time used 8 Ci Ir-192 source with 1.6 mm diameter and 5 mm length, which can be applied intracavitarily as well as interstitially. For the interstitial brachytherapy, only metallic needle applicators with a diameter of 2.2 mm and quite big length of 27 cm were provided. The machine produces dose distribution by continuously oscillating the Ir-192 source within an applicator, whose range and mode are determined by a rotating disc. By changing the disc, different active length and dose distribution could be obtained. The greatest problem at that time was that there was no dedicated treatment planning computer for the afterloading machine. Additionally possibilities of obtaining the optimal dose distribution were greatly limited because the dose distribution was determined by the set of changeable discs. In contrast, the machines which attain dose distribution by stepwise retraction of radiation source have possibilities of almost infinite number of combinations of dose distributions. The remote afterloading machine has only one Ir-192 source and only one afterloading channel to which the applicator is connected. Therefore, after finishing irradiation of one applicator, connection of the channel must be changed manually to the next applicator. Currently all commercially available Ir-192 afterloading machines have one source with multichannels, and radiation can be delivered to multiple applicators without manually changing the connection between applicator and afterloading channel. The single source will be transported sequentially to all the applicators connected to the channels.

In the early 1980s, HDR interstitial brachytherapy was reported only from Germany, and how it can be prescribed remains largely to be studied. Overcoming many hurdles, Itami et al. began HDR interstitial brachytherapy for the first time in Japan [14]. They reported results of 23 cases undergoing HDR interstitial brachytherapy, of which 15 cases had recurrent tumors and 4 cases had unresectable locally advanced tumors. Applicators were placed parallelly with smaller than 2 cm interapplicator distances. Dose was prescribed to the plane 1 cm lateral to the applicators. Diameter of the hyperdose sleeve was kept less than 1 cm in most cases. Since the very long metallic applicators were intolerable for the patients, single fractional interstitial brachytherapy was performed with a big fractional dose of 15 Gy. External beam radiation therapy was also delivered in all cases. According to Jacobs

et al., who performed HDR interstitial brachytherapy very eagerly in the early 1980s in Germany, 20 Gy single fractional HDR interstitial brachytherapy was reported to be safe and effective after 40 Gy of a conventionally fractionated external beam radiation therapy in local recurrence of rectal cancer [15]. Despite recurrent or advanced nature of the cases, local control was obtained in 13 cases; however, grade 3 morbidities were seen in three cases. Two of the three cases had mandibular exposure after tongue cancer treatment in the very early phase of the study, probably caused by an inadequate spacing between the treated tongue and gingiva. After the incidence, HDR interstitial brachytherapy for tongue cancer was stopped. High incidence of morbidities is probably due to the big fractional dose. It seems very remarkable that three cases out of four with local recurrence of rectal cancer could be controlled who were treated by transperineal implantation guided by CT. The transperineal interstitial brachytherapy was, for the first time, realized due to the changeable active lengths of applicators in HDR brachytherapy.

The first experience of HDR interstitial brachytherapy in Japan ended with quite unsatisfactory results partially caused by a big fractional dose and single fractional irradiation which was obliged by a poor armamentarium of the applicators and the afterloading machine and a lack of dedicated treatment planning machine. For further development of HDR interstitial brachytherapy, availability of Nucletron machine in 1991 must be awaited.

2.5 One of the Earliest HDR Intraluminal Brachytherapies of Malignant Bile Duct Obstruction

English literature almost always neglects accomplishments written in non-English languages. The application of HDR intracavitary irradiation in patients with malignant bile duct obstruction was reported first by Köster et al. in German language in 1984 [16]. They applied 15 Gy in one fraction to the points 1 cm lateral to the source. Itami et al. subsequently published a report of HDR intracavitary irradiation of inoperable malignant bile duct obstruction in 1986, also written in German language [17]. They used Buchler afterloading machine with 8 Ci of Ir-192 and a curved metallic interstitial applicator, whose tip was made dull and rounded for intracavitary insertion. After percutaneous transhepatic drainage of bile duct, drainage tube was advanced through the obstruction. Afterloading applicator was inserted through drainage tube over the obstructed site. Because of rigidness of the applicator, insertion through the drainage tube was very difficult. Although the report of Itami et al. dealt with 7 patients, 11 patients in total underwent HDR intraluminal brachytherapy of bile duct obstruction, and no patients underwent chemotherapy. The prescription point of HDR was similar to Köster, and a fractional dose was between 7 Gy and 20 Gy, but mainly 15 Gy in 1 cm from the applicator was employed. The total dose of HDR brachytherapy ranged from 15 to 45 Gy. External beam radiation therapy was performed in 8 of 11 patients (Table 2.1). In two patients with an obstruction extending to both right and left hepatic ducts, applicator was inserted through drainage tubes inserted through right hepatic duct 1 day and

Table 2.1 Patients undergoing HDR intraluminal endobiliary brachytherapy with Bucher afterloading machine

#	Sex	Age	Diagnosis	External beam radiation therapy	HDR intraluminal endobiliary brachytherapy	Removal of PTCD	Tube-free survival	Local recurrence	Survival length	Cause of death
1	Male	79	Bile duct cancer	50 Gy/25 Fr/40 d	Right hepatic duct 7 Gy + 15 Gy × 2 + 8 Gy Left hepatic duct 15 Gy	Removed	45 days and restenosis due to fibrosis	No	240 days	Generalized metastasis
2	Female	70	Bile duct cancer	30 Gy/15 Fr/24 d	Right hepatic duct 20 Gy × 2	Removal not possible		No	293 days	Cachexia
3	Male	69	Bile duct cancer	40 Gy/20 Fr/29 d	Right hepatic duct 20 Gy × 2	Removed	31 days	No	139 days	Lung metastasis
4	Female	73	Gall bladder cancer	50 Gy/25 Fr/32 d	Right hepatic duct 15 Gy × 2	Removed	200 days	No	261 days	Carcinomatous peritonitis
5	Female	66	Pancreatic cancer	34 Gy/17 Fr/45 d	Right hepatic duct 8.8 Gy + 12 Gy × 2	Patency confirmed but not removed		No	168 days	Lung metastasis
6	Female	73	Bile duct cancer	Not performed	Right hepatic duct 15 Gy × 2	Removed	96 days	No	768 days	Lung metastasis
7	Male	56	Bile duct cancer	45 Gy/22 Fr/27 d	Right hepatic duct 15 Gy × 2 Left hepatic duct 15 Gy × 1	Removed	236 days	Yes	678 days	Local recurrence

(continued)

Table 2.1 (continued)

#	Sex	Age	Diagnosis	External beam radiation therapy	HDR intraluminal endobiliary brachytherapy	Removal of PTCD	Tube-free survival	Local recurrence	Survival length	Cause of death
8	Male	59	Bile duct cancer	Not performed	Right hepatic duct 15 Gy × 2	Patency confirmed but not removed		Yes	60 days	Local recurrence
9	Male	57	Bile duct cancer	30 Gy/15 Fr/28 d	Right hepatic duct 15 Gy × 2	Removal not possible		No	90 days	Septic shock
10	Male	67	Bile duct cancer	40 Gy/20 Fr/26 d	Right hepatic duct 15 Gy × 2	Removed	260 days	No	333 days	Lung metastasis
11	Male	64	Bile duct cancer	Not performed	Right hepatic duct 15 Gy × 1	Removal not possible		No	139 days	Cachexia

through left hepatic duct some other day. Remarkably in eight patients, bile duct obstruction was alleviated, and in six of them drainage catheter was removed without any stents. In these six patients, drainage tube free length ranged from 31 days to 260 days with a median of 148 days. Despite a big fractional dose of HDR brachytherapy, bleeding or perforation of bile duct was not observed, but one patient irradiated with 45 Gy by HDR brachytherapy and 50 Gy of external beam radiation therapy suffered from fibrosing stenosis of the irradiated bile duct with an ensuing jaundice. If dose to the duodenum is closely observed, gastrointestinal ulcer can be avoided [18]. All the patients died of cancer with a median survival of 240 days; however, evident local recurrence was seen in only two patients. HDR intraluminal brachytherapy of malignant bile duct obstruction was shown to be effective in the palliation of bile duct obstruction. But because of the technical difficulties in inserting rigid applicator into the bile duct, the therapy was not performed anymore. However, currently introduction of the flexible catheter-like applicator makes easy to perform fractional HDR intraluminal biliary irradiation and simultaneous irradiation of bilateral hepatic ducts through percutaneous transhepatic drainage tubes placed in left and right hepatic ducts. Palliative significant effect of HDR intraluminal biliary brachytherapy was repeatedly reported [18, 19]. It must be emphasized that the world's first application of HDR intraluminal biliary brachytherapy was performed in Germany and soon followed by Japanese group. This fact was not referred in most English literatures.

2.6 Interstitial Brachytherapy of Tongue Cancer HDR Versus LDR

The first modern remote afterloading system in Japan using small source of Ir-192 in a high specific activity (microSelectron-HDR, Nucletron, the Netherlands) was installed in Osaka University Hospital with all the flexible interstitial applicators and treatment planning computer. The machine enabled HDR interstitial brachytherapy without the difficulties posed by the prototype Bucher machine installed in the early 1980s. HDR interstitial brachytherapy of tongue cancer was performed by inserting multiple catheters in a single plane from submandible to the tongue. Phase III trial of HDR interstitial versus LDR interstitial brachytherapy in tongue cancer was performed in Osaka University Hospital from 1992 to 1996 [20]. They determined fractional and total doses of HDR brachytherapy by performing phase I/II study, and 6 Gy bid up to 60 Gy within a week was applied in the phase III trial [21]. For LDR brachytherapy, Ir-192 hairpins in a single plane were used to deliver 65–75 Gy (median 70 Gy) over 75–217 hours (median 117 hours). Spacer packing between the implanted tongue and gingiva was performed to lower the dose to the gingiva. In the study period, 51 patients were recruited with 26 treated by LDR and 25 by HDR. With a median follow-up length of 85 months in LDR and 78 months in HDR, 5-year local control rate was 87% and 84% for HDR and LDR brachytherapy, respectively, without a significant difference. Concerning adverse events, tongue ulcer was seen each in one patient, and two patients suffered from bone

exposure in HDR brachytherapy. HDR and LDR brachytherapies seem to be equally effective in the management of early-stage tongue cancer, although the statistical power was quite low because of low number of patients. However, this kind of randomized trials comparing LDR and HDR brachytherapies is presently very difficult to perform in Japan and in other countries also, because shielded ward is abolished very rapidly and LDR brachytherapy is no more possible. This study remains the only one phase III trial comparing HDR and LDR brachytherapies in the tongue cancer.

2.7 World's First Application of HDR Brachytherapy Alone in Prostate Cancer Without External Beam Radiation Therapy

Yoshioka et al. from Osaka University performed and reported HDR interstitial brachytherapy alone for management of prostate cancer for the first time in the world [22, 23]. As shown in foregoing sections, Radiation Oncology Group from Osaka University Hospital has contributed greatly in the development of brachytherapy with their motto, "brachytherapy is the therapy with a top precision." Their great confidence in brachytherapy can be read in the *Introduction* of Yoshioka's distinguished work reporting HDR interstitial brachytherapy without external beam radiation therapy in *International Journal of Radiation Oncology, Biology, and Physics* [22], "If we include external beam irradiation, the dose of brachytherapy has to be reduced to prevent adverse effects, which spoils the advantage of brachytherapy that enables us to deliver an increased dose to the local lesion." Actually, the first HDR interstitial brachytherapy of prostate cancer combined with external beam radiation in Japan has begun in Osaka University Hospital. With the accumulated technique of the brachytherapy in prostate cancer, they launched the phase I/II study to elucidate efficacy of HDR alone in prostate cancer in 1994 [22]. That was quite surprising if we see that it was 5 years before Brenner and Hall first suggested low α/β ratio of prostate cancer and a possible efficacy of hypofractionated radiation [24]. Yoshioka et al. used quite long sessions of HDR brachytherapy of 8 to 9 fractions bid up to 48 to 54 Gy mainly in intermediate- and high-risk prostate cancers. Applicators remaining in the patient body for 5 days can be quite stressful to the patients, but continuous epidural anesthesia, meticulous patient care, and seemingly patient's expectation that therapy will be finished within 5 days help to overcome all the obstacles. Combined with androgen deprivation therapy, 5-year PSA failure-free survival of 79% was obtained in high-risk patients with a median follow-up of 5.4 years [23]. Currently many groups are performing the clinical trials of HDR brachytherapy without external beam in prostate cancer.

Conclusions

HDR brachytherapy was introduced very early in Japan, and their indications and prescription were intensively studied and published. Their contribution in this field has been quite obvious and must be valued properly.

References

1. Henschke UK. “Afterloading” applicator for radiation therapy of carcinoma of the uterus. Radiology. 1960;74:834.
2. Wakabayashi M, Irie G, Sugawara T, Mitsuhashi H, Yamaguchi N, Shigematu K, Hanashima N, Katou N, Matsuda S, Inui Y, Tachika K, Hirayama Y. Manufacturing of remote afterloading machine. Rinshou Houshasen. 1966;11:678–84. (in Japanes)
3. Henschke UK, Hilaris BS, Mahan GD. Remote afterloading for intracavitary radiation therapy. Radiology. 1964;83:344–5.
4. Arai T, Morita S, Iinuma T, Nakamura J, Fukuhisa K, Kubo H, Onai Y, Tomaru T, Masubuchi K, Tuya A, Kawahara Y, Tazaki H. Radiation therapy of cervical cancer by high dose rate intracavitary irradiation. Relationship between optimal dose and fraction number. Gan No Rinsho. 1979;25:605–12. (in Japanese)
5. Liversage WE. A general formula for equating protracted and acute regimens of radiation. Br J Radiol. 1969;42:432–40.
6. Ellis F. Fractionation and dose-rate, I. The dose-time relationship in radiotherapy. Brit J Radiol. 1963;36:153–62.
7. Joslin CAF, Eng C, Smith W, Mallik A. The treatment of cervix cancer using high activity 60Co sources. Br J Radiol. 1972;45:257–70.
8. Kottmeier HL, Gray ML. Rectal and bladder injuries in relation to radiation dosage in carcinoma of the cervix. Am J Obstet Gynecol. 1961;82:74–82.
9. Inoue T, Hori S, Miyata S, Ozeki S, Shigematsu Y. High versus low dose rate intracavitary irradiation of carcinoma of the uterine cervix. A preliminary report. Acta Radiol Oncol Radiat Phys Biol. 1978;17:277–82.
10. Teshima T, Inoue T, Ikeda H, Miyata Y, Nishiyama K, Ta I, Maruyama S, Yamasaki H, Kozuka T. High-dose rate and low-dose rate intracavitary therapy for carcinoma of the uterine cervix. Final results of Osaka university hospital. Cancer. 1993;72:2409–14.
11. Hareyama M, Sakata K, Oouchi A, Nagakura H, Shido M, Someya M, Koito K. High-dose-rate versus low-dose-rate intracavitary therapy for carcinoma of the uterine cervix. Cancer. 2002;94:117–24.
12. Liu R, Wang X, Tian JH, Yang K, Wang J, Jiang L, Hao XY. High dose rate versus low dose rate intracavitary brachytherapy for locally advanced uterine cervix cancer (review). Cochrane Database Syst Rev. 2014;10. https://doi.org/10.1002/14651858.CD007563.pub3.
13. Mundinger F, Sauerwein K. “GammaMed”, ein neues Gerät zur interstitiellen, nur einige Minuten dauernden Bestrahlung von Hirngeschwülsten mit Radioisotopen, auch intraoperativ anwendbar. Acta Radiol. 1966;5:48–52.
14. Itami J. Clinical application of high dose rate interstitial radiation therapy. Nippon Acta Radiologica. 1989;49:929–40. (in Japanese)
15. Jakobs H, Teusch P, Schleppi U, Schmieder A, Moncke G. Interstitielle Brachytherapie-Erste Erfahrungen mit Ir-192 in der Kurzeittherapie. Strahlentherapie. 1984;160:8–14.
16. Köster R, Schmidt H, Greuel H. Bestrahlung von malignen Gallengangsverschlüssen in Afterloading-Techinik. Strahlentherapie. 1982;158:678–80.
17. Itami J, Saegusa K, Tsuchiya Y, Mamiya T, Miyoshi T, Ohto M, Arimizu N. Intrakavitäre High-dose-rate-Afterloading-Bestrahlung beim inoperablen malignen Gallengangverschluss. Strahlenther Onkol. 1986;162:105–10. (in German)
18. Kamada T, Saitou H, Takamura A, Noima T, Okushiba S. The role of radiotherapy in the management of extrahepatic bile duct cancer: an analysis of 145 consecutive patients treated with intraluminal and/or external beam radiotherapy. Int J Radiat Oncol Biol Phys. 1996;34:767–74.
19. Yoshioka Y, Ogawa K, Okawa H, Onishi H, Kanesaka N, Tamamoto T, Kosugi T, Hatano K, Kobayashi M, Ito Y, Takayama M, Takemoto M, Karasawa K, Nagakura H, Imai M, Kosaka Y, Yamazaki H, Ishohashi F, Nemoto K, Nishimura Y, the Japanese Radiation Oncology Study Group (JROSG). Impact of intraluminal brachytherapy on survival outcome for radiation therapy for unresectable biliary tract cancer: a propensity-score matched-pair analysis. Int J Radiat Oncol Biol Phys. 2014;89:822–9.

20. Ta I, Inoue T, Yoshida K, Yoshioka Y, Shimamoto S, Tanaka E, Yamazaki H, Shimizutani K, Teshima T, Furukawa S. Phase III trial of high- vs. low-dose-rate interstitial radiotherapy for early mobile tongue cancer. Int J Radiat Oncol Biol Phys. 2001;51:171–5.
21. Teshima T, Inoue T, Ikeda H, Murayama S, Furukawa S, Shimizutani K. Phase I/II study of high-dose rate interstitial radiotherapy for head and neck cancer. Strahlenther Onkol. 1992;168:617–21.
22. Yoshioka Y, Nose T, Yoshida K, Ta I, Yamazaki H, Tanaka E, Shiomi H, Imai A, Nakamura S, Shimamoto S, Inoue T. High-dose-rate interstitial brachytherapy as a monotherapy for localized prostate cancer: treatment description and preliminary results of a phase I/II clinical trial. Int J Radiat Oncol Biol Phys. 2000;48:675–81.
23. Yoshioka Y, Konishi K, Sumida I, Takahashi Y, Ishohashi F, Ogata T, Koizumi M, Yamazaki H, Nonomura N, Okuyama A, Ta I. Monotherapeutic high-dose-rate brachytherapy for prostate cancer: five-year results of an extreme hypofractionation regimen with 54 Gy in nine fractions. Int J Radiat Oncol Biol Phys. 2011;80:469–75.
24. Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. Int J Radiat Oncol Biol Phys. 1999;43:1095–101.

3 Modern Computational Technologies for Establishing Precision Brachytherapy: From Non-rigid Image Registration to Deep Learning

Kazuma Kobayashi

Abstract

Integration of medical imaging into the practice of brachytherapy has a potential to improve the precision in estimating clinical outcomes. Here, we will discuss state-of-the-art computational techniques to incorporate spatial consideration into the prediction of radiation toxicities in the various contexts of brachytherapy.

Keywords

Brachytherapy · Toxicity prediction · Non-rigid registration · Tensor regression · Deep learning

Abbreviations

2D	Two dimensional
3D	Three dimensional
CNN	Convolutional neural network
CT	Computed tomography
DVH	Dose-volume histogram
EBRT	External beam radiotherapy
GMM	Gaussian mixture model
IGBT	Image-guided brachytherapy
MRI	Magnetic resonance imaging
OAR	Organ at risk
PCA	Principal component analysis

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3.1 Introduction

Recent technological advances have integrated three-dimensional (3D) sectional imaging into brachytherapy treatment planning with visualization of target volumes [1–3], which is termed as image-guided brachytherapy (IGBT). IGBT has a potential to deliver a high radiation dose to the tumor and to avoid organs at risk (OARs) at the same time, improving local control and reducing toxicities [4]. Moreover, frequent use of imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) in clinical practice provides us detailed information on spatiotemporal changes of the entire tumor during the treatment and follow-up. However, exploiting potential information from medical imaging is only possible when proper computational techniques are available.

In a daily clinical practice of IGBT, dose-volume histogram (DVH) has been widely used for dose reporting within various volumes of OARs. One of the significant limitations of DVH is that it does not provide any spatial information since DVH reduces 3D information in the target into two-dimensional (2D) relationship between the dose and volume. This is partly because to correlate treatment outcome with spatial dose distribution is technically challenging due to varying patient anatomies. Thus, there exists significant room for improving methodologies to incorporate spatial information into the modeling of dose-response relationships in brachytherapy.

So far, we have developed some computational technologies and frameworks to analyze organ motion and deformation, spatial dose-response correspondence, and intra-organ heterogeneity of radiosensitivity. Such spatiotemporal modeling by modern computational techniques will be necessary for establishing precision brachytherapy in the future. In this article, we describe three techniques: (1) how to track internal organ motion and deformation for dose assessment, (2) how to topologically correlate local dose effect in an organ, and (3) how to detect intra-organ heterogeneity of radiosensitivity. Finally, we will discuss recent rapid progress of the application of deep learning in the field of brachytherapy.

3.2 Tracking Inter-fractional Organ Motion by Non-rigid Registration

Among several contributing factors to the overall uncertainty in clinical brachytherapy, Kirisits et al. demonstrated that the most substantial dose deviation was related to inter- and intra-fractional anatomical differences [5]. Because even a small change of spatial dose distribution may cause severe consequences due to the steep dose gradients of brachytherapy, evaluation of organ deformation occurring over the course of radiotherapy is essential to analyze the risk of acute and late adverse events of OARs [6]. In this section, we discuss inter-fractional organ motion and its dosimetric impact in the treatment of cervical cancer. Because of highly mobile nature of pelvic organs, there have been limitations of the current treatment planning system to calculate cumulative dose distributions over the course of

fractionated brachytherapy since tracking large deformation of anatomies such as the bladder and rectum is challenging.

Non-rigid registration is an essential technique to quantify the anatomical and dosimetric changes during multiple brachytherapy fractions, which is a process to estimate transformation parameters between two images and to bring them into the same coordinate space [7]. Since almost all imaging data are taken at different timeframes, aligning two different coordinates of varying organs on a reference frame is necessary for computational analysis such as calculating dose accumulation and tracking organ motion. There are multiple types of non-rigid registration algorithms depending on matching criteria, transformation function, and optimization method [8], widening their ranges of application in radiotherapy more extensively.

In an article [9], we presented a novel framework to calculate spatiotemporal dose summation in accordance with organ motion and deformation and compared it with simple addition of DVH-based parameters in multi-fractionated brachytherapy. For the core of the framework, we adopted a surface-based non-rigid registration based on Gaussian mixture model (GMM) to document the changing patient anatomy [10]. The surface-based algorithm has been employed in handling targets with a large deformation such as organs in the pelvic region due to its higher accuracy and feasibility.

3.2.1 Theoretical Background of Non-rigid Registration Based on GMM

A Gaussian mixture is defined as a convex combination of Gaussian component densities $(x|\ \mu_i, \Sigma_i)$, where μ_i is a mean vector and Σ_i is a covariance matrix. The probability density function is explicitly given as $p(x) = \sum_{i=1}^{k} \varpi_i \phi(x \mid \mu_i, \ _i)$, where ϖ_i are weights associated with the components. Assuming no prior information, the model proposed by Jian et al. [10] is simplified as follows: (1) the number of Gaussian components is the number of the points in the set; (2) each Gaussian component has the same weight; (3) the mean vector of each component is given by the location of each point; and (4) each Gaussian component has the same spherical covariance matrix. Thus, they treated the problem of point set registration as that of aligning two Gaussian mixtures by minimizing a certain dissimilarity between the two corresponding mixtures. For measuring similarity, the L_2 distance between Gaussian mixtures was selected. Therefore, the registration method between a model set M and a scene set S finds a parameter θ of a parametrized transformation model T, which minimizes the following cost function as

$$d_{L_2}(S, M, \theta) = \int \left\{ \mathrm{gmm}(S) - \mathrm{gmm}(T(M, \theta)) \right\}^2 \mathrm{d}x, \tag{3.1}$$

where gmm(P) refers to a Gaussian mixture density constructed from a point set P. Practically, registration process begins with estimation of an initial scale σ from input point sets and specifies an initial parameter θ from an identity transform. Each

annealing step sets up and optimizes the objective function $d_{L_2}(S,M,\theta)$ by using a numerical optimization engine. With updated parameter from the minimized objective function and decreased scale, the annealing step is repeated until some stopping criteria are satisfied. Since the objective cost function tends to be smoother with a larger scale than a smaller scale, decreasing scale in each step implements a hierarchical approach from a coarse-to-fine fashion avoiding the trap of local minima.

Andersen et al. performed a considerable study to evaluate 3D dose distribution after two fractions of pulse-dose-rate brachytherapy by using the similar computational technique [11]. However, a difficulty lies in modeling a reference frame for simultaneously registering multiple structures in fractionated high-dose-rate brachytherapy, which usually needs more than four applications. Because the algorithm treated two point sets as two mixtures of Gaussians in a symmetrical manner, the deformations were independent of the direction of the registration. Therefore, we created a patient-specific average organ structure as a reference frame for dose summation.

Our result demonstrated that even though a systematic dose difference was small between two applications, cumulative dosimetric uncertainties could not be negligible (Fig. 3.1). In particular, $D_{0.1\text{cm}^3}$ for both the bladder and rectum showed a consistent difference from the simple DVH parameter addition. The systematic and random dose deviation is considerable so that the simple addition of DVH parameters should be applied with a caution during the course of a large number of brachytherapy fractions. Furthermore, the result naturally brings up the question whether the spatial dose accumulation calculated by the non-rigid registration has an actual association with the site of radiation injury. In the next section, we will discuss how to topologically correlate local dose effect in an organ from this point of view.

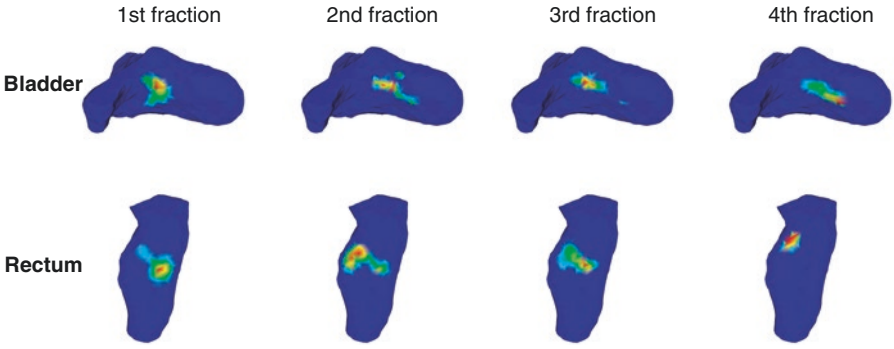

Fig. 3.1 Inter-fractional locational variation of high-dose volumes on the bladder and rectum in a patient with uterine cervical cancer, who underwent a total of four fractions of intracavitary brachytherapy

3.2.2 Dose Reconstruction for Locating the Development of Radiation Toxicities

Small organ subvolume irradiated by a high dose has been considered to contributing to severe complication after radiotherapy. However, evidence directly demonstrating a correspondence between the high-dose volume and the location of radiation toxicity was limited. In each fraction of high-dose-rate brachytherapy, maximally irradiated subvolume of OARs will be different according to the anatomical variations of shape, location, and volume. Since DVH cannot incorporate spatial consideration, non-rigid registration might be essential to investigate how high-dose volume topologically correlates with the position of radiation morbidity. In this section, we discuss the method how to discover the locational correspondence between the spatial dose distribution and the portion of radiation injury [12].

We experienced a case of an 80-year-old man, who developed tracheobronchial stenosis as a late radiation morbidity after high-dose-rate endobronchial brachytherapy followed by external beam radiotherapy (EBRT) for tracheal cancer. Endobronchial brachytherapy can be a treatment of choice for early-stage tracheal cancer as a boost for EBRT or as a definitive therapy [13–15]. However, in some cases with longer follow-up, endobronchial brachytherapy leads to severe complications such as radiation-induced bronchitis, bronchial stenosis, and fatal hemoptysis [16, 17]. Thus, spatiotemporal dose assessment of bronchial brachytherapy is necessary for improving its safety and efficacy.

Using non-rigid registration, we developed a dose reconstruction technique to investigate a locational correspondence between the region irradiated by high dose and the site where late radiation injury appeared as tracheobronchial stenosis (Fig. 3.2). Non-rigid registration based on GMM accurately aligned pre- and posttreatment organ structures with low distance error, even though the posttreatment tracheobronchial surface showed a severe anatomical deformation.

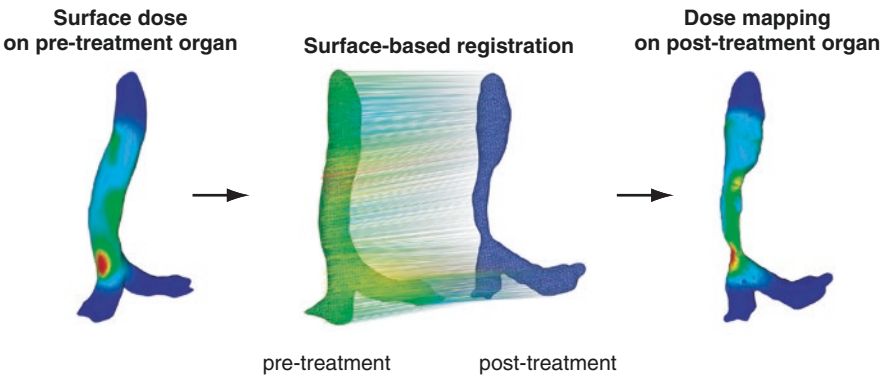

Fig. 3.2 Schematic of the image-processing pipeline for the dose reconstruction technique. The core of the framework is the surface-based non-rigid registration, enabling to estimate irradiated doses to the posttreatment organ from the dose distribution of the pretreatment organ

Consequently, the reconstructed local dose on the tracheobronchial surface significantly corresponded with the degree of radiation stenosis, demonstrating an efficacy of non-rigid registration to predict the location-by-location difference in the severity of late radiation injury. Since there have been few reports on the spatial correspondence between high-dose volume and the site of radiation injury [18], this approach is crucial because it has a potential to locate subsites in OARs where the severe radiation toxicity will develop. The dose reconstruction technique might be applicable to other treatment sites. For sophisticating and standardizing to predict radiation toxicity with spatial consideration, we will move on to the next section and discuss how to detect intra-organ heterogeneity of radiosensitivity.

3.2.3 3D Statistical Model to Detect Heterogeneous Intra-organ Radiosensitivity

Some acute and late complications of radiotherapy are not only related to volumetric aspects of the dose but particularly to the spatial pattern of dose distribution. However, DVH is unable to correlate the treatment outcome with a particular dose pattern, because it considers organs as having homogeneous radiosensitivity and reduces the 3D dose distribution to the 2D histogram. Since different dose distributions with similar DVHs sometimes lead to different clinical consequences, the method to unravel heterogeneous intra-organ radiosensitivity underlying between local dose and toxicity at a voxel level is necessary for establishing precision brachytherapy. Here, we discuss regarding the relationship between iodine-125 seed implantation and the development of lower urinary toxicities to investigate heterogeneous intra-organ radiosensitivity.

Several approaches have been made to detect particular dose pattern related to clinical outcomes. Buettner et al. demonstrated the shape of the dose distribution is related to a late complication of the rectum after prostate radiotherapy [19]. They also proposed a parameterized representation of the spatial dose distribution in the rectal wall and showed its superior performance to DVH-based model regarding the capacity of toxicity prediction [20]. More recently, Liang et al. proposed a method applying for non-rigid image registration in combination with principal component analysis (PCA) regression to identify particularly vulnerable regions associated with acute hematologic toxicity after the pelvic irradiation [21].

There are two difficulties in modeling spatial parameters to predict radiation toxicity from a population-based dataset. One is considerable difference of individual anatomies and dose distributions, which makes it difficult to compare spatial dose distributions with each other. As shown in previous sections, non-rigid image registration is necessary for standardizing all the data to a common reference frame, where voxel-wise analysis can be reasonable. Here is an example of our method to align different shapes of the individual prostate into a standard reference frame, which was obtained as an average morphology of the prostates in the population. This image-processing technique is often referred to as *anatomical standardization* (Fig. 3.3).

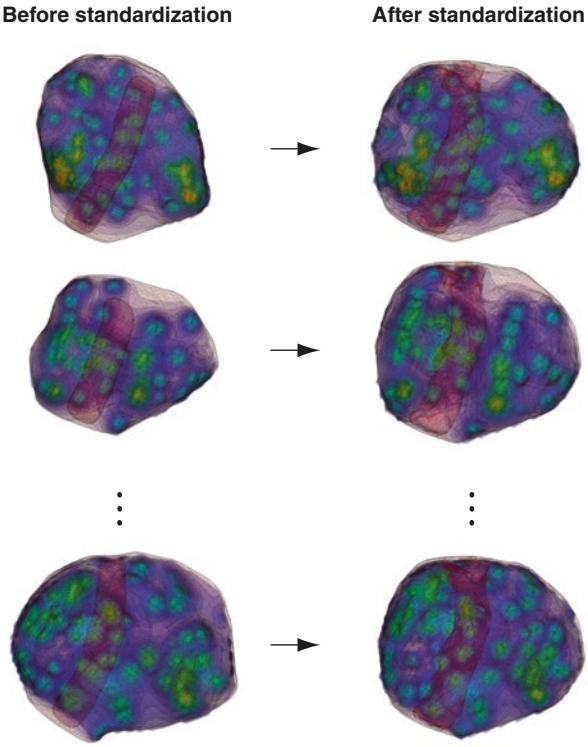

Fig. 3.3 Anatomical standardization using non-rigid registration. Individually different intraprostatic dose distributions were aligned to a common reference frame, which was created to be the average shape from the 75 prostates

Another is in manipulating the high dimensionality of variables contained in each data. Since dose distribution and medical imaging usually take forms of 3D arrays, the traditional statistical analysis is often insufficient to identify a significant spatial pattern of covariates. To cope with it, we will discuss three possible approaches.

3.2.3.1 Voxel-Wise *p*-Value Mapping

Voxel-wise *t*-test to quantify the difference between two datasets has been used mainly in the field of neuroimaging [22]. Regions with low *p*-value are considered significant. Although this approach can be easily implemented, a significant drawback is that all voxels are treated as independent units, and spatial correlation cannot be taken into consideration.

3.2.3.2 Principal Component Analysis

PCA is useful for dimensional reduction and feature extraction from high-dimensional data. Here, we describe an example calculation how to apply PCA to detect intra-organ heterogeneous radiosensitivity. We first align the data of N patients with

$\boldsymbol{M}$ variables into a dose matrix $\boldsymbol{D} \in \mathrm{R}^{N \times M}$. When dose distributions were standardized to a common reference frame, the position of each element in the column vector corresponds to a specific location. PCA will produce a matrix $\boldsymbol{E} \in \mathrm{R}^{N \times M}$, which is composed of eigenvectors corresponding to the nonzero eigenvalues in descending order of their values. Since the sample size of $\boldsymbol{N}$ is usually much less than the number of dose voxels of $\boldsymbol{M}$, there will be at most $\boldsymbol{N}$ independent eigenvectors. Now, dose array of i-th patient was uniquely represented as

$$d_i = \sum_{N}^{k=1} \theta_{ik} e_k, \tag{3.2}$$

where θ_k and e_k represent k-th principal component score and eigenvector, respectively. Thus, if we can identify a set of significant eigenvectors $(\boldsymbol{e}_k)_{k \in I}$ associated with a clinical consequence by linear regression with principal component scores $(\theta_1, \ldots \theta_N)$ as predictor variables, the model can be represented as

$$y_i = \sum_{k \in I} \beta_k \theta_{ik} = \sum_{k \in I} \beta_k e_k \cdot d_i, \tag{3.3}$$

where β_k is a regression coefficient with statistical significance. Therefore, hypothetical parameter distribution representing intra-organ radiosensitivity can be considered as sum of the eigenvectors weighted by significant regression coefficients $\left(b_i = \sum_{k \in I} \beta_k e_k\right)$.

The main limitation of PCA is that it requires rearrangement by vectorizing images into an array with considerable loss of spatial information, making it difficult to interpret some principal components.

3.2.3.3 Tensor Regression-Based Model

Tensor provides a natural representation for multidimensional data. A first-order tensor is a vector, a second-order tensor is a matrix, and tensors of order 3 or higher are called higher-order tensors. Here, we hypothesize that a toxicity of prostate can be predicted by a parallel architecture model [23] and formulate its complication probability model as

$$y = \langle B, X \rangle, \tag{3.4}$$

where: $B \in \mathbb{R}^{p_1 \times \cdots \times p_D}$ and $X \in \mathbb{R}^{p_1 \times \cdots \times p_D}$ represent 3D ($D = 3$) radiation sensitivity and dose distribution, respectively. Inner product between two tensors is defined as $B, X = \sum_{i_1 \ldots i_D} \beta_{i_1 \ldots i_D} x_{i_1, \ldots i_D}$. To overcome ultrahigh dimensionality of the model, Zhou *et al.* proposed tensor regression in combination with low rank tensor decomposition [24]. A tensor of $B \in \mathbb{R}^{p_1 \times \cdots \times p_D}$ admits a rank-R decomposition as

$$B = \sum_{R}^{r=1} \beta_1^{(r)} \circ \cdots \circ \beta_D^{(r)}, \tag{3.5}$$

where $\beta_d^{(r)} \in \mathbb{R}^{p_d}$ is column vector, approximating the original signal with a small number of parameters. In this context, the mode-d matricization and the vec operator have the following relationship [25]:

$$B_{(d)} = B_d \left(B_D \odot \cdots \odot B_{d+1} \odot B_{d-1} \odot \cdots \odot B_1 \right) \tag{3.6}$$

and

$$\mathrm{vec}B = \left(B_D \odot \cdots \odot B_1 \right) \mathbf{1}_R, \tag{3.7}$$

where $B_d = \left[\beta_d^{(1)}, \cdots, \beta_d^{(R)} \right] \in \mathbb{R}^{p_d \times \cdots \times R}$, $B_D \odot \cdots \odot B_1 \in \mathbb{R}^{\prod_d p_d \times R}$ is the Khatri-Rao product [26], and 1_R is the vector of R ones. Therefore, the systemic part of the predictive model can be rewritten as

$$y = \langle B, X \rangle = \langle \sum_R^{r=1} \beta_1^{(r)} \circ \cdots \circ \beta_D^{(r)}, X \rangle = \langle \left(B_D \odot \cdots \odot B_1 \right) 1_R, \mathrm{vec}X \rangle \tag{3.8}$$

Estimation of all parameters of $\boldsymbol{B}$ can be handled in the framework of linear regression, since tensor decomposition turns their covariates into simple vectors. Block relaxation algorithm is useful for the parameter estimation [24], and the array inner product can be obtained as

$$\langle \sum_R^{r=1} \beta_1^{(r)} \circ \cdots \circ \beta_D^{(r)}, X \rangle = \langle B_d, X_d \left(B_D \odot \cdots \odot B_{d+1} \odot B_{d-1} \odot \cdots \odot B_1 \right) \rangle. \tag{3.9}$$

Finally, we can iteratively run this block updating calculation in the range of its dimension until the likelihood ceases to increase.

The tensor regression-based model predicted that a region close to the prostate base could be sensitive to the development of urinary toxicity after iodine-125 seed implantation for prostate cancer (Fig. 3.4). Since the number of parameters still exceeded the sample size even for a low-rank model, regularization might be necessary for stabilizing the estimates to avoid overfitting. Consequently, the problem of detecting heterogeneous radiosensitivity from the standardized dose distribution can be treated as a structure-preserving dimension reduction method. Among the three proposed approaches, we consider that the tensor regression-based model is suitable for both reducing dimension and incorporating spatial consideration to predict normal tissue complication probability without any a priori knowledge.

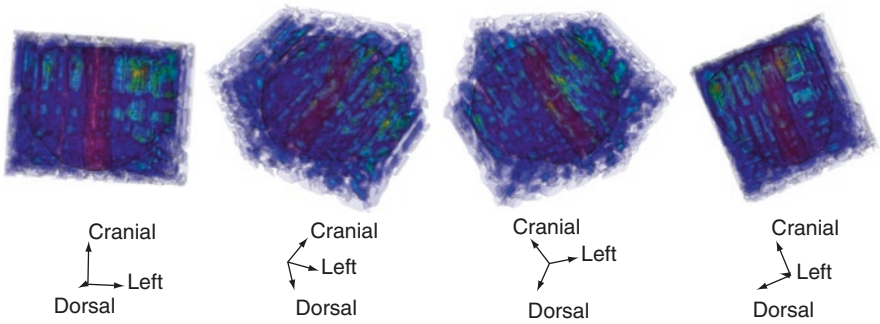

Fig. 3.4 The parameters calculated by the tensor regression model, showing the region close to the prostate base might be sensitive to the urinary toxicity

3.2.4 Future Direction Driven by Deep Learning

Deep learning is an emerging technology as a particular type of artificial neural network resembling the multilayered human cognition system. Because of its potential to perform some visual and auditory recognition tasks at superhuman levels, it is gaining a great deal of attention for the possible application in the wide range of real-world tasks. The most successful type of deep learning for image analysis is convolutional neural networks (CNNs), which won an overwhelming victory by a large margin in the worldwide computer vision competition, ImageNet Classification, in 2012 [27]. In subsequent years, CNNs have exhibited impressive performances superior to human in various tasks, including medical imaging [28].

Recently, Zhen et al. introduced a CNN-based model to analyze rectum dose distribution and predict rectum toxicity for 42 patients with cervical cancer treated with EBRT and brachytherapy [29]. Because training a large CNN from scratch with a limited number of clinical data would be impractical, they alternatively utilized transfer learning from a pre-trained model and fine-tuned the model to predict a new classification task, which distinguished toxicity and nontoxicity from dose distributions. Prediction performance was reported to be satisfactory, and the gradient-weighted class activation maps showed the geometric consistency of distribution, indicating possible location of rectum toxicity.

Because deep learning offers end-to-end learning paradigm, eliminating the need for handcrafted features, it is considerably flexible and easy to apply for various tasks. The number of application reported in the field of brachytherapy is still limited; however, deep learning as an emerging state-of-the-art technology would have a significant impact not only on the brachytherapy but also in medicine as a whole.

For establishing the precision brachytherapy, we reviewed several computational approaches mainly focusing on how to incorporate spatial consideration into the prediction of toxicities. Further in-depth investigation and validation on a large cohort are warranted to provide practical insight into the development and sophistication of algorithms.

References

1. Haie-Meder C, Pötter R, Van Limbergen E, Briot E, De Brabandere M, Dimopoulos J, et al. Recommendations from Gynaecological (GYN) GEC-ESTRO working group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Oncol. 2005;74(3):235–45. http://www.ncbi.nlm.nih.gov/pubmed/15763303
2. Pötter R, Dimopoulos J, Kirisits C, Lang S, Haie-Meder C, Briot E, et al. Recommendations for image-based intracavitary brachytherapy of cervix cancer: the GYN GEC ESTRO working group point of view: in regard to nag et al. (Int J Radiat Oncol biol Phys 2004;60:1160–1172). Int J Radiat Oncol. 2005;62(1):293–5. http://www.ncbi.nlm.nih.gov/pubmed/15850940
3. Nag S, Cardenes H, Chang S, Das IJ, Erickson B, Ibbott GS, et al. Proposed guidelines for image-based intracavitary brachytherapy for cervical carcinoma: report from image-guided brachytherapy working group. Int J Radiat Oncol. 2004;60(4):1160–72. Available from:http://www.ncbi.nlm.nih.gov/pubmed/15519788

4. Pötter R, Georg P, Dimopoulos JCA, Grimm M, Berger D, Nesvacil N, et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. Radiother Oncol. 2011;100(1):116–23. http://www.ncbi.nlm.nih.gov/pubmed/21821305
5. Kirisits C, Rivard MJ, Baltas D, Ballester F, De Brabandere M, van der Laarse R, et al. Review of clinical brachytherapy uncertainties: analysis guidelines of GEC-ESTRO and the AAPM. Radiother Oncol. 2014;110(1):199–212. http://www.ncbi.nlm.nih.gov/pubmed/24299968
6. Nesvacil N, Tanderup K, Hellebust TP, De Leeuw A, Lang S, Mohamed S, et al. A multicentre comparison of the dosimetric impact of inter- and intra-fractional anatomical variations in fractionated cervix cancer brachytherapy. Radiother Oncol. 2013;107(1):20–5. http://www.ncbi.nlm.nih.gov/pubmed/23602372
7. Ghose S, Holloway L, Lim K, Chan P, Veera J, Vinod SK, et al. A review of segmentation and deformable registration methods applied to adaptive cervical cancer radiation therapy treatment planning. Artif Intell Med. 2015;64(2):75–87. http://www.ncbi.nlm.nih.gov/pubmed/26025124
8. Oh S, Kim S. Deformable image registration in radiation therapy. Radiat Oncol J. 2017;35(2):101–11. http://www.ncbi.nlm.nih.gov/pubmed/28712282
9. Kobayashi K, Murakami N, Wakita A, Nakamura S, Okamoto H, Umezawa R, et al. Dosimetric variations due to interfraction organ deformation in cervical cancer brachytherapy. Radiother Oncol. 2015;117(3):555–8. http://www.ncbi.nlm.nih.gov/pubmed/26316394
10. Jian B, Vemuri BC. Robust point set registration using Gaussian mixture models. IEEE Trans Pattern Anal Mach Intell. 2011;33(8):1633–45. http://ieeexplore.ieee.org/lpdocs/epic03/wrapper.htm?arnumber=5674050
11. Andersen ES, Noe KØ, Sørensen TS, Nielsen SK, Fokdal L, Paludan M, et al. Simple DVH parameter addition as compared to deformable registration for bladder dose accumulation in cervix cancer brachytherapy. Radiother Oncol. 2013;107(1):52–7. http://www.sciencedirect.com/science/article/pii/S016781401300042X
12. Kobayashi K, Murakami N, Inaba K, Wakita A, Nakamura S, Okamoto H, et al. Dose reconstruction technique using non-rigid registration to evaluate spatial correspondence between high-dose region and late radiation toxicity: a case of tracheobronchial stenosis after external beam radiotherapy combined with endotracheal brachytherapy. J Contemp Brachytherapy. 2016;8(2):156–63. http://www.termedia.pl/Dose-reconstruction-technique-using-non-rigid-registration-to-evaluate-spatial-correspondence-between-high-dose-region-and-late-radiation-toxicity-a-case-of-tracheobronchial-stenosis-after-external-be,54,27484,0,1.html
13. Furuta M, Tsukiyama I, Ohno T, Katano S, Yokoi K, Sawafuji M, et al. Radiation therapy for roentgenographically occult lung cancer by external beam irradiation and endobronchial high dose rate brachytherapy. Lung Cancer. 1999;25(3):183–9. http://www.ncbi.nlm.nih.gov/pubmed/10512129
14. Marsiglia H, Baldeyrou P, Lartigau E, Briot E, Haie-Meder C, Le Chevalier T, et al. High-dose-rate brachytherapy as sole modality for early-stage endobronchial carcinoma. Int J Radiat Oncol Biol Phys. 2000;47(3):665–72. http://www.ncbi.nlm.nih.gov/pubmed/10837950
15. Kawamura H, Ebara T, Katoh H, Tamaki T, Ishikawa H, Sakurai H, et al. Long-term results of curative intraluminal high dose rate brachytherapy for endobronchial carcinoma. Radiat Oncol. 2012;7:112. http://www.ncbi.nlm.nih.gov/pubmed/22824158
16. Hara R, Itami J, Aruga T, Kozuka T, Nakajima K, Yamashita H, et al. Risk factors for massive hemoptysis after endobronchial brachytherapy in patients with tracheobronchial malignancies. Cancer. 2001;92(10):2623–7. http://www.ncbi.nlm.nih.gov/pubmed/11745197
17. Speiser BL, Spratling L. Radiation bronchitis and stenosis secondary to high dose rate endobronchial irradiation. Int J Radiat Oncol Biol Phys. 1993;25(4):589–97. http://www.ncbi.nlm.nih.gov/pubmed/7681050
18. Georg P, Kirisits C, Goldner G, Dörr W, Hammer J, Pötzi R, et al. Correlation of dose-volume parameters, endoscopic and clinical rectal side effects in cervix cancer patients treated with definitive radiotherapy including MRI-based brachytherapy. Radiother Oncol. 2009;91(2):173–80. http://www.sciencedirect.com/science/article/pii/S016781400900036X

19. Buettner F, Gulliford SL, Partridge M, Sydes MR, Dearnaley DP, Webb S. Assessing correlations between the spatial distribution of dose to the rectal wall and late rectal toxicity after prostate radiotherapy. IFMBE Proc. 2009;25(1):908–11. http://www.ncbi.nlm.nih.gov/pubmed/19826203
20. Buettner F, Gulliford SL, Webb S, Partridge M. Modeling late rectal toxicities based on a parameterized representation of the 3D dose distribution. Phys Med Biol. 2011;56(7):2103–18. http://www.ncbi.nlm.nih.gov/pubmed/21386140
21. Liang Y, Messer K, Rose BS, Lewis JH, Jiang SB, Yashar CM, et al. Impact of bone marrow radiation dose on acute hematologic toxicity in cervical cancer: principal component analysis on high dimensional data. Int J Radiat Oncol Biol Phys. 2010;78(3):912–9. http://www.ncbi.nlm.nih.gov/pubmed/20472344
22. Worsley KJ, Taylor JE, Tomaiuolo F, Lerch J. Unified univariate and multivariate random field theory. NeuroImage. 2004;23:S189–95. http://www.ncbi.nlm.nih.gov/pubmed/15501088
23. Jackson A, Kutcher GJ, Yorke ED. Probability of radiation-induced complications for normal tissues with parallel architecture subject to non-uniform irradiation. Med Phys. 1993;20(3):613–25. http://www.ncbi.nlm.nih.gov/pubmed/8350812
24. Zhou H, Li L, Zhu H. Tensor regression with applications in neuroimaging data analysis. J Am Stat Assoc. 2013;108(502):540–52. http://www.tandfonline.com/doi/abs/10.1080/01621459.2013.776499
25. Kolda T. Multilinear operators for higher-order decompositions. California: Tech rep Sandia Natl Lab; 2006.
26. Rao C, Mitra S. Generalized inverse of matrices and its applications. New York-L: John Wiley Sons Inc; 1971.
27. Krizhevsky A, Sutskever I, Hinton GE. ImageNet classification with deep convolutional neural networks; 2012. p. 1097–105. https://papers.nips.cc/paper/4824-imagenet-classification-with-deep-convolutional-neural-networks
28. Suzuki K. Overview of deep learning in medical imaging. Radiol Phys Technol. 2017;10(3):257–73. http://link.springer.com/10.1007/s12194-017-0406-5
29. Zhen X, Chen J, Zhong Z, Hrycushko BA, Zhou L, Jiang SB, et al. Deep convolutional neural network with transfer learning for rectum toxicity prediction in cervical cancer radiotherapy: a feasibility study. Phys Med Biol. 2017;62(21):8246–63. http://iopscience.iop.org/article/10.1088/1361-6560/aa8d09

Part II

Gynecology

Moving on from LDR to HDR

4

Takashi Nakano and Masaru Wakatsuki

Abstract

Low-dose-rate (LDR) intracavitary brachytherapy for the uterine cervix was a standard treatment modality in the first half of the twentieth century. High-dose-rate (HDR) intracavitary brachytherapy was developed to overcome some drawbacks of LDR brachytherapy (e.g., exposure of the medical staff and long treatment time). After biological effects including fractionation effects of HDR brachytherapy were determined by basic and clinical studies, HDR intracavitary brachytherapy increasingly has been used by the early twenty-first century. Advantage of adjustability of dose distribution in HDR brachytherapy accelerated the clinical application by development and introduction of CT/MRI images in image-guided brachytherapy (IGBT) in these days.

Keywords

LDR to HDR · Brachytherapy · IGBT

4.1 Introduction

Intracavitary radiation therapy has been recognized as one of the most effective treatment modalities for uterine cervical cancer. In the first half of the twentieth century, low-dose-rate (LDR) intracavitary brachytherapy had produced successful clinical results, such as Stockholm method, Paris method, and Manchester methods. This modality, however, has some drawbacks (e.g., exposure of the medical staff

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and physical and psychological load to the patients caused by long treatment time and difficulty keeping the precise positioning of applicators during treatment). High-dose-rate (HDR) intracavitary brachytherapy was developed by Henschke et al. and O'Connel et al. in 1964 to overcome these drawbacks [1, 2] and was introduced in Japan by Wakabayashi et al. in 1965 [3]. At that time, the treatment was not successful because of overdosage due to ignorance of the biological effects of HDR brachytherapy. Arai et al. developed HDR intracavitary brachytherapy in 1968, and this chapter introduced the moving on from LDR to HDR in Japan.

4.2 Development of the Applicators for Afterloading Intracavitary Radiation Therapy

In Japan around 1960, intracavitary brachytherapy for uterine cervical cancer had not been established on the standard treatment methods. In 1962, Tazaki, Arai, and Oryu introduced the original applicator (TAO applicator) for afterloading intracavitary radiation therapy for cervical cancer, which can be capable of placing the radium source in the standard position of Manchester methods [4] (Fig. 4.1). The shape of the outer surface of ovoids was curved according to dose distribution of ovoid sources to give as homogeneous dose to the surface of the vagina as possible.

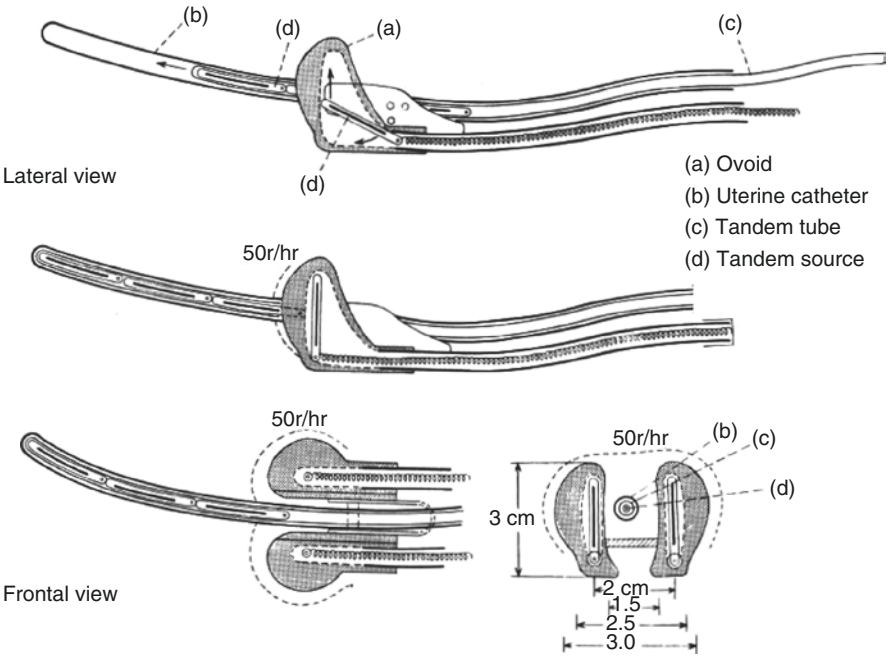

Fig. 4.1 TAO applicators

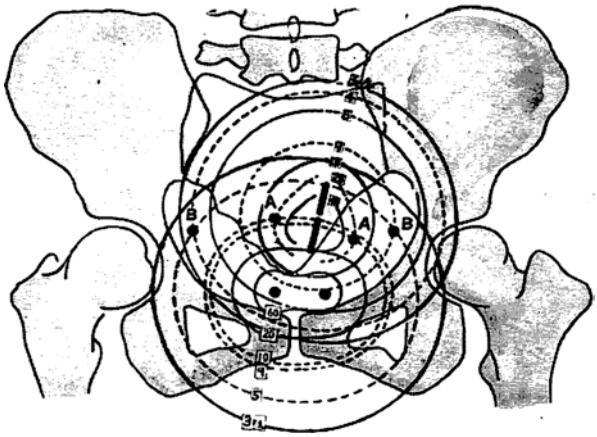

Fig. 4.2 Schema of dose calculation at point A and point B. Two doses of Dose distribution charts of Tanndem and Ovoids on transparent films are added to calculate doses of Points A and B

In addition, exposure to the medical staff can be decreased to 1/10 by using these afterloading applicators [4]. After then, they have made dose distribution chart for TAO applicators, which were corresponding to each length and angle of a tandem and each length between ovoids (Fig. 4.2). These afterloading applicators and dose distribution chart could establish the standard treatment methods of remote afterloading of LDR intracavitary brachytherapy for uterine cervical cancer.

4.3 Clinical Trial of HDR Intracavitary Brachytherapy for Patients with Cervical Cancer

High-dose-rate intracavitary brachytherapy was developed by Henschke et al. and O'Connel et al. in 1964 to overcome these drawbacks and was introduced in Japan by Wakabayashi et al. in 1965 [1–3]. At that time, the treatment was not successful because of overdosage due to ignorance of the biological effects of HDR brachytherapy. Arai et al. initiated the clinical trial to identify equivalent doses for treatment between LDR and HDR intracavitary brachytherapy for patients with cervical cancer in 1968 [5, 6]. They conducted the phase I study which had planned HDR brachytherapy schedule similar to the LDR schedule for stage I–II cervical cancers. The HDR intracavitary brachytherapy is performed on a fractionation schedule with one insertion per week, giving five fractions during a period of external pelvis irradiation with central shielding so that the most susceptive area of the rectum and the bladder by brachytherapy was not irradiated by external beams. The equivalent dose linear line showed that biologically equivalent point A dose of LDR brachytherapy was 1.7 times higher than that of HDR brachytherapy (Fig. 4.3). The dose of HDR intracavitary brachytherapy sets four levels: level 1, 7 Gy per fraction; level 2, 6 Gy per fraction; level 3, 5 Gy per fraction; and level 4, 4 Gy per fraction. The results of this clinical trial are shown in Table 4.1. These results suggested dose of level 2, which was 30 Gy/5 fractions, might be the recommended dose for stage I–II disease in terms of good local control with acceptable low severe complication.

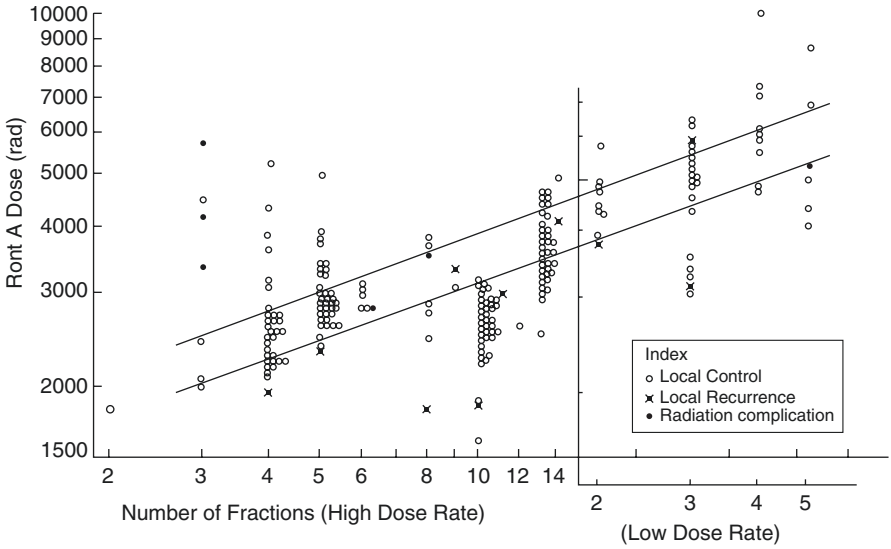

Fig. 4.3 Relation between dose and fractionation (high- and low-dose-rate intracavitary irradiation). Stage I and II patients irradiated with central shielding external irradiation

Table 4.1 Dose escalation study of HDR-intracavitary brachytherapy

	Dose	Number of cases	Local control	Acute toxicities for rectum or bladder
Level 1	35 Gy/5fr	10	10/10	Mild
Level 2	30 Gy/5fr	10	10/10	None
Level 3	25 Gy/5fr	10	8/10	None
Level 4	20 Gy/5fr	5	3/5	None

4.4 Twenty-Year Experience of HDR Intracavitary Radiation Therapy for Cancer of the Uterine Cervix

Retrospective analysis was performed on 1022 patients with squamous cell carcinoma of the uterine cervix who were treated with HDR intracavitary brachytherapy at the National Institute of Radiological Sciences [7] from 1968 to 1982 in comparison with LDR intracavitary brachytherapy. The patient's population consisted of 147 patients with Stage I disease, 256 patients with Stage II disease, 515 patients with Stage III disease, and 104 patients with Stage IV disease. Before 1968, 257 patients with cervical cancers were treated with LDR intracavitary brachytherapy. There were 13 patients with Stage I disease, 5 patients with Stage IIa disease, 5 patients with Stage IIb disease, 143 patients with Stage IIIb disease, 21 patients with Stage IVa disease, and 10 patients with Stage IVb disease. The treatment schedule

of Japanese standard protocol of radiation therapy for cervical cancer is shown in Table 4.2.

Absolute 5-year survival rates for stage Ib, IIa, IIb, IIIb, IVa, and IVb diseases were 88.1%, 76.9%, 67.0%, 52.2%, 24.1%, and 13.3, respectively. For comparison, absolute 5-year survival rates of treated patients with stage Ib, IIb, IIIb, and IVa diseases were 83.3%, 73.8%, 63.1%, 46.5%, and 13.5, respectively. Figures 4.4 and 4.5 show survival rates of the patients for HDR and LDR brachytherapy with external pelvis irradiation according to stages. There were no significant differences between LDR and HDR series.

The late complications induced by radiation after HDR and LDR brachytherapy are shown in Table 4.3. The rates of severe complication of grade 3 and 4 were 4.1% for the rectosigmoid colon, 1.2% for the bladder, and 1.1% for the small intestine. There were no significant differences between LDR and HDR series.

In the case of stage I to II disease, the optimal dose from intracavitary sources was suggested to be 29 Gy ± 2 Gy at point, with four to five fractions of 6 to 7 Gy delivered

Table 4.2 Treatment protocol for cervical cancer

	External irradiation		Intracavitary irradiation	
Size of tumor	WP (cGy)	CS (cGY)	High D-R (cGy/fr)	Low D-R (cGy/fr)
Ib	0	4500	2900/5	5000/5
II				
Small	0	5000	2900/5	5000/5
Large	2000	3000	2300/4	4000/3
III				
Small	2000–3000	2000–3000	2300/4	4000/3
Large	3000–4000	1500–2500	1500/3~2400/4	2500/2~4000/3
IVa	4000–5000	1000–2500	1500/3~2000/4	2500/2~3300/3

WP: whole-pelvis field; CS: pelvis field with central shielding; D-R: dose rate; fr: fraction
Arai T et al. Cancer. 1992;69:175–180

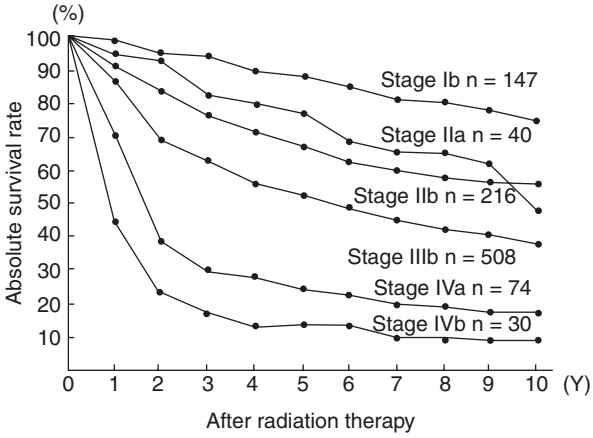

Fig. 4.4 Absolute survival rates of patients treated with high-dose-rate intracavitary radiation therapy [7]

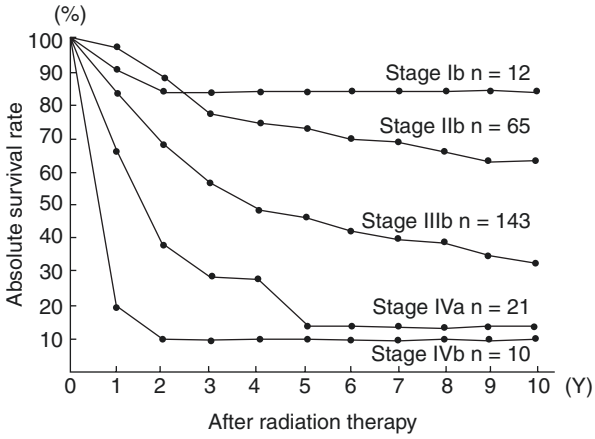

Fig. 4.5 Absolute survival rates of patients treated with low-dose-rate intracavitary radiation therapy [7]

Table 4.3 Complication rates of patients after HDR and LDR intracavitary brachytherapy

Complication Rates of patients after HDR intracavitary brachytherapy					
	Grades of severity (%)				
Site	0	1	2	3	4
Rectosigmoid colon	82.0	7.5	6.5	1.9	2.2
Bladder	85.3	8.0	5.5	0.8	0.4
Small intestine	95.9	1.3	1.8	1.0	0.1
Complication Rates of patients after LDR intracavitary brachytherapy					
	Grades of severity (%)				
Site	0	1	2	3	4
Rectosigmoid colon	70.8	10.9	15.6	2.0	0.4
Bladder	85.6	6.6	7.0	0.4	0.4
Small intestine	98.5	0.8	0	0.4	0

over 4 to 5 weeks (Fig. 4.6). This result suggested that HDR intracavitary radiation therapy provided clinical results comparable to those of the LDR technique [8].

4.5 Establishment of the Standard Treatment Schedule

According to this clinical trial and clinical experiences, Arai et al. established the standard treatment of radiation therapy for uterine cervical cancer and introduced the General Rules for Clinical and Pathological Management of Uterine Cervical Cancer in 1987 [9]. In the same period, Nakano and Arai et al. introduced image-guided brachytherapy (IGBT) with use of MR images to coordinate the dose from brachytherapy in early 1987 [10] and researched the optimum dose of HDR brachytherapy for uterine cervical cancer. Terahara and Nakano et al. reported the retrospective analysis of the relationship between dose distribution and local control using a dose-volume histogram (DVH) based on CT images in 1996 [11]. In local recurrence, a patient's absolute dose volume (<24Gy/4 fractions) was significantly

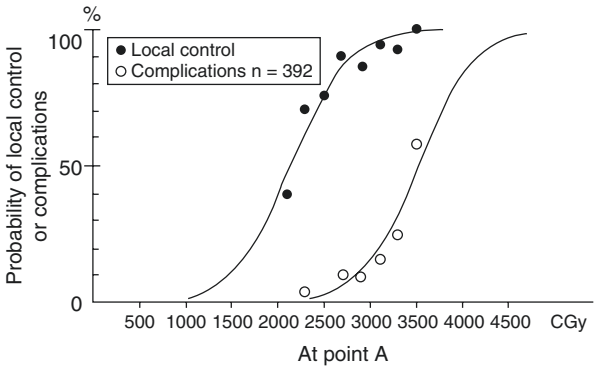

Fig. 4.6 Correlation between dose at point A and probabilities of local control and complication in 392 patients with stage I and II diseases. Dose at point A represents dose delivered from intracavitary sources

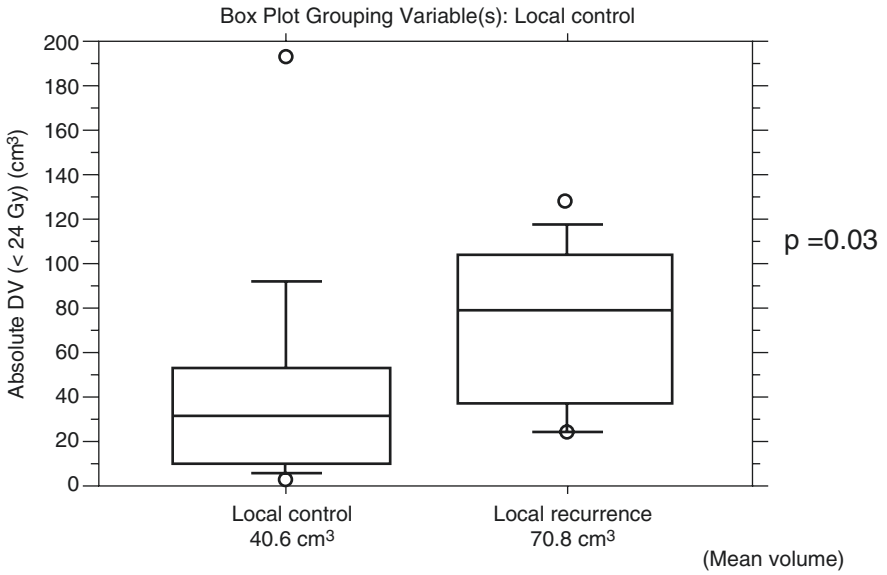

Fig. 4.7 The relationship between local control and absolute DV(<24 Gy). In local recurrence patient's absolute DV (<24 Gy) was significantly larger compared with that in patients with local control

larger compared with that in patients with local control (Fig. 4.7). These data suggested current prescribed dose system for IGBT.

In conclusion, moving from LDR to HDR started around 1960 and was established in 1987 in Japan. After then, there are many experiences for patients of uterine cervical cancer treated with HDR brachytherapy in Japan. In the twenty-first century, the USA and Euro countries have been moving from LDR to HDR, and there were several reports on this. Their treatment strategies are different from the Japanese strategy, such as central shielding and fractions of brachytherapy. In the future, we need to respect the long experiences of HDR brachytherapy in Japan and develop and improve more effective treatment strategies.

References

1. Henschke UK, Hilaris BS, Mahan GD. Remote after-loading with intracavitary applicators. Radiology. 1964;83:344–5.
2. O'Connell D, Howard N, Joslin CAF, Ramsey NW, Liversage WE. A new remotely controlled unit for the treatment of uterine carcinoma. Lancet. 1965;18:570–1.
3. Wakabayashi M, Irie G, Sugawara T, et al. The trial production of remote after-loading system unit. Jpn J Clin Radiol. 1966;11:638–48.
4. Tazaki E, Arai T, Oryu S. A new applicator for intracavitary irradiation of carcinoma of the cervix. Jpn J Clin Radiol. 1965;10:768–75.
5. Arai T, Morita S, Iinuma Y, et al. Radiation treatment of cervix cancer using high dose rate remote after-loading intracavitary irradiation: an analysis of the correlation between optimal dose range and fractionation. Jpn J Cancer Clin. 1979;25:605–12.
6. Arai T, Morita S, Kutsutani Y, et al. Relationship between total iso-effect dose and number of fractionations for the treatment of uterine cervical carcinoma by high dose rate intracavitary irradiation. In: Bates TD, Berry RJ, editors. High dose rate after-loading in the treatment of cancer of the uterus. London: The British Institute of Radiology. Br J rad special report 17; 1980. p. 89–92.
7. Arai T, Nakano T, Morita S, et al. High-dose-rate remote after-loading intracavitary radiation therapy for cancer of the uterine cervix: a 20-year experience. Cancer. 1992;69:175–80.
8. Nakano T, Kato S, Ohno T, et al. Long-term results of high-dose rate intracavitary brachytherapy for squamous cell carcinoma of the uterine cervix. Cancer. 2005;103:92–101.
9. General Rules for Clinical and Pathological Management of Uterine Cervical Cancer in Japan 1987.
10. Nakano T, Arai T, Gomi H, et al. Clinical evaluation of MRI applied to brachytherapy for cervical cancer. Jpn J Radiol. 1987;47:1181–8.
11. Terahara A, Nakano T, Ishikawa A, et al. Dose-volume histogram analysis of high dose rate intracavitary brachytherapy for uterine cervix cancer. Int J Radiat Oncol Biol Phys. 1996;35:549–54.

Intracavitary Brachytherapy from 2D to 3D

5

Takafumi Toita

Abstract

Intracavitary brachytherapy (ICBT) has played an important role as the definitive radiotherapy modality for patients with cervical cancer over the last 100 years. ICBT has been performed based on the two-dimensional (2D) planning with the use of orthogonal X-ray films for a long time. Doses are prescribed at point A according to the classical or modified Manchester systems. Recently, a dramatic shift has occurred from 2D to three-dimensional (3D) on ICBT planning. 3D-ICBT improves dose coverage of the cervical tumor while limiting overdosage of the surrounding normal organs. In this paper, we reviewed the history and clinical results of the 2D- and 3D-ICBT procedures. We also mentioned the issues and future challenges of image-guided brachytherapy (3D-IGBT) in the treatment of uterine cervical cancer.

Keywords

Uterine cervical neoplasms · Radiotherapy · Image-guided · Intracavitary brachytherapy

5.1 Introduction

Standard definitive radiotherapy (RT) for cervical cancer patients consists of external beam radiotherapy (EBRT) to the whole pelvis and intracavitary brachytherapy (ICBT) [1]. Recently, some institutions have started to use EBRT with advanced technologies such as intensity-modulated RT (IMRT) and/or stereotactic body RT (SBRT) as alternative treatments to ICBT [2, 3]. Han et al. measured the utilization

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Table 5.1 Treatment planning of ICBT for cervical cancer

	Surveillance	2D	3D	
Country	Year	X-ray	CT	MRI
USA [4, 5]	2007	43%	55%	2%
	2014	15%	95%	34%
Canada [6, 7]	2009	52%	43%	5%
	2012	21%	75%	38%
	2015	4%	96%	57%
UK [8]	2008	73%	22%	4%
	2011	26%	51%	20%
Netherlands [9]	2015	0%	55%	100%
Japan [10, 11]	2012	80%	14%	1%
	2016	40%	56%	4%
Brazil [12]	2013	92%	8%	0%

ICBT intracavitary brachytherapy, *CT* computed tomography, *MRI* magnetic resonance imaging

rate of ICBT in the USA between 1988 and 2009 with data from the Surveillance, Epidemiology, and End Results database [2]. They found that the rate decreased from 83% in 1988 to 58% in 2009. They also found that EBRT alone was associated with significantly worse oncologic outcomes (overall survival, cause-specific survival) compared with ICBT [2]. Based on the evidence, the NCCN Clinical Practice Guidelines in Oncology for Cervical Cancer, Version 1.2017 clearly stated that "conformal external beam radiotherapies (such as IMRT) should not be used as routine alternatives to brachytherapy for treatment of central disease of an intact cervix" [1].

Three-dimensional conformal RT (3D-CRT) planned mainly with computed tomography (CT) images has been the standard since the 1990s. Clinical application of IMRT for whole pelvic RT has been rapidly increasing for definitive treatment as well as for postoperative treatment in recent years. On the other hand, ICBT has been performed based on the two-dimensional (2D) planning with the use of X-ray films for a long time. However, a dramatic shift of treatment planning and evaluation from 2D to 3D-ICBT has occurred in the past 10 years (Table 5.1).

In this article, we review the history and clinical results of 2D- and 3D-ICBT. We also mention the issues and future challenges of image-guided brachytherapy (3D-IGBT).

5.2 Evidence and Issues in the Era of 2D-ICBT

5.2.1 Low-Dose Rate (LDR) vs High-Dose Rate (HDR)

With the development of a remote afterloading system (RALS), the clinical application of high-dose-rate ICBT (HDR-ICBT) spread rapidly from the 1980s in Japan [13]. Favorable treatment results were reported from the early years [14–18]. There are potential biological disadvantages of HDR-ICBT compared with low-dose-rate ICBT (LDR-ICBT), although HDR has many clinical advantages [19].

Two randomized clinical trials were performed comparing treatment results of HDR-ICBT and LDR-ICBT for cervical cancer patients in Japan [20, 21]. Both studies demonstrated equivalent oncologic outcomes as well as the incidence of severe late toxicities with the two treatments. Based on the study results and some known clinical benefits, HDR-ICBT has become to be a standard treatment method for cervical cancer patients treated with definitive RT [22]. In contrast, there were deep-rooted apprehensions of HDR among some US radiation oncologists for several years [23]. The Pattern of Care Studies (PCS) indicated slow spread of the HDR-ICBT in the US actual clinical practice [24]. However, its application increased very quickly from the 2000s [25]. High flexibility on source dwell position and time of the new-generation HDR-ICBT machines has strongly contributed on the subsequent development of novel three-dimensional image-guided brachytherapy (3D-IGBT).

5.2.2 Optimum Dose Considerations

Japanese treatment schedules of definitive RT for cervical cancer using HDR-ICBT were determined empirically based on extensive clinical experiences of the HDR-ICBT in Japan [14, 15]. Although those were not determined through prospective trials, large amount of clinical data have validated favorable local control with acceptable incidences of late complications [15–18, 26]. A large discrepancy in total dose is observed between the Japanese schedules and those of the USA. Table 5.2 shows standard treatment schedules in the 2D-ICBT era from the two countries [27, 28]. The Japanese doses appear lower compared with those of the USA. The US schedules were determined mathematically based on a radiobiological formula with LDR-ICBT clinical data from large US centers [29–34]. Similar to the Japanese schedules, the US schedules have never been tested through prospective clinical studies. In addition to that, clinical data of the US schedules were limited [35]. One of the major technical features of the Japanese definitive RT is the use of central shielding (CS) for part of whole pelvis EBRT. The use of CS might compromise the

Table 5.2 Standard dose schedules of definitive radiotherapy for uterine cervical cancer

		EBRT	HDR-ICBT	Cumulative
		(at central pelvis)	(at point A)	EQD2 (at point A)
USA (ABS)	All stages	45 Gy	4 × 7 Gy	83.9 Gy
		45 Gy	5 × 6 Gy	84.3 Gy
		45 Gy	6 × 5 Gy	81.8 Gy
		45 Gy	5 × 5.5 Gy	79.8 Gy
Japan (JASTRO)	Early stage	20 Gy	4 × 6 Gy	52 Gy
	Advanced	30 Gy	4 × 6 Gy	62 Gy
		40 Gy	3 × 6 Gy	64 Gy

EBRT external beam radiotherapy, *HDR-ICBT* high-dose-rate intracavitary brachytherapy
EQD2 equivalent dose in 2 Gy/fraction
ABS American Brachytherapy Society, *JASTRO* Japanese Society for Radiation Oncology

accurate evaluation of the cumulative dose of EBRT and ICBT. Petereit et al. stated that some EBRT radiation could get transmitted through the CS or point A might be defined differently [35]. In Japan, two multi-institutional prospective clinical studies were conducted to explore whether the Japanese schedules with lower cumulative doses were appropriate [36, 37]. One was a study of definitive radiotherapy without chemotherapy for patients with stage IB–IIB cervical cancer whose tumors were smaller than 4 cm in diameter as assessed by MRI (JAROG0401/JROSG04-2) [36]. The other was a study of concurrent chemoradiotherapy for stage III–IVA patients (JGOG1066) [37]. To maintain RT quality, protocols of the studies included an integrated RT quality assurance (QA) process. Credentialing of participating institutions and individual case reviews for all patients were performed [38, 39]. Both studies demonstrated that Japanese schedules could achieve oncologic outcomes equivalent to those of the global schedules using higher cumulative doses, with less toxicity [36, 37]. There were two retrospective studies that reported the clinical results of cervical cancer patients treated with definitive RT using the US schedules [40, 41]. Although favorable local control rates were demonstrated, the incidence of late toxicities was high compared with those of the Japanese schedules [40, 41]. In my opinion, equivalent dose calculation converted from data of LDR-ICBT to that of HDR-ICBT, which was undertaken in the USA, has potential pitfalls. LDR-ICBT requires longer treatment times (2–3 days) compared with HDR-ICBT (10–20 min). During the longer time period of LDR-ICBT, some degree of applicator displacement may have occurred, which would have led to poor adaptation to the tumor shapes. As a result, the actual dose delivered may have been lower than expected with LDR-ICBT. This could be one of the reasons that lower doses would be adequate for treatment with HDR-ICBT compared with those biologically calculated based on clinical data of LDR-ICBT. On the other hand, local control for patients with large tumors (>70 mm in diameter) was poor with Japanese schedules (cumulative point A equivalent dose in 2 Gy/fraction [EQD2] of 62–66 Gy) in a subset analysis of the JGOG1066 [37]. This result suggested that the Japanese schedules are inadequate to achieve local control for patients with bulky tumors.

Basically, no clear dose-response relationship in tumor control has been demonstrated in the definitive RT, which consists of EBRT and ICBT, for cervical cancer in the 2D era [33–35]. Dose evaluation at a single point A is the most critical problem for the issue. It is definitely difficult to determine the optimum dose at a single point because of various tumor diameters, shapes, and extensions among different patients. In other words, overdose could occur for tumors of small volume, and underdose could occur for large tumors. In addition to that, the dose at point A dose could vary with its definition [42]. Furthermore, use of the CS for EBRT adds another difficulty to dose-response evaluation [43]. In the current practice of EBRT, dose response is evaluated based on dose-volume histogram (DVH) parameters. In definitive RT for cervical cancer, which consists of a combination of EBRT and ICBT, dose-response analyses should also be conducted in terms of the DVH parameters. To perform this type of appropriate evaluation, 3D-based planning will be essential also for ICBT.

5.3 History: Shift from 2D-ICBT to 3D-IGBT

In the ICRU Report 38, the concept of reference volume (e.g., 60 Gy) and its three-dimensional diameter was proposed [44]. This was based on the consideration that a dose description at one reference point is inadequate due to a significantly steep dose gradient around the sources of ICBT. The reference volume concept appeared to be appropriate and had potential to lead to an update of the concepts of 3D-IGBT [45]. However, this concept did not become popular, because there was a critical limitation with lack of actual tumor volume data [46].

In 1982, early clinical experiences of 3D-IGBT using CT were reported [47, 48]. After those, advanced clinical studies of CT-based 3D-IGBT with a quantitative DVH evaluation were reported from Japan [49, 50]. These studies indicated that DVH parameters as well as tumor volume were predictive for tumor control [49, 50]. In 1987, Nakano et al. firstly reported the clinical experiences of MRI-based IGBT in the treatment of cervical cancer [51].

The early studies of 3D-IGBT revealed some limitations in the dose evaluation used in 2D-ICBT. First, dose to organs at risk (OAR) may be underestimated with 2D-ICBT [52–54]. These studies indicated that doses calculated at specific points (e.g., rectum and bladder) tended to be underestimated when compared with doses calculated based on volumes on CT [52–54]. More importantly, dosimetric evaluations also revealed that dose evaluation at point A is insufficient for cervical tumors [54, 55].

From the early 2000s, vigorous efforts have been made to standardize the 3D-IGBT methods used by the USA and Europe. Nag first published guidelines for image-based ICBT for cervical cancer in 2004, developed by the Image-Guided Brachytherapy Working Group, which consisted of several study group members [56]. In 2005, another recommendation was published from Europe independently by the Gynecological (GYN) GEC-ESTRO Working Group [57]. The American Brachytherapy Society (ABS) members agreed with the GEC-ESTRO recommendations, and additional guidelines were subsequently published from GEC-ESTRO [58, 59].

5.4 Clinical Data of the 3D-IGBT

A large amount of clinical data have been published from the mid-2000s onward from cervical cancer patients treated with the 3D-IGBT [60–76]. These studies demonstrated excellent local control and fewer toxicities compared with those of 2D-ICBT (Table 5.3). Dose-response relationships in both local control [78–81] and complications [82] have been demonstrated in several studies. The ABS recommended ≥80 Gy as the planning aim of HR-CTV D90 for patients with either a complete response or a partial response with residual disease smaller than 4 cm and 85–90 Gy for patients with poor response or those with residual disease larger than 4 cm [27]. The same doses were recommended for 2D-ICBT prescribed at point A in the guidelines [27]. Dimopoulos et al. analyzed clinical data of patients treated

Table 5.3 Clinical results of 3D-IGBT for cervical cancer: literature review

Authors	Period	*n*	Stage (% ≥ 2B)	Tumor size (% > 4 cm)	ICBT dose rate	Images	IC/IS	D90 (median) HR-CTV	D2 (median) Rectum/bladder	Median Follow-up (months)	Outcome Local control	Overall survival	Late toxicity (grade)
Tan et al. [60]	2005–2007	28			HDR	CT	0	NS	NS	23	96% (3-year)	81% (3-year, CSS)	14% (serious)
Kang et al. [61]	2001–2003	133	79%	41%	HDR	2D	–	72 Gy	–	56	91% (3-year)	80% (3-year, PFS)	13% (rectal, severe)
	2003–2005	97	61%	43%	HDR	CT	0	82 Gy	NS	41	97% (3-year)	80% (3-year, PFS)	2% (rectal, severe), p = 0.02
Pötter et al. [77]	2001–2008	156	84%	66% (>5 cm)	HDR	MRI	44%	93 Gy	65 Gy/86 Gy	42	95% (3-year)	68% (3-year)	4%: GI, 2%: GU (G3–4)
Charra-Brunaud et al. [62]	2005–2007	118	36% (>III)	49 mm (mean)	PDR	2D	–	68 Gy	65 Gy/64 Gy	24	74% (2-year)	65% (2-year)	23%: GI, 23%: GU (G3–4)
	2005–2007	117	25% (>III)	49 mm (mean)	PDR	CT/MRI	0	73 Gy	67 Gy/66 Gy	24	79% (2-year)	74% (2-year)	1%: GI, 2%:GU (G3–4)
Tharavichitkul et al. [63]	2008–2011	47	100%	NS	HDR	CT/MRI	0	93 Gy	70 Gy/88 Gy	26	98% (2-year)	94% (2-year)	2%: GI, 2%: GU (G3–4)

Lindegaard et al. [64]	1994–2000	99	100%	7 cm (mean)	PDR	2D	–	–	–	3.0y	76% (3-year, PC)	63% (3-year)	8%: GI, 2%: GU (G3–4)
	2005–2011	140	86%	6 cm (mean)	PDR	MRI	43%	91 Gy	66–62/79–69	2.9y	85% (3-year, PC)	79% (3-year)	3%: GI, 1%: GU (G3–4)
Nomden et al. [65]	2006–2008	46	70%	50 mm (median)	PDR/ HDR	MRI	50%	84 Gy	66 Gy/83 Gy	41	93% (3-year)	65% (3-year)	9.5%: GI, 2%: GU (G3–4)
Murakami et al. [66]	2008–2010	51	51% (>III)	45 mm (mean)	HDR	CT	0	65 Gy	NS	39	92% (3-year)	82% (3-year)	2%: GI, 0: GU (G4)
Rijkmans et al. [67]	2000–2007	43	70%	77%	LDR/ HDR	2D	–	74 Gy	–	122	68% (3-year)	51% (3-year)	12%: GI, 7%: GU (G3–4)
	2007–2012	83	65%	75%	HDR	MRI	13%	81 Gy	66 Gy/76 Gy	42	93% (3-year)	86% (3-year)	6%: GI, 0%: GU (G3–4)
Gill et al. [68]	2007–2013	128	75%	5 cm (median)	HDR	MRI-CT	5%	83 Gy	NS	24	92% (2-year)	82% (2-year, PFS)	1% (G3–4)
Tinkle et al. [69]	2003–2009	111	80%	70% (>4 cm)	HDR	MRI	100%	85 Gy	75 Gy/85 Gy(D1cc)	42	94% (4-year)	64% (4-year)	4%: GI, 2%: GU (G3–4)
Simpson et al. [70]	2007–2014	76	64%	NS	HDR	CT	0	86 Gy	68 Gy/75 Gy	17	94% (2-year)	75% (2-year)	2%: GI, 0:GU (G3)

(continued)

Table 5.3 (continued)

Authors	Period	*n*	Stage (% ≥ 2B)	Tumor size (% > 4 cm)	ICBT dose rate	Images	IC/IS	D90 (median) HR-CTV	D2 (median) Rectum/bladder	Median Follow-up (months)	Outcome Local control	Overall survival	Late toxicity (grade)
Lakosi et al. [71]	2007–2014	85	60%	54% (>5 cm)	PDR	MRI	12%	84 Gy	65 Gy/77 Gy	36	94% (3-year)	81% (3-year)	8%: GI, 5%: GU (G3–4)
Zolciak-Siwinska et al. [72]	2010–2011	216	30% (>III)	NS	HDR	CT	40%	NS	NS	47	90% (5-year)	66% (5-year)	4%: GI, 3%: GU (G3–4)
Ribeiro et al. [73]	2002–2012	170	82%	49% (>5 cm)	PDR	MRI	16%	85 Gy	62 Gy/83 Gy	37	96% (5-year)	65% (5-year)	5%: GI, 6%: GU (G3–4)
Sturdza et al. [74]	1998–2012	731	78%	46 mm (median)	HDR/PDR	MRI/CT	23%	87 Gy	64 Gy/81 Gy	43	84% (5-year)	65% (5-year)	7%: GI, 5%: GU (G3–5)
Ohno et al. [75]	2008–2011	80	67%	64% (>4 cm)	HDR	CT	18%	67-69 Gy	NS	60	94% (5-year)	86% (5-year)	0: GI, 1%: GU (G3)
Kusada et al. [76]	2011–2014	68	65%	66%	HDR	CT	0%	72 Gy	53 Gy/69 Gy	32	83% (2-year)	92% (2-year)	4%: GI, 0 GU (G3–4)

3D-IGBT Three-dimensional image-guided brachytherapy, *ICBT* intracavitary brachytherapy, *IC/IS* intracavitary/interstitial, *HR-CTV* high-risk clinical target volume
HDR high dose rate, *PDR* pulsed dose rate, *LDR* low dose rate
PC pelvic control, *CSS* cause-specific survival, *PFS* progression-free survival, *GI* gastrointestinal, *GU* genitourinary, *G* grade

with 3D-IGBT and suggested that a clinical cutoff value of 87 Gy for EBRT plus IGBT for HR-CTV D90 [78]. They also conducted dose-response analyses in the subgroups sorted by initial tumor width and tumor response to prior EBRT [79]. They demonstrated that the threshold doses to achieve local control were 91–92 Gy as the HR-CTV D90 in patients with large or poor response tumors [79]. Mazeron et al. reported similar results: that 92 Gy was required to achieve 90% local control in patients with tumor volume ≥30 cm^3 [80]. Tanderup et al. suggested that 90–95 Gy should be dose planning aims of HR-CTV D90 based on the data from the retroEMBRACE [81].

The ABS guidelines also gave recommendations on dose limits for OARs [27]. The recommended EQD2 limit for the D2cc for the rectum and the sigmoid colon was 75 Gy and was 90 Gy for the bladder [27]. These dose limits were based on the single institutional clinical data of 3D-IGBT reported by Georg et al. [83]. Recently, Mazeron et al. reported more detailed dose-volume effect relationships for rectal morbidity in the prospective multicenter EMBRACE study [82]. They demonstrated that D2cc < 65 Gy was associated with more minor and less frequent rectal morbidity, whereas a D2cc ≥ 75 Gy was associated with more major and more frequent rectal morbidity [82].

It is generally difficult to achieve these goals within the dose limits of OARs. Limitations of dose distribution in usual cervical ICBT with tandem and ovoid as well as tandem and ring applicators were also revealed through the 3D-IGBT planning process [79]. This observation prompted the idea of adding interstitial needles to the volume that had received an insufficient dose with the usual ICBT [84]. A combination of ICBT and interstitial brachytherapy, called hybrid brachytherapy, achieves satisfactory dose distribution to adequately cover the entire HR-CTV, especially for tumor of huge and/or asymmetric shape [85]. Clinical data were reported as showing excellent local control without increasing complications [63, 65, 72, 77].

As in the 2D-ICBT series, reported values of HR-CTV D90 from Japan were also smaller compared with those from international institutions [66, 75, 76] (Table 5.3). Median HR-CTV D90 ranged from 60 to 70 Gy in the Japanese series [66, 75, 76]. Despite the lower dose being delivered, oncologic outcomes were equivalent to those of other international series. While the actual reason is not clear, there are two possibilities. One might be the use of CS as part of EBRT. Tamaki et al. demonstrated that not accounting for the effects of CS on the dose led to a substantial underestimation of the actual doses delivered to the central tumor, in their excellent phantom study [86]. In other words, the cumulative EQD2 of HR-CTV D90 actually delivered might be higher than the simply summated EQD2 that completely omitted doses from EBRT with CS [86]. Secondly, images utilized for IGBT might affect the HR-CTV D90.

Overall treatment time (OTT) was also pointed out as an important predictive factor for local control in the 3D-IGBT series [80, 81], as was also observed in the 2D-ICBT series [33]. Tanderup et al. indicated that 5 Gy of HR-CTV is required to compensate for a 1-week increase in OTT [81].

5.5 Issues to Be Addressed in the 3D-IGBT

5.5.1 Imaging Modalities for IGBT

The GEC-ESTRO and international experts recommend the use of MRI T2WI as the gold standard imaging modality for 3D-IGBT for cervical cancer [57, 87]. The main reason is its excellent soft tissue resolution, which can distinguish between tumor and normal tissues [88]. This is a strong advantage of the MRI-based IGBT over the CT-based IGBT: the ability to achieve minimum variation of CTV contouring among physicians and institutions. Standardization of HR-CTV contouring as well as goal and constraint of the doses has been developed with MRI-based IGBT, and excellent MRI-based IGBT clinical data have been published. However, limited access to and length time of MRI examinations in clinical situations could be a serious barrier to its routine applications. As shown in Table 5.1, CT has been utilized as an alternative to MRI in the clinical practice in many countries. Some investigators have claimed that CT-based contouring has some uncertainty compared with MR-based contouring [89–91]. Viswanathan reported that OAR delineation was nearly comparable between CT and MRI, but HR-CTV delineated with CT was larger than that of MRI [89]. To overcome the potential risk of variation of HR-CTV contouring, standardization of CT-based contouring will be important to achieve. Recently, the Japanese Radiation Oncology Group (JROSG) published consensus-based guidelines regarding CT-based HR-CTV [92]. The guidelines recommend referring to MR images obtained immediately before the first ICBT session to help draw the appropriate HR-CTV with CT images [92]. This process was also recommended by the US experts [5]. However, it is sometimes difficult to distinguish normal organs, e.g., bowel loop and/or ovaries, from the uterine body with CT images, especially in thin patients. Another difficulty in correct referencing of MRI findings into CT series is recognition of the cervical canal and of change in uterine flexion. The cervical canal is not always visualized on MRI without insertion of a tandem applicator. Changes in uterine flexion make it difficult to fuse MR images without applicators into CT images with applicators.

Nasvacil et al. reported the feasibility of adaptive IGBT planning in a setting with limited access to MRI, using MRI for the first ICBT fraction and planning of subsequent fractions on CT [93]. They demonstrated that the difference between the MRI-based HR-CTV and transferred virtual HR-CTV on CT was generally small, and as a result, the difference between the virtual and real D90 was also small [93]. This strategy is promising because this could be applied even in a busy clinical situation in which perform MRI for all ICBT fraction. There are some limitations in cases with large tumors and complex applications, as well as situations with unfavorable OAR topography. This strategy has also been adopted in some Japanese institutions [94].

5.5.2 Design of Multi-Institutional Clinical Trial Involving ICBT as a Part of Protocol Treatments

Several multi-institutional prospective clinical trials are ongoing regarding definitive concurrent chemoradiotherapy for cervical cancer patients. Some of these trials

are designed to compare the oncologic outcomes of patients administered different drugs. Most of the trial protocols allow the use of both 2D-ICBT and 3D-IGBT. In each study, doses are prescribed and evaluated in two different ways: point A and D90 of the HR-CTV. Despite the lack of randomized studies, some investigators have demonstrated that 3D-IGBT was associated with significant improvement of local control rate as well as decreased toxicity compared with 2D-ICBT [61, 62, 64, 67, 77]. In such a situation, there might be some concern whether the results could be interpreted properly because the application of 3D-IGBT itself might have positive impact on the outcomes. Effective statistical and/or other types of mechanism would be encouraged to reach valid interpretation of the results in the clinical trials which allows the use of both 2D-ICBT and 3D-IGBT.

5.5.3 Other Issues for 3D-IGBT

Tanderup et al. performed a comprehensive review regarding uncertainties in IGBT for cervical cancer [95]. They presented an uncertainty budget quantitatively for one ICBT fraction [95]. They showed several uncertainties that might have had an impact on planning and prescription [95]. They noted intra- and inter-fraction (intra-application) uncertainties were most significant, with 12% for target (HR-CTV) and 21–26% for OARs (D2cc) [95]. This might indicate that individual treatment planning per ICBT fraction is essential to achieve proper dose evaluation. However, there are institutions in which IGBT planning is performed in the first session only. The ICRU Report 89 covers issues of inter-application uncertainties in such conditions [96]. Even in a situation in which 3D-IGBT planning per fraction is difficult, 3D image acquisition in every IGBT session should be minimum requirement to perform IGBT appropriately.

This situation might be due to limited manpower, machine time, and insufficient reimbursement. I think that adequate reimbursement is the most important issue for the appropriate delivery of ICBT especially for 3D-IGBT. 3D-IGBT is a highly time- and labor-intensive treatment and requires great skill to perform. ICBT is a very important component of curative treatment for patients with cervical cancer [1]. Without appropriate application of ICBT, treatment outcomes would be compromised. Therefore, the effort to achieve sufficient reimbursement has high priority.

Several types of applicators that are compatible with CT/MRI-based IGBT are commercially available. Fletcher family applicator sets consisting of tandem and ovoids are the most popular in the Asian countries, including Japan. Tandem and ring systems are also commonly utilized in other countries but not in Japan. The main reason why ring systems are unavailable in Japan is the size of the sets: applicators suited for small Asian women are warranted. Proper adaptability of the applicators is one of the most important basic conditions [97]. In addition, additional interstitial needles as hybrid-IGBT are usually inserted manually without template devices in Japan [85], as no template devices are commercially available in Japan. In this situation, the application quality of hybrid-IGBT would strongly depend on the skill of the radiation oncologists. In such situations, safe and standardized

performance is difficult in hybrid-IGBT. Vendors should make special efforts to design and deliver new devices that fit Asian women with small organs, with acceptable costs.

A combination of ICBT and additional interstitial brachytherapy, so-called hybrid-IGBT, is an excellent strategy especially for patients with bulky and/or irregular-shaped HR-CTV. Inverse planning is commercially available and has been tested clinically. Inverse planning has potential in cases treated with hybrid-IGBT [98]. Tinkle et al. reported excellent clinical outcomes for cervical cancer patients treated with inverse planned IGBT [70]. To further promote the investigation and clinical use of the hybrid-IGBT with inverse planning, applicators with appropriate templates, enabling the insertion of interstitial needles into the intended region, should be strongly encouraged.

References

1. Cervical cancer. NCCN Clinical Practice Guidelines in Oncology. 2017. https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed 27 Sept 2017.
2. Han K, Milosevic M, Fyles A, et al. Trends in the utilization of brachytherapy in cervical cancer in the United States. Int J Radiat Oncol Biol Phys. 2013;87(1):111–9. https://doi.org/10.1016/j.ijrobp.2013.05.033.
3. Gill BS, Lin JF, Krivak TC, et al. National Cancer Data Base analysis of radiation therapy consolidation modality for cervical cancer: the impact of new technological advancements. Int J Radiat Oncol Biol Phys. 2014;90(5):1083–90. https://doi.org/10.1016/j.ijrobp.2014.07.017.
4. Viswanathan AN, Erickson BA. Three-dimensional imaging in gynecologic brachytherapy: a survey of the American Brachytherapy Society. Int J Radiat Oncol Biol Phys. 2010;76(1):104–9. https://doi.org/10.1016/j.ijrobp.2009.01.043.
5. Grover S, Harkenrider MM, Cho LP, et al. Image guided cervical brachytherapy: 2014 survey of the American Brachytherapy Society. Int J Radiat Oncol Biol Phys. 2016;94(3):598–604. https://doi.org/10.1016/j.ijrobp.2015.11.024.
6. Pavamani S, D'Souza DP, Portelance L, et al. Image-guided brachytherapy for cervical cancer: a Canadian Brachytherapy Group survey. Brachytherapy. 2011;10(5):345–51. https://doi.org/10.1016/j.brachy.2010.12.004.
7. Taggar AS, Phan T, Traptow L, et al. Cervical cancer brachytherapy in Canada: a focus on interstitial brachytherapy utilization. Brachytherapy. 2017;16(1):161–6. https://doi.org/10.1016/j.brachy.2016.10.009.
8. Tan LT. Implementation of image-guided brachytherapy for cervix cancer in the UK: progress update. Clin Oncol (R Coll Radiol). 2011;23(10):681–4. https://doi.org/10.1016/j.clon.2011.07.011.
9. de Boer P, Jürgenliemk-Schulz IM, Westerveld H, et al. Patterns of care survey: radiotherapy for women with locally advanced cervical cancer. Radiother Oncol. 2017;123(2):306–11. https://doi.org/10.1016/j.radonc.2017.04.005.
10. Ohno T, Toita T, Tsujino K, et al. A questionnaire-based survey on 3D image-guided brachytherapy for cervical cancer in Japan: advances and obstacles. J Radiat Res. 2015;56:897–903. https://doi.org/10.1093/jrr/rrv047.
11. Toita T, Ohno T, Ikushima H et al. Current status of intracavitary brachytherapy for cervical cancer in Japan. The 30th annual meeting of the Japanese Society for Radiation Oncology, Nara, 26–27 May 2017.
12. da Silva RM, Pinezi JC, Macedo LE, et al. Current situation of high-dose-rate brachytherapy for cervical cancer in Brazil. Radiol Bras. 2014;47(3):159–64. https://doi.org/10.1590/0100-3984.2013.1859.

13. Inoue T. The trail of the development of high-dose-rate brachytherapy for cervical cancer in Japan. Jpn J Clin Oncol. 2003;33:327–30.
14. Arai T. Standard radiation treatment for carcinoma of the uterine cervix. Rinsho Hoshasen. 1984;29(13):1499–504.
15. Arai T, Nakano T, Morita S, et al. High-dose-rate remote afterloading intracavitary radiation therapy for cancer of the uterine cervix. A 20-year experience. Cancer. 1992;69(1):175–80.
16. Kataoka M, Kawamura M, Nishiyama Y, et al. Results of the combination of external-beam and high-dose-rate intracavitary irradiation for patients with cervical carcinoma. Gynecol Oncol. 1992;44(1):48–52.
17. Ito H, Kutuki S, Nishiguchi I, et al. Radiotherapy for cervical cancer with high-dose rate brachytherapy correlation between tumor size, dose and failure. Radiother Oncol. 1994;31(3):240–7.
18. Nakano T, Kato S, Ohno T, et al. Long-term results of high-dose rate intracavitary brachytherapy for squamous cell carcinoma of the uterine cervix. Cancer. 2005;103:92–101.
19. Nag S, Erickson B, Thomadsen B, et al. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. Int J Radiat Oncol Biol Phys. 2000;48:201–11.
20. Teshima T, Inoue T, Ikeda H, et al. High-dose rate and low-dose rate intracavitary therapy for carcinoma of the uterine cervix. Final results of Osaka University Hospital. Cancer. 1993;72(8):2409–14.
21. Hareyama M, Sakata K, Oouchi A, et al. High-dose-rate versus low-dose-rate intracavitary therapy for carcinoma of the uterine cervix: a randomized trial. Cancer. 2002;94(1):117–24.
22. Toita T, Kodaira T, Shinoda A, et al. Patterns of radiotherapy practice for patients with cervical cancer (1999–2001): patterns of care study in Japan. Int J Radiat Oncol Biol Phys. 2008;70:788–94. https://doi.org/10.1016/j.ijrobp.2007.10.045.
23. Eifel PJ. High-dose-rate brachytherapy for carcinoma of the cervix: high tech or high risk? Int J Radiat Oncol Biol Phys. 1992;24(2):383–6. discussion 387–8
24. Erickson B, Eifel P, Moughan J, et al. Patterns of brachytherapy practice for patients with carcinoma of the cervix (1996–1999): a patterns of care study. Int J Radiat Oncol Biol Phys. 2005;63(4):1083–92.
25. Smith GL, Jiang J, Giordano SH, et al. Trends in the quality of treatment for patients with intact cervical cancer in the United States, 1999 through 2011. Int J Radiat Oncol Biol Phys. 2015;92(2):260–7. https://doi.org/10.1016/j.ijrobp.2015.01.037.
26. Ariga T, Toita T, Kato S, et al. Treatment outcomes of patients with FIGO Stage I/II uterine cervical cancer treated with definitive radiotherapy: a multi-institutional retrospective research study. J Radiat Res. 2015;56(5):841–8. https://doi.org/10.1093/jrr/rrv036.
27. Viswanathan AN, Beriwai S, De Los Santos JF, et al. American brachytherapy society consensus guidelines for locally advanced carcinoma of the cervix. Part II: High dose-rate brachytherapy. Brachytherapy. 2012a;11:47–52. https://doi.org/10.1016/j.brachy.2011.07.002.
28. JASTRO radiotherapy guideline, 2016.
29. Perez CA, Breaux S, Madoc-Jones H, et al. Radiation therapy alone in the treatment of carcinoma of uterine cervix. I. Analysis of tumor recurrence. Cancer. 1983;51(8):1393–402.
30. Perez CA, Breaux S, Bedwinek JM, et al. Radiation therapy alone in the treatment of carcinoma of the uterine cervix. II. Analysis of complications. Cancer. 1984;54(2):235–46.
31. Eifel PJ, Morris M, Wharton JT, et al. The influence of tumor size and morphology on the outcome of patients with FIGO stage IB squamous cell carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys. 1994;29(1):9–16.
32. Logsdon MD, Eifel PJ. FIGO IIIB squamous cell carcinoma of the cervix: an analysis of prognostic factors emphasizing the balance between external beam and intracavitary radiation therapy. Int J Radiat Oncol Biol Phys. 1999;43(4):763–75.
33. Lanciano RM, Martz K, Coia LR, et al. Tumor and treatment factors improving outcome in stage III-B cervix cancer. Int J Radiat Oncol Biol Phys. 1991;20:95–100.
34. Perez CA, Fox S, Lockett MA, et al. Impact of dose in outcome of irradiation alone in carcinoma of the uterine cervix: analysis of two different methods. Int J Radiat Oncol Biol Phys. 1991;21:885–98.

35. Petereit DG, Pearcey R. Literature analysis of high dose rate brachytherapy fractionation schedules in the treatment of cervical cancer: is there an optimal fractionation schedule? Int J Radiat Oncol Biol Phys. 1999;43:359–66.
36. Toita T, Kato S, Niibe Y, et al. Prospective multi-institutional study of definitive radiotherapy with high-dose-rate intracavitary brachytherapy in patients with nonbulky (<4-cm) stage I and II uterine cervical cancer (JAROG0401/JROSG04-2). Int J Radiat Oncol Biol Phys. 2012a;82(1):e49–56. https://doi.org/10.1016/j.ijrobp.2011.01.022.
37. Toita T, Kitagawa R, Hamano T, et al. Phase II study of concurrent chemoradiotherapy with high-dose-rate intracavitary brachytherapy in patients with locally advanced uterine cervical cancer: efficacy and toxicity of a low cumulative radiation dose schedule. Gynecol Oncol. 2012b;126:211–6. https://doi.org/10.1016/j.ygyno.2012.04.036.
38. Toita T, Oguchi M, Ohno T, et al. Quality assurance in the prospective multi-institutional trial on definitive radiotherapy using high-dose-rate intracavitary brachytherapy for uterine cervical cancer: the individual case review. Jpn J Clin Oncol. 2009;39(12):813–9. https://doi.org/10.1093/jjco/hyp105.
39. Toita T, Kato S, Ishikura S, et al. Radiotherapy quality assurance of the Japanese Gynecologic Oncology Group study (JGOG1066): a cooperative phase II study of concurrent chemoradiotherapy for uterine cervical cancer. Int J Clin Oncol. 2011;16(4):379–86. https://doi.org/10.1007/s10147-011-0196-4.
40. Anker CJ, Cachoeira CV, Boucher KM, et al. Does the entire uterus need to be treated in cancer of the cervix? Role of adaptive brachytherapy. Int J Radiat Oncol Biol Phys. 2010;76:704–12. https://doi.org/10.1016/j.ijrobp.2009.02.044.
41. Forrest JL, Ackerman I, Barbera L, et al. Patient outcome study of concurrent chemoradiation, external beam radiotherapy, and high-dose rate brachytherapy in locally advanced carcinoma of the cervix. Int J Gynecol Cancer. 2010;20(6):1074–8. https://doi.org/10.1111/IGC.0b013e3181e6f321.
42. Potish RA, Gerbi BJ. Role of point A in the era of computerized dosimetry. Radiology. 1986;158:827–31.
43. Fenkell L, Assenholt M, Nielsen SK, et al. Parametrial boost using midline shielding results in an unpredictable dose to tumor and organs at risk in combined external beam radiotherapy and brachytherapy for locally advanced cervical cancer. Int J Radiat Oncol Biol Phys. 2011;79(5):1572–9. https://doi.org/10.1016/j.ijrobp.2010.05.031.
44. ICRU, International Commission on Radiation Units and Measurement "Dose and volume specification for reporting intracavitary therapy in gynecology". ICRU Report 38, 1985, Bethesda, MD, USA.
45. Pötter R, Knocke TH, Fellner C, et al. Definitive radiotherapy based on HDR brachytherapy with iridium 192 in uterine cervix carcinoma: report on the Vienna University Hospital findings (1993–1997) compared to the preceding period in the context of ICRU 38 recommendations. Cancer Radiother. 2000;4(2):159–72.
46. Pötter R, Van Limbergen E, Gerstner N, et al. Survey of the use of the ICRU 38 in recording and reporting cervical cancer brachytherapy. Radiother Oncol. 2001;58(1):11–8.
47. Yu WS, Sagerman RH, Chung CT, et al. Anatomical relationships in intracavitary irradiation demonstrated by computed tomography. Radiology. 1982;143(2):537–41.
48. Sewchand W, Prempree T, Patanaphan V, et al. Value of multi-planar CT images in interactive dosimetry planning of intracavitary therapy. Int J Radiat Oncol Biol Phys. 1982;8(2):295–301.
49. Mizoe J. Analysis of the dose-volume histogram in uterine cervical cancer by diagnostic CT. Strahlenther Onkol. 1990;166(4):279–84.
50. Terahara A, Nakano T, Ishikawa A, et al. Dose-volume histogram analysis of high dose rate intracavitary brachytherapy for uterine cervix cancer. Int J Radiat Oncol Biol Phys. 1996;35(3):549–54.
51. Nakano T, Arai T, Gomi H, et al. Clinical evaluation of the MR imaging for radiotherapy of uterine carcinoma. J Jpn Radiol Soc. 1987;47:1181–8.
52. Ling CC, Schell MC, Working KR, et al. CT-assisted assessment of bladder and rectum dose in gynecological implants. Int J Radiat Oncol Biol Phys. 1987;13(10):1577–82.

53. Kapp KS, Stuecklschweiger GF, Kapp DS, et al. Dosimetry of intracavitary placements for uterine and cervical carcinoma: results of orthogonal film, TLD, and CT-assisted techniques. Radiother Oncol. 1992;24:137–46.
54. Schoeppel SL, LaVigne ML, Martel MK, et al. Three-dimensional treatment planning of intracavitary gynecologic implants: analysis of ten cases and implications for dose specification. Int J Radiat Oncol Biol Phys. 1994;28:277–83.
55. Tanderup K, Nielsen SK, Nyvang GB, et al. From point A to the sculpted pear: MR image guidance significantly improves tumour dose and sparing of organs at risk in brachytherapy of cervical cancer. Radiother Oncol. 2010;94(2):173–80. https://doi.org/10.1016/j.radonc.2010.01.001.
56. Nag S, Cardenes H, Chang S, et al. Image-Guided Brachytherapy Working Group. Proposed guidelines for image-based intracavitary brachytherapy for cervical carcinoma: report from Image-Guided Brachytherapy Working Group. Int J Radiat Oncol Biol Phys. 2004;60(4):1160–72.
57. Haie-Meder C, Pötter R, Van Limbergen E, et al. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Oncol. 2005;74:235–45.
58. Pötter R, Haie-Meder C, Van Limbergen E, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy—3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol. 2006;78:67–77.
59. Dimopoulos JC, Petrow P, Tanderup K, et al. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (IV): basic principles and parameters for MR imaging within the frame of image based adaptive cervix cancer brachytherapy. Radiother Oncol. 2012;103(1):113–22. https://doi.org/10.1016/j.radonc.2011.12.024.
60. Tan LT, Coles CE, Hart C, et al. Clinical impact of computed tomography-based image-guided brachytherapy for cervix cancer using the tandem-ring applicator—the Addenbrooke's experience. Clin Oncol (R Coll Radiol). 2009;21:175–82. https://doi.org/10.1016/j.clon.2008.12.001.
61. Kang HC, Shin KH, Park SY, et al. 3D CT-based high-dose-rate brachytherapy for cervical cancer: clinical impact on late rectal bleeding and local control. Radiother Oncol. 2010;97:507–13. https://doi.org/10.1016/j.radonc.2010.10.002.
62. Charra-Brunaud C, Harter V, Delannes M, et al. Impact of 3D image based PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: results of the French STIC prospective study. Radiother Oncol. 2012;103:305–13. https://doi.org/10.1016/j.radonc.2012.04.007.
63. Tharavichitkul E, Chakrabandhu S, Wanwilairat S, et al. Intermediate-term results of image-guided brachytherapy and high-technology external beam radiotherapy in cervical cancer: Chiang Mai University experience. Gynecol Oncol. 2013;130(1):81–5. https://doi.org/10.1016/j.ygyno.2013.04.018.
64. Lindegaard JC, Fokdal LU, Nielsen S, et al. MRI-guided adaptive radiotherapy in locally advanced cervical cancer from a Nordic perspective. Acta Oncol. 2013;52(7):1510–9. https://doi.org/10.3109/0284186X.2013.818253.
65. Nomden CN, de Leeuw AA, Roesink JM, et al. Clinical outcome and dosimetric parameters of chemo-radiation including MRI guided adaptive brachytherapy with tandem-ovoid applicators for cervical cancer patients: a single institution experience. Radiother Oncol. 2013;107(1):69–74. https://doi.org/10.1016/j.radonc.2013.04.006.
66. Murakami N, Kasamatsu T, Wakita A, et al. CT based three dimensional dose–volume evaluations for high-dose rate intracavitary brachytherapy for cervical cancer. BMC Cancer. 2014;14:447. https://doi.org/10.1186/1471-2407-14-447.
67. Rijkmans EC, Nout RA, Rutten IH, et al. Improved survival of patients with cervical cancer treated with image-guided brachytherapy compared with conventional brachytherapy. Gynecol Oncol. 2014;135:231–8. https://doi.org/10.1016/j.ygyno.2014.08.027.
68. Gill BS, Kim H, Houser CJ, et al. MRI-guided high-dose-rate intracavitary brachytherapy for treatment of cervical cancer: the University of Pittsburgh experience. Int J Radiat Oncol Biol Phys. 2015;91:540–7. https://doi.org/10.1016/j.ijrobp.2014.10.053.

69. Tinkle CL, Weinberg V, Chen LM, et al. Inverse planned high-dose-rate brachytherapy for locoregionally advanced cervical cancer: 4-year outcomes. Int J Radiat Oncol Biol Phys. 2015;92(5):1093–100. https://doi.org/10.1016/j.ijrobp.2015.04.018.
70. Simpson DR, Scanderbeg DJ, Carmona R, et al. Clinical outcomes of computed tomography-based volumetric brachytherapy planning for cervical cancer. Int J Radiat Oncol Biol Phys. 2015;93:150–7. https://doi.org/10.1016/j.ijrobp.2015.04.043.
71. Lakosi F, de Cuypere M, Viet Nguyen P, et al. Clinical efficacy and toxicity of radio-chemotherapy and magnetic resonance imaging-guided brachytherapy for locally advanced cervical cancer patients: a mono-institutional experience. Acta Oncol. 2015;54(9):1558–66. https://doi.org/10.3109/0284186X.2015.1062542.
72. Zolciak-Siwinska A, Gruszczynska E, Bijok M, et al. Computed tomography-planned high-dose-rate brachytherapy for treating uterine cervical cancer. Int J Radiat Oncol Biol Phys. 2016;96:87–92. https://doi.org/10.1016/j.ijrobp.2016.04.025.
73. Ribeiro I, Janssen H, De Brabandere M, et al. Long term experience with 3D image guided brachytherapy and clinical outcome in cervical cancer patients. Radiother Oncol. 2016;120:447–54. https://doi.org/10.1016/j.radonc.2016.04.016.
74. Sturdza A, Pötter R, Fokdal LU, et al. Image guided brachytherapy in locally advanced cervical cancer: improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. Radiother Oncol. 2016;120:428–33. https://doi.org/10.1016/j.radonc.2016.03.011.
75. Ohno T, Noda SE, Okonogi N, et al. In-room computed tomography-based brachytherapy for uterine cervical cancer: results of a 5-year retrospective study. J Radiat Res. 2017a;58(4):543–51. https://doi.org/10.1093/jrr/rrw121.
76. Kusada T, Toita T, Ariga T, et al. Computed tomography-based image-guided brachytherapy for cervical cancer: correlation between dose-volume parameters and clinical outcomes. J Radiat Res. 2018;59(1):67–76.
77. Pötter R, Georg P, Dimopoulos JC, et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. Radiother Oncol. 2011;100(1):116–23. https://doi.org/10.1016/j.radonc.2011.07.012.
78. Dimopoulos JC, Lang S, Kirisits C, et al. Dose-volume histogram parameters and local tumor control in magnetic resonance image-guided cervical cancer brachytherapy. Int J Radiat Oncol Biol Phys. 2009a;75(1):56–63. https://doi.org/10.1016/j.ijrobp.2008.10.033.
79. Dimopoulos JC, Pötter R, Lang S, et al. Dose-effect relationship for local control of cervical cancer by magnetic resonance image-guided brachytherapy. Radiother Oncol. 2009b;93(2):311–5. https://doi.org/10.1016/j.radonc.2009.07.001.
80. Mazeron R, Castelnau-Marchand P, Dumas I, et al. Impact of treatment time and dose escalation on local control in locally advanced cervical cancer treated by chemoradiation and image-guided pulsed-dose rate adaptive brachytherapy. Radiother Oncol. 2015;114(2):257–63. https://doi.org/10.1016/j.radonc.2014.11.045.
81. Tanderup K, Fokdal LU, Sturdza A, et al. Effect of tumor dose, volume and overall treatment time on local control after radiochemotherapy including MRI guided brachytherapy of locally advanced cervical cancer. Radiother Oncol. 2016;120(3):441–6. https://doi.org/10.1016/j.radonc.2016.05.014.
82. Mazeron R, Fokdal LU, Kirchheiner K, et al. EMBRACE collaborative group . Dose-volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: results from the prospective multicenter EMBRACE study. Radiother Oncol. 2016;120(3):412–9. https://doi.org/10.1016/j.radonc.2016.06.006.
83. Georg P, Lang S, Dimopoulos JC, et al. Dose-volume histogram parameters and late side effects in magnetic resonance image-guided adaptive cervical cancer brachytherapy. Int J Radiat Oncol Biol Phys. 2011;79(2):356–62. https://doi.org/10.1016/j.ijrobp.2009.11.002.
84. Kirisits C, Lang S, Dimopoulos J, et al. The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: design, application, treatment planning, and dosimetric results. Int J Radiat Oncol Biol Phys. 2006;65(2):624–30.

85. Wakatsuki M, Ohno T, Yoshida D, et al. Intracavitary combined with CT-guided interstitial brachytherapy for locally advanced uterine cervical cancer: introduction of the technique and a case presentation. J Radiat Res. 2011;52:54–8.
86. Tamaki T, Ohno T, Noda SE, et al. Filling the gap in central shielding: three-dimensional analysis of the EQD2 dose in radiotherapy for cervical cancer with the central shielding technique. J Radiat Res. 2015;56(5):804–10. https://doi.org/10.1093/jrr/rrv029.
87. Harkenrider MM, Alite F, Silva SR, et al. Image-based brachytherapy for the treatment of cervical cancer. Int J Radiat Oncol Biol Phys. 2015;92(4):921–34. https://doi.org/10.1016/j.ijrobp.2015.03.010.
88. Mitchell DG, Snyder B, Coakley F, et al. Early invasive cervical cancer: tumor delineation by magnetic resonance imaging, computed tomography, and clinical examination, verified by pathologic results, in the ACRIN 6651/GOG 183 Intergroup Study. J Clin Oncol. 2006;24(36):5687–94.
89. Viswanathan AN, Dimopoulos J, Kirisits C, et al. Computed tomography versus magnetic resonance imaging-based contouring in cervical cancer brachytherapy: results of a prospective trial and preliminary guidelines for standardized contours. Int J Radiat Oncol Biol Phys. 2007;68:491–8. https://doi.org/10.1016/j.ijrobp.2006.12.021.
90. Viswanathan AN, Erickson B, Gaffney DK, et al. Comparison and consensus guidelines for delineation of clinical target volume for CT- and MR-based brachytherapy in locally advanced cervical cancer. Int J Radiat Oncol Biol Phys. 2014;90:320–8. https://doi.org/10.1016/j.ijrobp.2014.06.005.
91. Swanick CW, Castle KO, Vedam S, et al. Comparison of computed tomography- and magnetic resonance imaging-based clinical target volume contours at brachytherapy for cervical cancer. Int J Radiat Oncol Biol Phys. 2016;96(4):793–800. https://doi.org/10.1016/j.ijrobp.2016.07.035.
92. Ohno T, Wakatsuki M, Toita T, et al. The working group of the gynecological tumor committee of the Japanese Radiation Oncology Study Group (JROSG). Recommendations for high-risk clinical target volume definition with computed tomography for three-dimensional image-guided brachytherapy in cervical cancer patients. J Radiat Res. 2017;58(3):341–50. https://doi.org/10.1093/irthrw109.
93. Nesvacil N, Pötter R, Sturdza A, et al. Adaptive image guided brachytherapy for cervical cancer: a combined MRI-/CT-planning technique with MRI only at first fraction. Radiother Oncol. 2013;107(1):75–81. https://doi.org/10.1016/j.radonc.2012.09.005.
94. Watanabe M, Iwai Y, Togasaki G, et al. Preliminary results of a new workflow for MRI/CT-based image-guided brachytherapy in cervical carcinoma. Jpn J Radiol. 2017;35(12):760–5.
95. Tanderup K, Nesvacil N, Potter R, et al. Uncertainties in image guided adaptive cervix cancer brachytherapy: impact on planning and prescription. Radiother Oncol. 2013;107:1–5. https://doi.org/10.1016/j.radonc.2013.02.014.
96. Volumetric dose assessment. Prescribing, recording, and reporting brachytherapy for cancer of the cervix. ICRU Report 89. P123–131, 2016.
97. Viswanathan AN, Moughan J, Small W Jr, et al. The quality of cervical cancer brachytherapy implantation and the impact on local recurrence and disease-free survival in radiation therapy oncology group prospective trials 0116 and 0128. Int J Gynecol Cancer. 2012;22:123–31. https://doi.org/10.1097/IGC.0b013e31823ae3c9.
98. Yoshio K, Murakami N, Morota M, et al. Inverse planning for combination of intracavitary and interstitial brachytherapy for locally advanced cervical cancer. J Radiat Res. 2013;54(6):1146–52. https://doi.org/10.1093/jrr/rrt072.

Midline Block (Central Shielding)

6

Tomoaki Tamaki

Abstract

In radiotherapy for cervical cancer, because brachytherapy can provide concentrated dose to the primary tumor, midline block (central shielding) has been applied at least partially in external beam therapy to lower the dose to rectum and bladder and avoid severe complications. Although this practice has been decreased over the years globally, the central shielding technique continues to be used as standard in Japan. The use of central shielding in Japan has resulted in relatively low incidence of late complications in the rectum and bladder without compromising the disease control. Recent study of composite dose distributions of the treatment regimen using central shielding revealed its characteristics which explains the benefit of this technique. This chapter will cover the history, philosophy, analysis of composite dose distributions, issues of dose reporting, and the future prospect of this technique.

Keywords

Cervical cancer · Brachytherapy · Central shielding · Midline block · Composite dose distributions · DVH parameters

6.1 History of Central Shielding

The current practice of radiotherapy for cervical cancer consists of external beam radiotherapy (EBRT) and brachytherapy. At the original time of radium therapy, however, the treatment was implemented with radium therapy alone. EBRT was

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added in order to treat lymph nodes metastasis and the tumor extension in the parametrial tissue where the radium brachytherapy cannot provide adequate radiation doses.

According to the Manchester method reported by Tod and Meredith in 1938, a method of 200–250 kV X-ray external beam irradiation to parametria was presented [1]. In this method, a strip of lead which completely shields the center of the pelvis was applied in the anterior and posterior fields to supplement the inadequate dose delivered to the parametria (dose to obturator nodes defined as Point B) and to avoid the unnecessary high dose to the cervix, rectum, and bladder. In addition, two anterior and two posterior diagonal ports were added to either sides so that adequate dose can be delivered to the parametria without the skin dose exceeding its maximum tolerance [1]. Thus, the first concept of central shielding was introduced. In 1959, Fletcher also described the possibilities and purpose of external irradiation stating "As the primary tumor can be adequately handled by intracavitary therapy, the aim is essentially to supplement the radium dosage in the paralethal zone (to bring it up to an adequate level) and, if possible, to supply the main treatment to the lateral aspects of the parametrium and the pelvic nodes, as these cannot be irradiated by any other means" [2].

As telecobalt machines and high-energy X-ray teletherapy machines have emerged, the EBRT became used to irradiate the whole pelvis including the primary lesion and the pelvic lymph node regions up to the common iliac region. The midline shielding or central shielding is applied by a rectangular or specially designed block to the AP/PA ports in the whole pelvis ports for a portion of the EBRT [3]. The use of midline block is to spare bladder and rectum while allowing brachytherapy to provide adequate amount of radiation dose to the primary tumor. In general, the use of midline block (central shielding) has decreased over the years in the United States and Europe, and the simple whole pelvis EBRT has been increasingly used in combination with brachytherapy. Wolfson et al. described that, in a survey conducted in 1995, 88% of 33 member and affiliated centers in the Gynecologic Oncology Group (GOG) used the midline shielding (76% standard block, 21% customized block, 3% "step wedge") [4]. The ABS Recommendations for HDR Brachytherapy for Carcinoma of the Cervix in 2000 mentioned that some institutions use a midline block for the pelvis EBRT after 20 Gy for patients with early disease. In 2012, the ABS Treatment Recommendations for Locally Advanced Carcinoma of the Cervix [5] stated that the most common treatment regimen for the pelvis is 45 Gy without any description of central shielding, implying a decreased use of midline block in the United States. Major clinical studies in the 1990s which analyzed the effectiveness of chemoradiotherapy for locally advanced cervical cancer did not use central shielding in the treatment of EBRT [6–9]. Pötter et al. reported that, for the treatment of small tumors, the central shielding according to the 7 Gy isodose line of brachytherapy was used in the AP/PA portals of the 4-field box pelvis irradiation during the period of 1993–1997 in Vienna University Hospital [10]. This methodology was continued in the treatment until 2003 and later changed to the whole pelvis irradiation without the use of central shielding [11]. A multi-institutional prospective observational clinical study EMBRACE (an intErnational study

on *M*RI-guided *Bra*chytherapy in locally advanced *Ce*rvical cancer) did not allow the use of central shielding in the EBRT schedule [12]. The ICRU Report 89, regarding the use of midline shielding blocks, mentioned that "no real consensus, however, has been reported regarding their use" [13].

In contrast to the situations in the United States and Europe, the use of central shielding continues to be a part of standard radiotherapy for cervical cancer in Japan. After the 1960s, the use of central shielding has been applied as the placement of central block in the AP/PA pelvis fields [14] (Fig. 6.1), and standardized treatment method which combines EBRT and intracavitary brachytherapy was published in 1984 by Arai et al. [15]. Many Japanese institutions have reported clinical results of radiotherapy for cervical cancer using central shielding techniques [16–27]. At present, central shielding is well practiced as a part of external irradiation in Japanese multi-institutional studies [28–30] and in combination with image-guided adaptive brachytherapy using volumetric prescription [31].

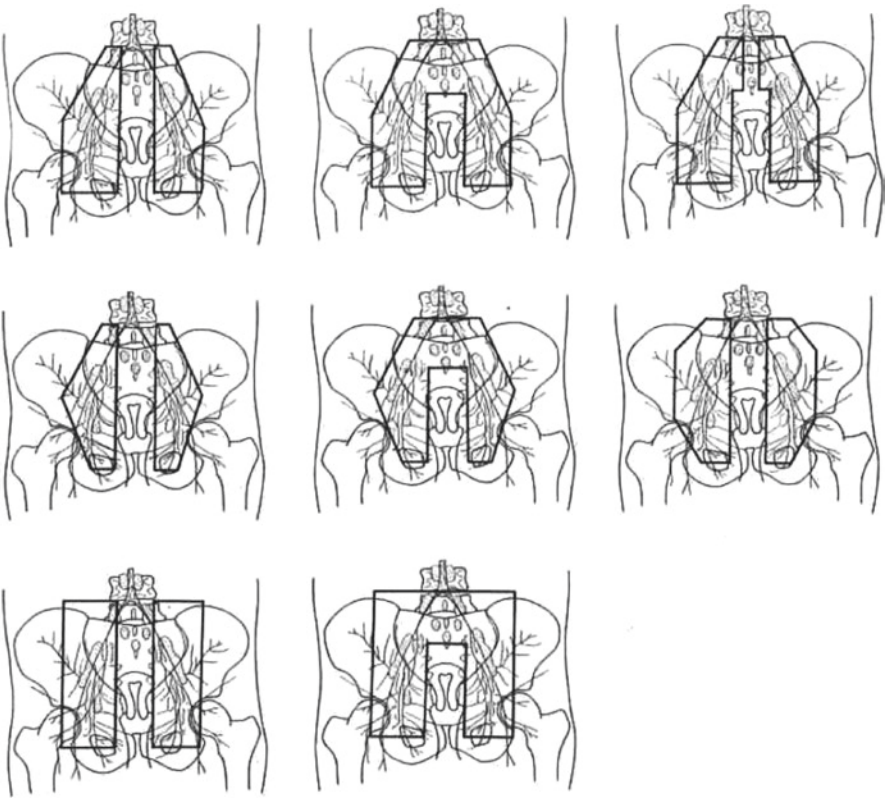


Fig. 6.1 Examples of central shielding fields shown as the Japanese standardized radiation therapy for cervical cancer (Arai et al. [15], with permission)

6.2 Philosophy Behind the Use of Central Shielding

The treatment philosophy behind the use of central shielding is to yield a good combination of EBRT and intracavitary brachytherapy which can provide adequate dose coverage of the primary tumors, parametrial extension, and the pelvic lymph node regions. The combination should not underdose the target volumes or overdose the organs at risk, which are the rectum, bladder, and bowel. The pelvic lymph node regions are predominantly covered by the dose from EBRT, and prophylactic dose of 45–50 Gy in conventional 1.8–2 Gy/fraction will be provided to irradiate microscopic diseases. The primary tumor in the cervix is to be covered by the combination of brachytherapy and EBRT. For early-stage disease which is manifested as a small primary lesion, the dose from brachytherapy may achieve adequate coverage without much contribution from EBRT; therefore, there may be more opportunities for central shielding. For advanced diseases with larger primary tumors, the ratio of EBRT may be increased (less central shielding) or brachytherapy may be increased, or both. If brachytherapy is implemented properly and able to achieve good dose coverage of the primary tumor, increased dose from brachytherapy should result in more concentrated dose to the target while avoiding excessive radiation dose to the organs at risk.

The doses of whole pelvis EBRT, centrally shielded EBRT, and high dose rate brachytherapy were standardized in Japan by Arai et al., as Table 6.1 [15]. In this scheme, even for treatment of Stage III disease with a large primary tumor or Stage IV disease, central shielding is still utilized to take advantage of the concentrated dose from brachytherapy and to minimize the dose to the rectum and bladder. It should be noted that, in this standardized schedule, brachytherapy is applied weekly soon after the central shielding is started to ensure that the target in the shielded region continues to receive irradiation and to ensure that the overall treatment time will not be prolonged.

Table 6.1 Standardized radiation treatment schedule for cervical cancer published in 1984 (Arai et al. [15], with permission)

Radiation methods		External beam radiation therapy		Intracavitary brachytherapy	
Stage (tumor size)		Whole pelvis	Central shielding	High dose rate (Point A prescription)	Low dose rate (Point A prescription)
I		0	45	29 Gy/5 fractions	50 Gy/4 fractions
II	(Small)	0	50	29/5	50/4
	(Large)	20	30 (EBRT total 50)	23/4	40/3
III	(Small-medium)	20–30	20–30 (total 50)	23/4	40/3
	(Large)	30–40	15–25 (total 50–55)	15/3–20/4	25/2–33/3
IV		40–50	10–15 (total 50–60)	15/3–20/4	25/2–33/3

While many institutions globally tend to shift away from the practice of central shielding in EBRT, it is worth noting that Mallinckrodt Institute of Radiology continued to adopt central shielding technique with the philosophy to "maximize the brachytherapy dose while minimizing bladder and rectal doses by limiting the external irradiation dose centrally," thus allowing most of the dose to the primary lesion to be delivered by brachytherapy [32].

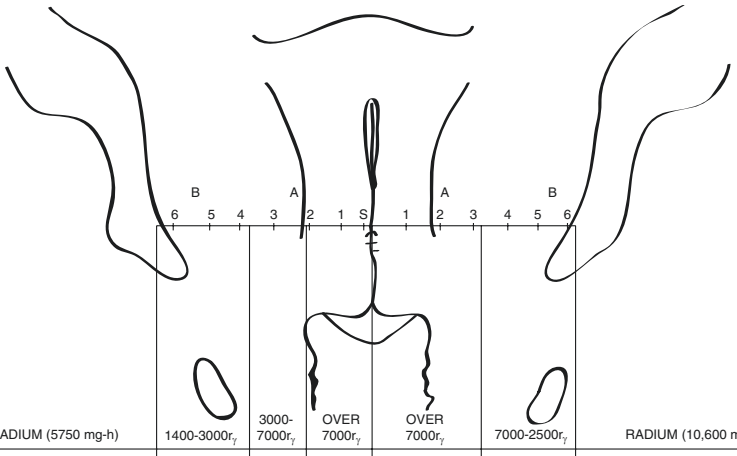
The distinction between "central shielding" as a part of the standard pelvis irradiation and "parametrial boost" after the completion of the standard pelvis irradiation should be clearly made, as such distinction is made in the ICRU Report 89 [13] (in 2.8 Radiation Therapy). Fenkell et al. point out that the "midline-blocked boost" of 9 Gy/5 fractions after their standard whole pelvis irradiation of 45 Gy/25 fractions can result in substantial dose increase in normal tissues such as the rectum, sigmoid, and bladder [33]. This concept of "midline-blocked boost" is different from the pelvis irradiation with central shielding which is familiar in the Japanese standard treatment schedule.

6.3 Composite Dose Distributions of Treatment Using Central Shielding

In the combination of EBRT and intracavitary brachytherapy, it is extremely important to understand the composite dose of all the treatment applied. This is a challenging task especially when the dose distributions originated from external beams are heterogenous within volumes of interests because of central shielding. In the Manchester system, multiple external beams were applied to the parametrium so that the summated doses from the radium therapy and external X-ray therapy become about 6500 R at Point B [1]. In this case, the summated dose to Point A could not be accurately reported. Fletcher also showed in his report some examples of planning the combination of radium therapy and EBRT [2]. In this example, the regions in the pelvis were divided into regions covered with different external beam fields, and dose contributions of each fields and modalities were calculated with dose ranges (Fig. 6.2).

Perez has shown model composite distribution of treatment by combination of an external high-energy photon beam therapy and intracavitary insertions. The total physical doses are shown in the diagram which depicted the characteristics of the treatment using central shielding [34] (Fig. 6.3). MacDonald et al. reported the transverse dose profiles of combinations of centrally shielded pelvis irradiation and brachytherapy [32]. However, these composite dose distributions are created in physical doses and unfortunately did not adequately reflect therapeutically relevant doses.

In GEC-ESTRO recommendation [35], reporting with the use of biologically weighted dose based on linear-quadratic model, EQD2 (equivalent dose given in 2 Gy fractions), which takes into account differences in dose-rate and fractionation schedules, is recommended. The use of biologically weighted dose enables calculation of combining external beam doses and brachytherapy doses within the



RADIUM (5750 mg-h)	1400-3000r_γ	3000-7000r_γ	OVER 7000r_γ	OVER 7000r_γ	7000-2500r_γ	RADIUM (10,600 mg-h)
FIELDS (4) 6 cm: WIDE 2 cm. from S 2000 r (AIR DOSE) 2500r (SKIN DOSE) Mx.T.D. 2500 × 1.5 = 3750 r Mn.T.D. 2500 × 1.3 = 3250 r	3250-3750 r (4 WEEKS)	3250-3750 r			4840-5280 r (6 WEEKS)	FIELDS (3) 4 cm. WIDE 3.25 cm. from S 4000 r (AIR DOSE) 4400 r (SKIN DOSE) Mx.T.D. 4400 × 1.2 = 5280r Mn.T.D. 4400 × 1.1 = 4840r
FIELDS NARROWED TO cm. WIDE 3cm. from S 2000 r (AIR DOSE) 2400r (SKIN DOSE) Mx.T.D. 2400 × 1.4 = 3500 r Mn.T.D. 1400 × 1.2 = 2880 r	2880-3360 r (3 WEEKS)					

On the right 5,750 mg. hr. have been delivered, contributing 1,400 r_γ to the pelvic wall. The anteroposterior diameter of the patient is 21 cm., and four parametrial portals (anterior, sacral, gluteal, and sciatic) are used. These portals are narrowed during the course of treatment. The maximum tumor dose (Mx. T. D.) to the pelvic wall from the x-rays is 7,000 r and the minimum tumor dose (Mn. T. D.) is 6,100 r in seven weeks.

On the left 10,800 mg. hr. have been delivered, contributing 2,500 r_γ to the pelvic wall. The anteroposterior diameter is 18 cm., and only three parametrial portals (anterior, sacral, and gluteal) are used, 4 cm. wide from the beginning. The maximum tumor dose from the x-rays is 5,200 r and the minimum tumor dose is 4,840 r in six weeks.

Fig. 6.2 Examples of treatment planning based on doses from radium therapy and from external radiation (Fletcher [2], with permission)

treatment of one patient, quantitative comparison of different treatment schedules, and production of dose distributions based on clinically relevant effects. Tamaki et al. reported on the dose distributions of the combination of centrally shielded EBRT and intracavitary brachytherapy and analyzed the composite doses on Point A [36] (Fig. 6.4) and DVH parameters with the focus on the amount of contribution from the centrally shielded EBRT [37].

The composite EQD2 dose distribution of the treatment shows how the central shielding would decrease the dose to bladder and rectum. By the use of central shielding for 20 Gy in the 50 Gy pelvis EBRT, the isodose lines of 60 Gy and 70 Gy (EQD2) is indented significantly in anterior-posterior direction. This indicates that the bladder and rectum are spared while the parametrium is irradiated. Physicians need to be aware the basic composite dose distribution when all the doses of EBRT are given to whole pelvis without using central shielding, as seen in Fig. 6.5 (furthest right at the bottom). This basic distribution should cover the target adequately in the lateral direction (right-left direction). By applying central shielding, the dose distributions in the anterior-posterior direction will shrink or become thinner in the

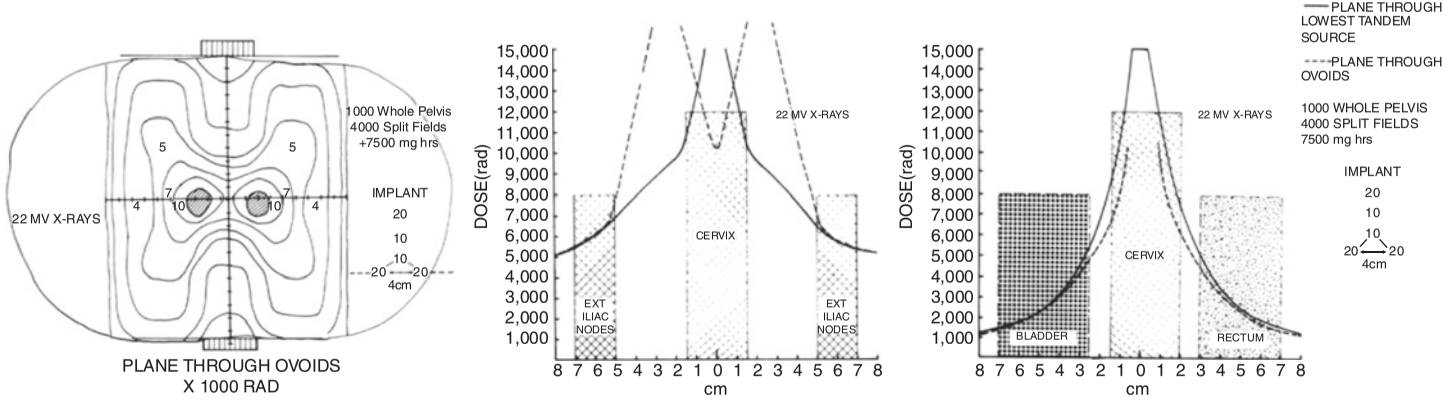


Fig. 6.3 Dose distribution for patients with Stage IB and IIA carcinoma of the cervix treated with radiation alone showing total contribution from external beam and intracavity. (Left) Isodose curves on the plane through ovoids. (Center) Dose profile in coronal plane. (Right) Dose profile in sagittal plane (Perez et al. [34], with permission)

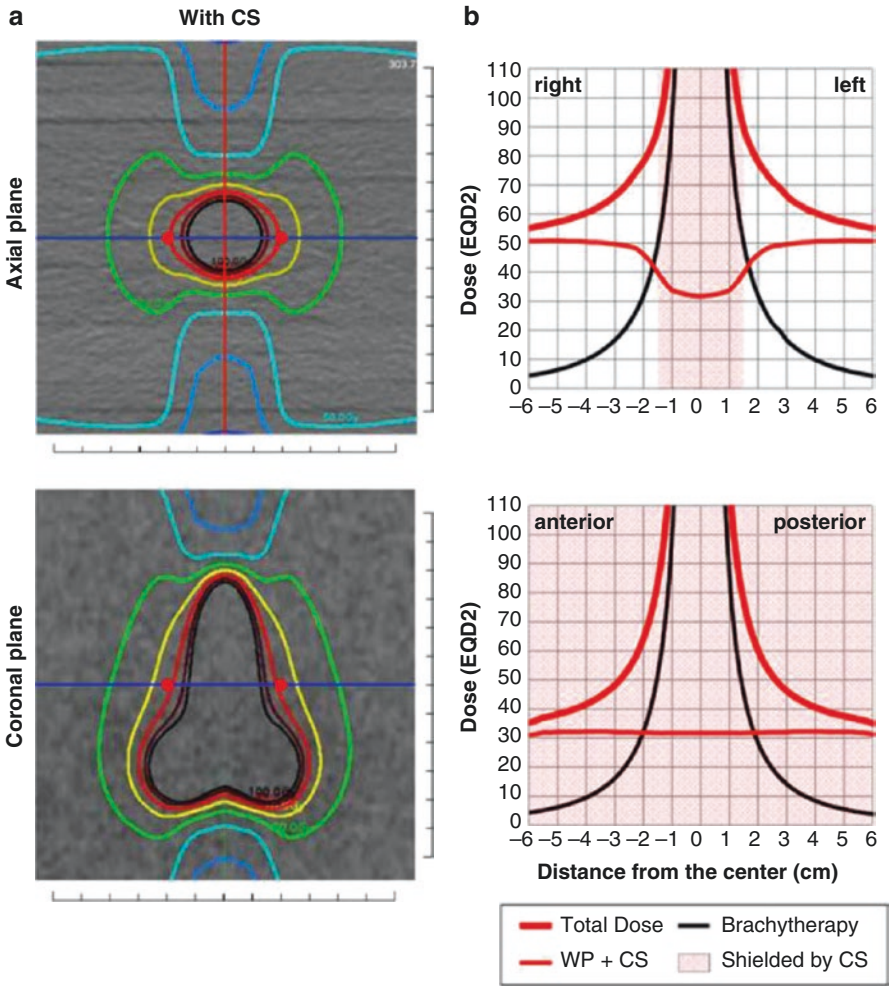


Fig. 6.4 Composite EQD2 dose distributions of the combination of whole pelvis 30 Gy/15 fractions, centrally shielded 20 Gy/10 fractions, and brachytherapy 24 Gy/4 fractions (Point A). (**a**) Isodose curves in EQD2 doses on the planes of Point A. (**b**) Dose profiles on the RL axis (blue line) and the AP axis (red line) (Figures from Tamaki et al. [36])

central region depending on the amount of shielding (Fig. 6.5, at the bottom row). The clinicians need to determine whether the target is covered adequately by the composite dose distributions in the anterior-posterior direction within the shielded area while minimizing the dose to the rectum and bladder in this shielded region. Therefore, identifying the shape of high risk CTV (HR-CTV) is extremely important. In the analysis of Tamaki et al., the HR-CTV of Stage II–III cervical cancer patients tended to be larger in lateral direction than in anterior-posterior direction at the time of the first brachytherapy session (about 30 Gy of whole pelvis irradiation) [37]. The analysis of the composite dose distributions may prove to favor the use of central shielding in the treatment of cervical cancers in general.

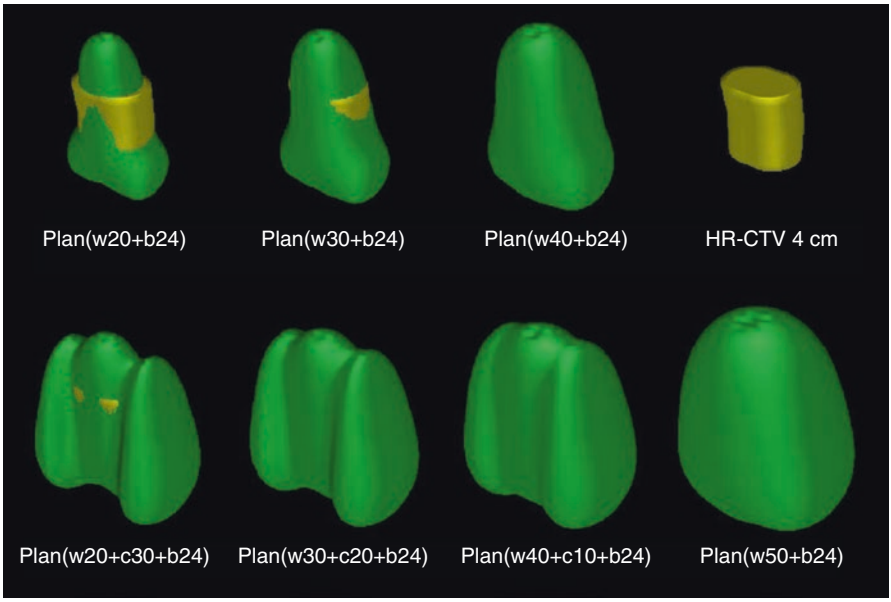


Fig. 6.5 The 3D distribution 60 Gy (EQD2) of various combinations of whole pelvis irradiation (w) and centrally shielded irradiation (c) and brachytherapy (b). The numbers following "w" or "c" indicate doses in Gy given in 2 Gy/fraction, and the brachytherapy is set as 24 Gy in four fractions at Point A (Tamaki et al. [37], with permission)

6.4 Dose Reporting with the Use of Midline Block (Central Shielding)

The ICRU report 89 stresses the importance of analyzing the integral dose to the target and organs at risk [13]. Such calculation of the integral dose is simple only when the EBRT is applied almost uniformly throughout the volumes. However, the DVH parameters such as HR-CTV D90 and D98 and rectum D2cc cannot be easily computed as integral values when the EBRT is applied with central shielding because radiation is applied unevenly to the target volumes and organs at risk. The dose from the centrally shielded field applies radiation in a manner which compensates for the decreased dose from brachytherapy in the parametrial regions. Tamaki et al. created a model of HR-CTV based on clinical data of anterior-posterior and right-left diameters and analyzed the contribution of doses given with centrally shielded EBRT to the integral D90 and D98 of HR-CTVs with diameters of 3, 4, and 5 cm [37]. In this analysis, the EBRT to a total of 50 Gy/25 fractions was applied to the pelvis, and four fractions of 6 Gy were applied to the Point A by intracavitary brachytherapy. The amount of central shielding used in this model was 30 Gy/15 fractions for 3 cm HR-CTV, 20 Gy/10 fractions for 4 cm HR-CTV, and 10 Gy/5 fractions for 5 cm HR-CTV, and the contribution of centrally shielded EBRT to the HR-CTV D90 were 24%, 42%, and 56% of the applied doses (for detailed analysis, please see [37]). This study of DVH parameters implies that,

while the analysis of composite dose distributions may be complex, the contribution from the centrally shielded EBRT should not be ignored. The contribution becomes relatively larger when (1) the width of the shielding is smaller, (2) the amount of centrally shielded EBRT dose is smaller, and (3) the tumor is larger. It may be misleading to report the total prescribed dose to the target by completely omitting the doses from the centrally shielded EBRT. For the organs at risk, the contribution of centrally shielded EBRT dose to the rectum D2cc were 9% in all cases and that to the bladder D2cc were 28%, 32%, and 28% for the cases of 3, 4, and 5 cm HR-CTVs, respectively. These data suggest that the benefit of central shielding to prevent adverse effect may be higher in the rectum than in the bladder. This result is mainly because the rectum anatomically tends to conform better to the shielding than the bladder, and the high dose region attributable from the radioactive sources in the ovoid applicators tend to reach the bladder wall which lies outside of the shielded region [37].

6.5 Clinical Results of the Treatment Schedule Using Central Shielding

The Japanese treatment schedule using central shielding has achieved excellent treatment outcomes for early-stage diseases and results comparable to data from the United States and Europe [16–27], and the results from the institutional studies have been validated in multi-institutional studies [28–30]. For non-bulky Stage I–II patients, the treatment regimen with whole pelvis external beam irradiation of 20 Gy/10 fractions, centrally shielded pelvis irradiation of 30 Gy/15 fractions, and high dose rate intracavitary brachytherapy of 24 Gy/4 fractions to Point A resulted in 96% 2-year pelvic disease progression-free (PDPF) survival and 95% 2-year overall survival with no Grade $\geq$ 3 late toxicities [28]. In JGOG1099 study, Phase II study of concurrent chemoradiotherapy based on the Japanese standardized radiotherapy schedule for Stage III–IVA patients has resulted in 73% PDPF survival and with 3% Grade $\geq$ 3 late toxicities at 2 years [29]. A multinational Asian clinical study of concurrent chemoradiotherapy using the similar treatment schedule as the Japanese standardized schedule for bulky Stage IIB–IIIB patients resulted in 87.1% local control rate and 79.6% overall survival rate with only 2.5% major rectal complication and no major bladder complication at 2 years [38].

A recent study from Gunma University on in-room CT-based image-guided adaptive brachytherapy with EBRT using central shielding has shown excellent results: the 5-year local control rate of 94%, PDPF rate of 90% with only 1% of Grade $\geq$ 3 late toxicities in patients with all clinical stages [31]. This study showed no significant differences in local control between clinical stages or sizes, indicating that the optimized image-guided adaptive brachytherapy may play a key role in the control of pelvic diseases while the dose provided to the primary disease through the EBRT may be adequate with the shielding of the rectum and bladder.

6.6 Future Prospects of Central Shielding

The effectiveness of central shielding in lowering late toxicities and providing favorable dose distributions for the treatment of cervical cancer has been shown and proven to be effective from the clinical reports of Japanese institutions. On the other hand, it is also true that this technique does not take into account individual varieties in shape, extension, location of tumors, and organs at risk. With the new development in EBRT technologies, such as intensity-modulated radiation therapy and volumetric arc therapy, and onboard imaging modalities, new therapeutic approach with the principle of "central shielding" is anticipated. Mallinckrodt Institute of Radiology is implementing a unique EBRT using IMRT technique called pseudo-step-wedge intensity modulation, which advanced from their original central shielding technique with customized step wedge, in order to further optimize dose to the target and organs at risk [32]. While the traditional practice of rectangular midline block may continue to be effectively used, the future evolution of this technique using modern radiotherapy and imaging technology should be sought to further enhance the clinical outcomes of the cervical cancer patients in the future.

References

1. Tod M, Meredith W. A dosage system for use in the treatment of cancer of the uterine cervix. Brit J Radiol. 1938;11:809–23.
2. Fletcher GH. Roentgen treatment of cancer of the cervix. Radiology. 1950;54(6):832–42.
3. Perez C, Kavanagh B. Uterine cervix. In: Halperin E, Perez C, Brady L, editors. Principles and practice of radiation oncology. 5th ed. PA: Lippincott Williams & Wilkins; 2008. p. 1532–609.
4. Wolfson AH, Abdel-Wahab M, Markoe AM, Raub WJ Jr, Diaz D, Desmond JJ, et al. A quantitative assessment of standard vs. customized midline shield construction for invasive cervical carcinoma. Int J Radiat Oncol Biol Phys. 1997;37(1):237–42.
5. Viswanathan AN, Beriwal S, De Los Santos JF, Demanes DJ, Gaffney D, Hansen J, et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: High-dose-rate brachytherapy. Brachytherapy. 2012;11(1):47–52.
6. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med. 1999;340(15):1137–43.
7. Whitney CW, Sause W, Bundy BN, Malfetano JH, Hannigan EV, Fowler WC Jr, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol. 1999;17(5):1339–48.
8. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med. 1999;340(15):1144–53.
9. Pearcey R, Brundage M, Drouin P, Jeffrey J, Johnston D, Lukka H, et al. Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. J Clin Oncol. 2002;20(4):966–72.
10. Potter R, Knocke TH, Fellner C, Baldass M, Reinthaller A, Kucera H. Definitive radiotherapy based on HDR brachytherapy with iridium 192 in uterine cervix carcinoma: report on the

Vienna University Hospital findings (1993–1997) compared to the preceding period in the context of ICRU 38 recommendations. Cancer Radiother. 2000;4(2):159–72.
11. Potter R, Georg P, Dimopoulos JC, Grimm M, Berger D, Nesvacil N, et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. Radiother Oncol. 2011;100(1):116–23.
12. Mazeron R, Fokdal LU, Kirchheiner K, Georg P, Jastaniyah N, Segedin B, et al. Dose-volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: results from the prospective multicenter EMBRACE study. Radiother Oncol. 2016;120(3):412–9.
13. Report 89. Journal of the ICRU. 2013;13(1–2):Np.
14. Tazaki E. Historical development of radiotherapy for the uterine cervical cancer in Japan. J Jpn Soc Ther Radiol Oncol. 1999;11:157–73.
15. Arai T, Akanuma A, Ikeda M, Inoue T, Kasamatsu T, Kubo H, et al. Standardized radiation treatment method for carcinoma of the uterine cervix. Jpn J Cancer Clin. 1984;30(5):496–500.
16. Shigematsu Y, Nishiyama K, Masaki N, Inoue T, Miyata Y, Ikeda H, et al. Treatment of carcinoma of the uterine cervix by remotely controlled afterloading intracavitary radiotherapy with high-dose rate: a comparative study with a low-dose rate system. Int J Radiat Oncol Biol Phys. 1983;9(3):351–6.
17. Okawa T, Kita M, Goto M, Tazaki E. Radiation therapy alone in the treatment of carcinoma of the uterine cervix: review of experience at Tokyo Women's Medical College (1969–1983). Int J Radiat Oncol Biol Phys. 1987;13(12):1845–9.
18. Teshima T, Chatani M, Hata K, Inoue T. High-dose rate intracavitary therapy for carcinoma of the uterine cervix: I. General figures of survival and complication. Int J Radiat Oncol Biol Phys. 1987;13(7):1035–41.
19. Akine Y, Arimoto H, Ogino T, Kajiura Y, Tsukiyama I, Egawa S, et al. Carcinoma of the uterine cervix treated by irradiation alone. Results of treatment at the National Cancer Center, Tokyo. Acta Oncol. 1990;29(6):747–53.
20. Arai T, Nakano T, Morita S, Sakashita K, Nakamura YK, Fukuhisa K. High-dose-rate remote afterloading intracavitary radiation therapy for cancer of the uterine cervix. A 20-year experience. Cancer. 1992;69(1):175–80.
21. Ito H, Kutuki S, Nishiguchi I, Shigematsu N, Kuribayashi T, Uematsu M, et al. Radiotherapy for cervical cancer with high-dose rate brachytherapy correlation between tumor size, dose and failure. Radiother Oncol. 1994;31(3):240–7.
22. Mitsuhashi N, Takahashi M, Nozaki M, Yamakawa M, Takahashi T, Sakurai H, et al. Evaluation of external beam therapy and three brachytherapy fractions for carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys. 1994;29(5):975–82.
23. Ogino I, Kitamura T, Okamoto N, Yamasita K, Aikawa Y, Okajima H, et al. Late rectal complication following high dose rate intracavitary brachytherapy in cancer of the cervix. Int J Radiat Oncol Biol Phys. 1995;31(4):725–34.
24. Uno T, Itami J, Aruga M, Kotaka K, Fujimoto H, Sato T, et al. High dose rate brachytherapy for carcinoma of the cervix: risk factors for late rectal complications. Int J Radiat Oncol Biol Phys. 1998;40(3):615–21.
25. Hareyama M, Sakata K, Oouchi A, Nagakura H, Shido M, Someya M, et al. High-dose-rate versus low-dose-rate intracavitary therapy for carcinoma of the uterine cervix: a randomized trial. Cancer. 2002;94(1):117–24.
26. Toita T, Kakinohana Y, Ogawa K, Adachi G, Moromizato H, Nagai Y, et al. Combination external beam radiotherapy and high-dose-rate intracavitary brachytherapy for uterine cervical cancer: analysis of dose and fractionation schedule. Int J Radiat Oncol Biol Phys. 2003;56(5):1344–53.
27. Nakano T, Kato S, Ohno T, Tsujii H, Sato S, Fukuhisa K, et al. Long-term results of high-dose rate intracavitary brachytherapy for squamous cell carcinoma of the uterine cervix. Cancer. 2005;103(1):92–101.
28. Toita T, Kato S, Niibe Y, Ohno T, Kazumoto T, Kodaira T, et al. Prospective multi-institutional study of definitive radiotherapy with high-dose-rate intracavitary brachytherapy in patients with nonbulky (<4-cm) stage I and II uterine cervical cancer (JAROG0401/JROSG04-2). Int J Radiat Oncol Biol Phys. 2012;82(1):e49–56.

29. Toita T, Kitagawa R, Hamano T, Umayahara K, Hirashima Y, Aoki Y, et al. Phase II study of concurrent chemoradiotherapy with high-dose-rate intracavitary brachytherapy in patients with locally advanced uterine cervical cancer: efficacy and toxicity of a low cumulative radiation dose schedule. Gynecol Oncol. 2012;126(2):211–6.
30. Ariga T, Toita T, Kato S, Kazumoto T, Kubozono M, Tokumaru S, et al. Treatment outcomes of patients with FIGO Stage I/II uterine cervical cancer treated with definitive radiotherapy: a multi-institutional retrospective research study. J Radiat Res. 2015;56(5):841–8.
31. Ohno T, Noda SE, Okonogi N, Murata K, Shibuya K, Kiyohara H, et al. In-room computed tomography-based brachytherapy for uterine cervical cancer: results of a 5-year retrospective study. J Radiat Res. 2017;58(4):543–51.
32. Macdonald DM, Lin LL, Biehl K, Mutic S, Nantz R, Grigsby PW. Combined intensity-modulated radiation therapy and brachytherapy in the treatment of cervical cancer. Int J Radiat Oncol Biol Phys. 2008;71(2):618–24.
33. Fenkell L, Assenholt M, Nielsen SK, Haie-Meder C, Potter R, Lindegaard J, et al. Parametrial boost using midline shielding results in an unpredictable dose to tumor and organs at risk in combined external beam radiotherapy and brachytherapy for locally advanced cervical cancer. Int J Radiat Oncol Biol Phys. 2011;79(5):1572–9.
34. Perez CA, Breaux S, Madoc-Jones H, Camel HM, Purdy J, Sharma S, et al. Correlation between radiation dose and tumor recurrence and complications in carcinoma of the uterine cervix: stages I and IIA. Int J Radiat Oncol Biol Phys. 1979;5(3):373–82.
35. Potter R, Haie-Meder C, Van Limbergen E, Barillot I, De Brabandere M, Dimopoulos J, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol. 2006;78(1):67–77.
36. Tamaki T, Ohno T, Noda SE, Kato S, Nakano T. Filling the gap in central shielding: three-dimensional analysis of the EQD2 dose in radiotherapy for cervical cancer with the central shielding technique. J Radiat Res. 2015;56(5):804–10.
37. Tamaki T, Noda SE, Ohno T, Kumazaki Y, Kato S, Nakano T. Dose-volume histogram analysis of composite EQD2 dose distributions using the central shielding technique in cervical cancer radiotherapy. Brachytherapy. 2016;15(5):598–606.
38. Kato S, Ohno T, Thephamongkhol K, Chansilpa Y, Yuxing Y, Devi CR, et al. Multi-institutional phase II clinical study of concurrent chemoradiotherapy for locally advanced cervical cancer in East and Southeast Asia. Int J Radiat Oncol Biol Phys. 2010;77(3):751–7.

Hybrid Brachytherapy

7

Keiko Nemoto Murofushi and Hideyuki Sakurai

Abstract

Image-guided adaptive brachytherapy (IGABT) has been widely implemented during last the 20 years; moreover 3D planning using magnetic resonance imaging (MRI) or computed tomography (CT) has been used for calculating the dose to the tumor and organs at risk (OARs). Guidelines published by the GEC-ESTRO (Groupe Européen de Curiethérapie—European SocieTy for Radiotherapy & Oncology) and the American Brachytherapy Society (ABS) defined the delineation and dose parameters of the clinical target volume and OARs. For tumors receiving inadequate doses by intracavitary brachytherapy (ICBT), interstitial-intracavitary brachytherapy can deliver sufficient doses to the tumor while sparing the OARs; a Japanese group first named this technique "hybrid brachytherapy" (HBT) in 2011. HBT involves implanting several needles into the section of the tumor that receives inadequate doses via ICBT; accurate and reproducible insertion is achieved by using tandem and ring/ovoid applicators, as the short distance between the ring/ovoid and target allows for greater control of needle placements. In recent studies, HBT delivered higher doses to bulky tumors, poor response tumors, and severe parametrial extensions, achieving improved local control in all cases. Furthermore, retrospective multi-institutional European study on MRI-guided brachytherapy in locally advanced cervical cancer (EMBRACE) showed excellent local control and less severe toxicity in patients treated with CT- or MRI-based IGABT, including HBT in the interstitial/intracavitary group defined as the facilities where more than 20% patients were treated with HBT. A prospective multicenter EMBRACE study includes more than 1350 patients treated with MRI-based brachytherapy including HBT. Based on the large success of these clinical trials, a consecutive

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EMBRACE II study was initiated to validate the evidence collected from original study. Furthermore, several clinical trials for evaluating the feasibility and safety of IGABT, including HBT, are ongoing in Japan.

Keywords
Brachytherapy · Hybrid brachytherapy · Interstitial-intracavitary brachytherapy
Image-guided adaptive brachytherapy (IGABT) · Cervical cancer · Bulky tumor

7.1 Background

The combination of external beam radiotherapy (EBRT) and brachytherapy has an important role in definitive radiotherapy for patients with cervical cancer. Brachytherapy can deliver a higher dose to the tumor while sparing adjacent organs; this leads to excellent local control. For a long time, brachytherapy was planned using X-ray images. In particular, intracavitary brachytherapy (ICBT), which mainly used Manchester method for planning, delivered the prescribed dose to point A until the International Commission on Radiation Units and Measurements (ICRU)-38 report recommended calculating the dose to point A plus organs at risk (OAR). This "conventional" ICBT and EBRT modality achieved local control in 80–90% of patients with early-stage cervical cancer [1, 2]. However, patients with bulky, extensive, and other tumors that may receive inadequate doses by conventional ICBT had poor local control [3, 4]. During the last 20 years, image-guided adaptive brachytherapy (IGABT) has become increasingly common, and 3D planning using magnetic resonance imaging (MRI) or computed tomography (CT) has made it possible to more accurately calculate the dose received by the tumor and OARs. The Groupe Européen de Curiethérapie—European SocieTy for Radiotherapy & Oncology (GEC-ESTRO) launched a gynecologic working group to establish definitions for the clinical target volume (CTV), OARs, consensual dosimetric parameters, and dose constrains [5], while the American Brachytherapy Society also published a guideline for the recommended dose to the tumor and dose limitations to OARs [6]. High-risk CTV (HR-CTV) is defined as a region that includes the gross tumor volume (GTV) at the time of brachytherapy, entire cervix, and gray zone on T2 sequence MRI; furthermore, the HR-CTV D_{90}, which is the minimum dose delivered to 90% of the target volume, is an important measurement of the dose delivered to the tumor [5]. In a prospective multi-institutional European study on MRI-guided brachytherapy in locally advanced cervical cancer (EMBRACE), several DVH recording and reporting are recommended (Table 7.1).

Syed et al. developed an interstitial-intracavitary brachytherapy technique involving implanting the needles into an area of the tumor that received an inadequate dose via ICBT [7], while Wakatsuki et al. reported performing

Table 7.1 Dose and volume recording and reporting in EMBRACE study

Total reference air kerma (TRAK)
Point A dose—left, right, and average
D90 and D100 for GTV, HR-CTV, and IR-CTV
D50 for HR-CTV
V100 for HR-CTV or IR-CTV
D0.1 cc and D2 cc of the bladder, rectum, and sigmoid colon
ICRU bladder and ICRU rectal point

Abbreviations: *D100*, *D90*, *D50* minimum dose to 100%, 90%, and 50% of the target volume, respectively, *V100%* percentage of the target volume receiving 100% of the prescribed dose, *D0.1 cc*, *D2 cc* minimum dose to maximally irradiated 0.1 and 2 cc of the organ, respectively, *HR-CTV* high-risk clinical target volume, *IR-CTV* intermediate-risk clinical target volume, *ICRU* International Commission on Radiation Units and Measurements

interstitial-intracavitary brachytherapy for the first time in Japan in 2011 and named this technique "hybrid brachytherapy" (HBT) [8]. In recent years, HBT has been implemented along with 3D-IGABT in several facilities, and Japanese clinical trials to evaluate the feasibility and safety of HBT for locally advanced cervical cancer patients are ongoing.

7.2 Brachytherapy Techniques

Brachytherapy techniques can be divided into three main types:

1. ICBT (Fig. 7.1)

ICBT has played a major role in the definitive treatment of cervical cancer for nearly 100 years, while the high-dose-rate (HDR) approach has been performed since the mid-1980s. Three sources that generally use intrauterine tandem and intravaginal ovoid applicators deliver a pear-shaped isodose curve including the prescribed dose to points A (or HR-CTV D_{90}). ICBT is a suitable approach for small cervical cancers and can be performed with minimal invasiveness.

2. Interstitial brachytherapy (IBT) (Fig. 7.2)

IBT is performed in patients who are unable to receive adequate doses with ICBT. IBT can achieve an isodose curve along the irregular shape of the tumor because multiple needles are inserted into or around the tumor along with applicators, for several days. IBT is considered a more invasive procedure than ICBT and HBT.

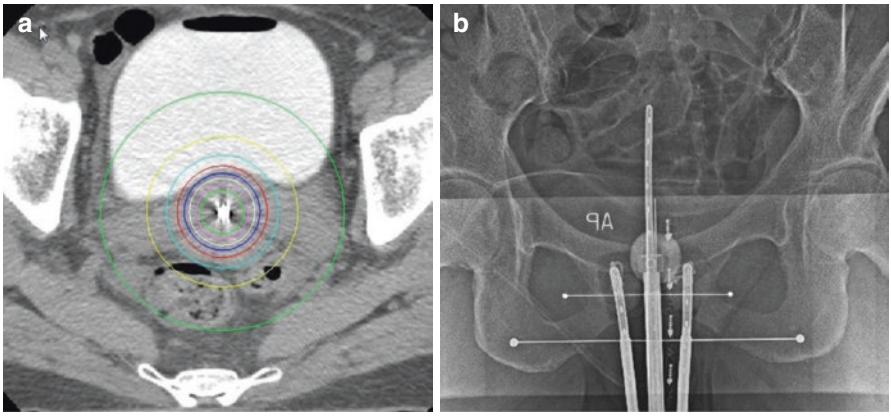

Fig. 7.1 Planning images of ICBT. (**a**) Dose distribution of ICBT in the planning CT. (**b**) Radiography

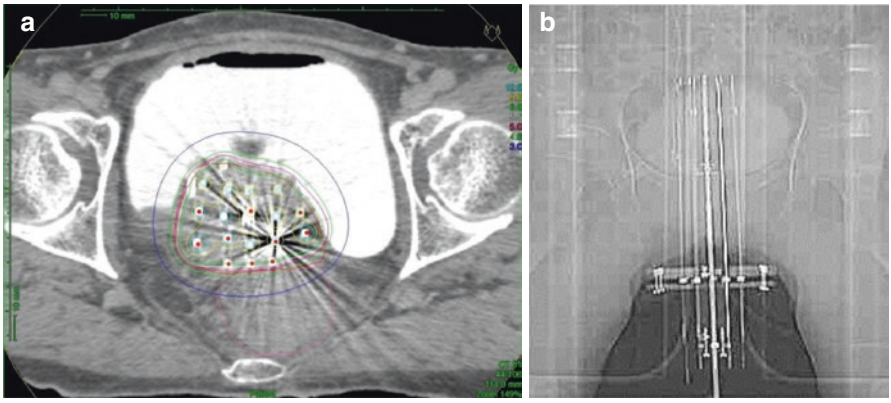

Fig. 7.2 Planning images of IBT. (**a**) Dose distribution of IBT in the planning CT. (**b**) Radiography

3. HBT (Fig. 7.3)

HBT involves implanting several needles into an area of the tumor that received an inadequate dose using ICBT. The invasiveness of HBT is higher than that of ICBT but lower than that of IBT. However, the IBT procedure is generally more difficult to perform than that of HBT.

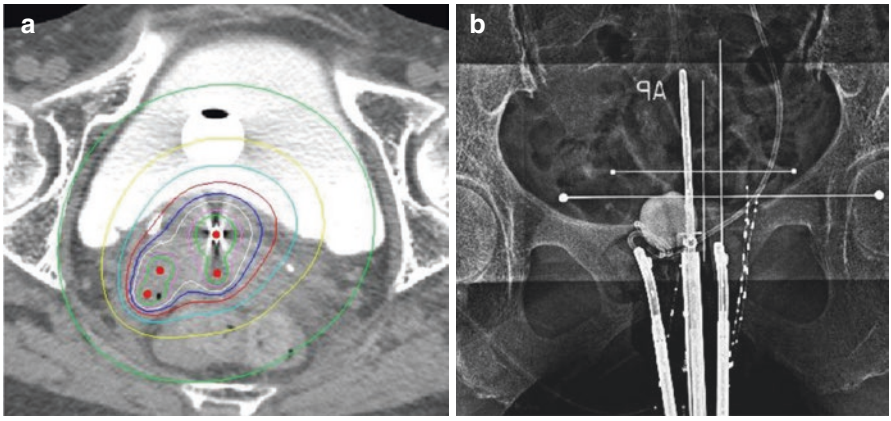

Fig. 7.3 Planning images of HBT. (**a**) Dose distribution of HBT in the planning CT. (**b**) Radiography

7.3 Recent Clinical Trials of IGABT, Including HBT

The dose volume effects and outcomes from mono-institutional clinical experiences have been reported [9, 10]; moreover, the retroEMBRACE and the EMBRACE studies were performed. The mature retroEMBRACE clinical results showed excellent local and pelvic control as well as significant dose-volume effects for IGABT [11]. The EMBRACE study of a prospective multicenter clinical trial included more than 1350 patients treated with MRI-based IGABT. Based on the large success of the retroEMBRACE and EMBRACE studies, a consecutive EMBRACE II study has been initiated. The radiotherapy protocol of the EMBRACE II study consists of MRI-based IGABT and EBRT that delivers 45 Gy in 25 fractions to the pelvis and/or para-aortic region as well as 10–15 Gy to the metastatic nodes in a simultaneous integrated boost (2.2–2.4 Gy per fraction) by using intensity-modulated radiotherapy or volumetric-modulated arc radiotherapy plus MRI-based IGABT.

7.4 Eligibility for HBT

HBT or IBT should be considered when an adequate dose to the HR-CTV D_{90} cannot be delivered via ICBT. Conventional ICBT may not deliver the prescribed dose in cases of (a) bulky tumor, (b) bulky parametrial extension, (c) extensive paravaginal or distal vaginal involvement, (d) narrow vagina, and (e) loss of endocervical

canal or obliterated fornices [7, 12]. The threshold for eligibility for HBT vs. IBT has not been determined to date. IBT generally has broader eligibility criteria because the more needles can be inserted into a wider treatment region compared with HBT. However, the most suitable brachytherapy technique should be chosen according to various factors such as tumor characteristics, procedure invasiveness, and the experience of the operators.

Several studies found that a bulky tumor is a poor prognostic factor for pelvic control in patients treated with conventional ICBT [3, 4, 13]. The Japanese Gynecologic Oncology Group 1066 study assessed the efficacy and toxicity for patients stage III–IVA cervical cancer treated with concurrent chemoradiotherapy combined with EBRT and conventional ICBT [13]. The 2-year pelvic disease progression-free survival rates were 85% for tumors <50 mm, 69% for tumors 50–70 mm, and 54% for tumors >70 mm. Perez et al. reported that patients with stage IIB cervical cancer extending into the lateral parametrium experienced significantly poorer pelvic control compared to those with medial parametrial involvement [3]. In patients with stage IIIB, there was significantly better pelvic control for those with unilateral non-bulky tumors compared to those with unilateral bulky tumors and bilateral non-bulky/bulky tumors. Kirisits et al. reported that, when one needle is loaded at 3 o'clock for a 34 mm normal diameter ring applicator, HBT can deliver the prescribed dose 31 mm lateral of the tandem axis, whereas the dose on the contralateral side can still be normalized at 20 mm from the tandem at the level of point A [14]. As an example, the dose distribution of HBT with one needle inserted at 20 mm lateral from the tandem axis and contributed 10% dwell weight is shown in Fig. 7.4b, and HBT can deliver higher dose to the lateral part compared with that of ICBT (Fig. 7.4a). However, it is important to note that the dose distribution depends on various factors such as the type and size of the applicator, its position and inserted length, as well as dwell weight of the needle.

The ABS recommends IBT for vaginal tumors thicker than 5 mm just before brachytherapy [15]. For tumors with extensive paravaginal or distal vaginal involvement, IBT may be more suitable than HBT; however, HBT using the transperineal approach may be able to deliver an adequate dose while sparing the OARs and high-dose sleeve of the vagina. In the EMBRACE study, only 6 of 960 patients (0.6%) had stage IIIA cervical cancer [16]. A suitable brachytherapy technique should be carefully chosen for tumors with severe vaginal or paravaginal invasion.

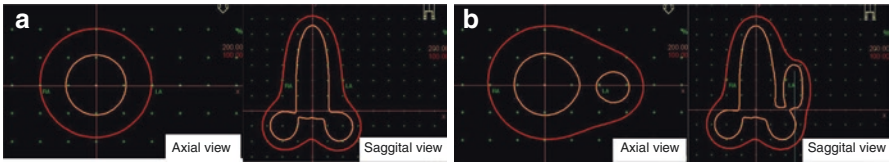

Fig. 7.4 Dose contributions. (**a**) Dose contribution of ICBT. (**b**) Dose contribution of HBT with one needle

IBT is considered if the applicators with tandem and ovoid/cylinder shapes cannot be inserted at normal positions owing to narrow vaginas, loss of the endocervical canal, and obliterated fornices.

In several recent studies of IGABT, HBT was performed on 17.5–47.0% of cervical cancer patients with stage IB–IVA [11, 16, 17]. In the retroEMBRACE study, 610 patients were divided into two groups including the intracavitary/interstitial (IC/IS) group (n = 300), who were defined as those treated at a facility where more than 20% of patients systematically received HBT; IC group comprised 310 patients [11]. While 141 patients (47%) received HBT in the IC/IS group, HBT was performed in only 4% of the IC group. In Japan, Ohno et al. reported that 14 of 80 patients (17.5%) with cervical cancer of stage IB–IVA received HBT [17].

In recent studies, HBT was mainly performed in patients with bulky stage IIB or IIIB tumors.

7.5 Management of HBT and Anesthesia

International brachytherapy practice patterns in Japan/Korea (Asia), Australia/New Zealand, Europe, and North America were surveyed by the Gynecologic Cancer Intergroup (GCIG) [18]. The tandem and ovoid applicators are most frequently used, with 54% of those surveyed using it for more than 75% of their cases annually; the tandem and ring applicators are used in 24% of cases, tandem and cylinder in 4%, tandem and interstitial in 3%, and interstitial only in 1%. For applicator insertion, anesthesia was administered to 97% patients; general anesthesia was used in 46% of patients, spinal in 27%, intravenous conscious sedation in 28%, and/or oral pain medication in 14%. However, the details of anesthesia for patients receiving HBT were not mentioned in their report; as such, anesthetic techniques may vary by country and facility.

The use of epidural catheters and subarachnoid anesthesia has also been reported with HBT [19–21]. Brachytherapy with two fractions in one application under spinal/epidural anesthesia caused acute stress disorder in 30% of patients 1 week after treatment, and posttraumatic stress disorder occurred in 41% 3 months after treatment [22]. In Kirchheiner et al.'s study, the source of stress appeared not to be the applicators insertion per se but the maintenance of these applicators under epidural anesthesia during brachytherapy. It is therefore necessary to assess patients' level of distress if applicators are inserted for lengthy periods.

Leong et al. reported that HBT is feasible and safe under moderate-to-deep sedation using intravenous conscious sedation, as well as with local anesthesia [23]. In the majority of Japanese facilities, it is difficult to operate under general anesthesia or epidural/spinal anesthesia because of the lack of personnel. In Japan, Watanabe et al. demonstrated that a new intravenous anesthetic protocol using a combination of propofol and ketamine achieved a median visual analog scale pain score of 0 (range, 0–10) in patients treated with ICBT [24].

7.6 Procedure and Applicators

The applicators used in patients undergoing HBT are generally of two types: tandem and ring and tandem and ovoid. The typical tandem and ring applicator is referred to as the "Vienna applicator" and is based on a CT/MRI-compatible tandem ring set (Nucletron, Veenendaal, The Netherlands). It has 2 mm-diameter holes that are drilled parallel to the ring axis; this axis is 2 mm from the outer ring surface (Fig. 7.5) [14]. The tandem and ovoid version is also referred to as the 'Utrecht applicator' and is based on a CT/MRI-compatible tandem ovoid set (Nucletron, Veenendaal, The Netherlands); its holes are drilled into the ovoid (Fig. 7.6) [25]. In both types of applicators, the needles are inserted into the holes of the ring or ovoid with a guiding system; this facilitates good reproducibility of the dose distribution. Dimopoulos et al. measured the absolute distance on the *x*- (latero-lateral) and *z*-axes (anterior-posterior) between the planned and achieved needle positions at the level of point A as a parameter of needle-to-tandem parallelism [21]. They found that the mean deviation of the *x*-axis was 0.5 mm while that of the *z*-axis was 0.6 mm. Accurate and reproducible insertion was achieved by using tandem and ring applicators because the short distance between the ring and target permitted greater control over the placement of needles. In several Japanese institutions, tandem and ovoid applicators with needles handled using free hand technique are utilized for HBT [8, 17] because Vienna and Utrecht applicators have not been approved for use in the country; moreover, the ring applicator may be too large for the majority of Asian women. Wakatsuki et al. demonstrated that HBT can be

Fig. 7.5 Vienna applicator (Nucletron, Veenendaal, The Netherlands)

Fig. 7.6 Utrecht applicator (Nucletron, Veenendaal, The Netherlands)

performed using a set of Fletcher-Suit Asian Pacific applicators (Nucletron, Veenendaal, The Netherlands) with a half-size ovoid [8].

For HBT, needles are generally inserted using the transvaginal approach, which is considered easier than the transperineal approach because the length of the needle in the former approach is shorter than that in the latter. However, the transperineal approach may have an advantage in patients with extensive paravaginal or distal vaginal involvement. The needle approach method is not defined for HBT and should be chosen according to the operators' experience, tumor characteristics, and other relevant factors.

In the retroEMBRACE study, tandem and ring applicators were used for 87% of patients in the HBT group, while tandem and ovoid applicators were used for 9% [11].

7.7 Planning Images

IGABT based on MRI is recommended according to the guidelines published by the GEC-ESTRO and ABS [5, 6] because the tumor can more clearly be detected and delineated on MRI compared to CT. Hence, it is important to install MRI (or if unavailable, CT) equipment in the operating room to safely perform needle insertion for HBT under image guidance. International brachytherapy practice patterns surveyed by the GCIG showed that CT is the most commonly used imaging modality for treatment planning (57%), while MRI is used in 25% of centers [18]. In the UK, a questionnaire survey conducted by the Royal College of Radiologists was published to document the implementation of IGABT [25] and found that IGABT based on MRI or CT had increased to 71% in 2011 compared to 26% in 2008. However, in the majority of Japanese institutions, CT is commonly used to plan and calculate the dose-volume histogram (DVH) parameters in 3D planning, and MRI is performed just before brachytherapy to evaluate the tumor response and refer to the delineation of the HR-CTV. A questionnaire-based survey regarding 3D-IGABT use was performed in Japan in 2011 [26]. Of the 141 facilities, 84% used radiography for treatment planning, 15% used CT, and only 1% used MRI. However, 3D-IGABT that mainly uses CT was planned for installation in 53% of the facilities; limited time and staffing were major impediments for performing 3D-IGABT. These data may also explain the obstacles against introducing new brachytherapy techniques such as HBT.

In the GEC-ESTRO MRI-based technical guidelines, T2 fast spin-echo for paraaxial, parasagittal, and para-coronal images of the cervix uteri should be obtained at the time of brachytherapy [27]. Viswanathan et al. reported that, in CT-based planning, the width of the HR-CTV is overestimated compared to that with MRI-based planning; this leads to an increase in the volume receiving the prescription dose (V_{100}) as well as the HR-CTV D_{90} and D_{100} [28]. Hence, planning images should be acquired with 1–5 mm thickness. The retroEMBRACE study included patients treated with both MRI- and CT-based brachytherapy, but the prospective multicenter EMBRACE trial comprised only of patients who underwent MRI-based planning.

7.8 Recommended Doses to the HR-CTV D_{90} and Limiting Doses to OARs

In the ABS guideline for HDR brachytherapy, an equivalent dose in 2 Gy fractions (EQD2) greater than 80 Gy is recommended for the HR-CTV D90 [6]. The Japanese standard regimen includes 50 Gy of pelvic irradiation, with central shielding inserted at 30–40 Gy, plus brachytherapy delivered at 18–24 Gy/3–4 fractions to point A. The totally administered dose, which includes the dose of pelvic irradiation before inserting the central shielding plus the point A, is approximately EQD2 60–65 Gy. Murakami et al. reported that the local control rates for patients receiving an HR-CTV D_{90} of >60 Gy vs. <60 Gy were 97.3% and 72.9%, respectively [29]. As for OARs, 90 Gy or less (EQD2) is recommended as the minimum dose delivered to the highest irradiated 2_{cm3} area (D_{2cc}) of the bladder, and 75 Gy or less to the rectum and sigmoid. Kato et al. reported that the D_{2cc} value were significantly higher in patients with late rectal toxicity (average 69.3 Gy) than in those without (average 57.2 Gy) ($p = 0.08$) [30]. Result from the EMBRACE study showed that grade 1 late rectal toxicity was observed in 20.1% of the patients, grade 2 in 6.0%, grade 3 in 1.6%, and grade 4 in 0.1%. The mean D_{ICRU}, $D_{0.1cc}$, and D_{2cc} were 66.2 ± 9.1 Gy, 72.9 ± 11.9 Gy and 62.8 ± 7.6 Gy, respectively. The EQD2 of D_{2cc} for a 10% probability of overall rectal grade 2 or greater toxicity was 69.5 Gy, and more severe rectal toxicities, with higher frequencies occurred with $D2_{cc}$ value of 75 Gy or more [16].

7.9 Dose Optimization and the Needle Insertion Procedure

In the EMBRACE II study protocol (www.embrace.dk), dose optimization is performed for implant geometry, dwell-time distribution, and fractionation. The HBT plan should be based on the ICBT plan in iterative steps. As a starting point for optimization, a pear-shaped isodose distributions normalized to point A should be used. In a stepwise procedure, the loading pattern and the dwell times are next optimized to achieve the planning aims. The same procedure should be used in the case of HBT, the dose distribution of which is obtained by using the dose distribution of the ICBT plus that of the needles to avoid hot and cold spots in any areas not directly controlled by dose points or dose-volume relations.

In recent studies, it took 15–50 min to insert the needles and 20–40 min for treatment planning [20, 21]. Liu et al. evaluated the feasibility of HBT in 52 patients with tumors larger than 5 cm at the time of the first brachytherapy [20]. In 260 HBT sessions undergone by these 52 patients, 1804 needles were inserted; 86.0% of them were placed at the lateral 2–5 and 7–10 o'clock positions in the uterine canal. The mean number of inserted needles was 6.9 ± 1.3 for each application, and the mean needle implantation depth was 3.0 ± 0.9 cm. Kirisits et al. reported the treatment planning and dosimetric results for 22 patients, with tumors that had a mean HR-CTV of 44 cm^3 and who were treated with the HBT using the Vienna applicator [14]. The mean number of the inserted needles was 3.5 (range, 1–8), whereas 0–6

needles were loaded (mean 2.8). The average relative dwell weight compared with the dwell time of the tandem and ring position was 16%. It is necessary to take sufficient caution and check that no needle is placed near an OAR if the dwell weight is greater than 20%. Nomden et al. reported the clinical use of the Utrecht applicator for HBT in 20 patients [31]. Fifty-four needles (range, 1–6 per application) were inserted with an average depth of 25 mm. The average needle contribution per application was 19% (range, 4–35%) and for individual needles was 7% (range, 2–14%).

7.10 Complications Related to the Procedure

Several studies indicated that the majority of complications related to HBT application did not require treatment [19–21]. Kuipers et al. reported that 2 of 41 patients (4.9%) treated with HBT experienced vaginal bleeding after removing the needle which was stopped via gauze packing [19]; the transfusion was not necessary in these cases. Following the management of bleeding, patients are discharged 24 h later after routine clinical examination to exclude bleeding [21].

Preliminary results from patients treated with HBT using the Vienna applicator [21] revealed that 23 of 170 needles (13.5%) were placed directly adjacent to the OARs; 15 needles were inserted into the sigmoid and 8 into the bladder. However, no signs of sigmoid or bladder wall penetration, or of peritoneal irritation, were observed. Liu et al. demonstrated that 5 of 52 patients (9.6%) experienced intestinal injury, but no obvious infections or other complications during insertion were observed [20]. In both of the abovementioned studies, the radioactive source was not loaded into the inserted area, and no special treatments for the injuries were required.

7.11 Clinical Outcomes for Patients Treated with HBT

Dimopoulos et al. reported clinical feasibility and preliminary results in 22 patients who had tumors with insufficient responses and/or unfavorable ICBT after EBRT and who were treated with HBT using Vienna applicators [21]. The mean tumor width in their study was 5.5 cm at diagnosis and was 5.3 cm at the time of brachytherapy. In DVH analysis, the mean HR-CTV D_{90} was 96 Gy, while the mean D_{2cc} values for the bladder, rectum, and sigmoid were 83, 66, and 67 Gy, respectively. Their study showed that a sufficient dose can be delivered to the HR-CTV while sparing the OARs. Actuarial local control and overall survival after 2 years were 95% and 43%, respectively. Furthermore, no grade 3 or greater gastrointestinal or genitourinary acute or chronic toxicity was observed. This study showed excellent local control and lower toxicity despite the high population of patients with very unfavorable prognosis. Long-term clinical results of low-dose-rate (LDR) IBT were also reported [7], showing that locoregional control was obtained in 82% of patients with locally advanced cervical cancer with tumors smaller than 6 cm; this result was similar to that obtained with HBT. However, 18 of 185 patients (10%) treated with LDR-IBT developed grade 3 or 4 gastrointestinal or genitourinary chronic toxicity.

The retroEMBRACE study evaluated the impact of HBT on local control and late toxicity in a multicenter population that included 610 patients divided into IC vs. IC/IS groups [11]. In patients of the IC/IS group who systematically underwent HBT, the average HR-CTV D_{90} was significantly higher (92 ± 13 Gy) than that of IC group (83 ± 14 Gy) ($p < 0.01$). Regardless of the delivery of a higher dose to the HR-CTV D_{90} in the IC/IS group, there were no significant differences in doses to OARs. The 3-year local control rates were 92% in all patients, 89% in the IC group, and 94% in the IC/IS group. In patients with HR-CTVs that were 30 cm^3 or larger, the 3-year local control rates were 82% in the IC group and 92% in the IC/IS group ($p = 0.02$). For smaller tumors (<30 cm^3), there was no significant difference in local control between the two groups ($p = 0.50$). The incidences of gastrointestinal or genitourinary grade 3–5 late toxicities were approximately 5% in both groups ($p = 0.85$ and 0.55, respectively), regardless of the significantly higher local control rate obtained in patients with large tumors in the IC/IS group. Patients in the IC/IS group trended to exhibit more late vaginal toxicity. An analysis from the EMBRACE study showed that the actuarial probability of grade 3 or higher vaginal toxicity was 3.6% at 2 years after definitive radiotherapy with IGABT, including HBT [32]. Stenosis developed most frequently, while vaginal bleeding was usually mild and observed infrequently. In a retrospective review, the maximum vaginal surface dose of 103 Gy and maximum cumulative BED of 878.6 Gy_3 that were delivered with HDR brachytherapy were not associated with fistulas, necrosis, or other grade 3 or higher toxicities [33].

In the EMBRACE study, a volumetric analysis was performed to divide patients into six groups according to the following criteria: (a) volume of the GTV_D (defined as high-signal intensity primary tumor extension within the cervix, uterine corpus, or parametrial tissue visualized on MRI at the time of diagnosis), (b) the ratio of the CTV_{HR} to GTV_D, and (c) the extent of residual parametrial disease at the time of brachytherapy [34]. The six groups were (G1) stage IB_1-like tumors, (G2) tumors with good responses of any size, (G3) small tumors with moderate responses, (G4) large tumors with moderate responses, (G5) tumors with poor responses, and (G6) tumor exhibiting progressive disease. Two hundred eighteen of 481 patients (45%) with stage IIB or IIIB cervical cancer received HBT, 2 of 55 patients (4%) in G1, 7 of 78 (9%) in G2, 53 of 123 (43%) in G3, 87 of 147 (59%) in G4, and 67 of 75 (89%) in G5; there were no patients in G6. The use of interstitial needles and the number of active needles progressively increased in higher-severity groups. In G5, the mean number of active needles was 6; one or two needles were inserted in only five patients (7%).

A Japanese study revealed excellent 5-year local control (94%) and overall survival (86%) rates in 80 patients with stage IB1-IVA tumors who were treated with IGABT, including 14 who were treated with HBT [17]. Ninety percent of patients received more than 60 Gy as their HR-CTV D_{90} value; there was no difference in HR-CTV D_{90} according to tumor sizes (<4, 4–6, and >6 cm). The proportion of patients with a D_{2cc} to the bladder of >90 Gy and a D_{2cc} to the rectum of >75 Gy were 93% and 99%, respectively. There was no significant difference in 5-year local control between stage I, stage II, and stage III–IV. Moreover, the tumor size was not

significantly related to local control. At the time of analysis, only one patient developed grade 3 bladder toxicity, and no grade 3 or higher gastrointestinal or genitourinary late toxicities were observed.

Conclusion

For the past 20 years, IGABT has incorporated the more recent HBT; this has led to the improvement of local control while achieving low incidence rates of severe late toxicities. In Japan, several single-institutional studies found that IGABT leads to excellent local control rates [17, 29], and multicenter clinical trial of IGABT that evaluated the safety and feasibility of IGABT, including HBT, has also been performed [35]. However, there are few institutions in Japan where 3D-IGABT can be performed and in which operators are experienced in needle insertion. Efforts should be made to establish HBT as the primary modality in the majority of Japanese institutions.

Clinical results showing excellent local control obtained by IGABT suggest that improvement of disease-free and overall survival rates rests on the ability to control pelvic dissemination or distant metastasis. Future studies ought to focus on improving EBRT and systemic therapy aimed at the improving overall survival, in addition to further investigation and popularization of HBT.

References

1. Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, III CLS, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med. 1999;340(15):1154–61.
2. Goksedef BP, Kunos C, Belinson JL, Rose PG. Concurrent cisplatin-based chemoradiation International Federation of Gynecology and Obstetrics stage IB2 cervical carcinoma. Am J Obstet Gynecol. 2009;200(2):175.e1–5.
3. Perez CA, Grigsby PW, Nene SM, Camel HM, Galakafos A, Kao M-S, et al. Effect of tumor size on the prognosis of carcinoma of the uterine cervix treated with irradiation alone. Cancer. 1992;69:2796–806.
4. Kovalic JJ, Perez CA, Grigsby PW, Lockett MA. The effect of volume of disease in patients with carcinoma of the uterine cerviax. Int J Radiat Oncol Biol Phys. 1991;21(4):905–10.
5. Potter R, Haie-Meder C, Van Limbergen E, Barillot I, De Brabandere M, Dimopoulos J, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol. 2006;78(1):67–77.
6. Viswanathan AN, Beriwal S, De Los Santos JF, Demanes DJ, Gaffney D, Hansen J, et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: High-dose-rate brachytherapy. Brachytherapy. 2012;11(1):47–52.
7. Syed AMN, Puthawala AA, Abdelaziz NN, el-Naggar M, Disaia P, Berman M, et al. Long-term results of low-dose-rate interstitial–intracavitary brachytherapy in the treatment of carcinoma of the cervix. Int J Radiat Oncol Biol Phys. 2002;54(1):67–78.
8. Wakatsuki M, Ohno T, Yoshida D, Noda SE, Saitoh JI, Shibuya K, et al. Intracavitary combined with CT-guided interstitial brachytherapy for locally advanced uterine cervical cancer: introduction of the technique and a case presentation. J Radiat Res. 2011;52(1):54–8.

9. Potter R, Georg P, Dimopoulos JC, Grimm M, Berger D, Nesvacil N, et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. Radiother Oncol. 2011;100(1):116–23.
10. Dimopoulos JC, Potter R, Lang S, Fidarova E, Georg P, Dorr W, et al. Dose-effect relationship for local control of cervical cancer by magnetic resonance image-guided brachytherapy. Radiother Oncol. 2009;93(2):311–5.
11. Fokdal L, Sturdza A, Mazeron R, Haie-Meder C, Tan LT, Gillham C, et al. Image guided adaptive brachytherapy with combined intracavitary and interstitial technique improves the therapeutic ratio in locally advanced cervical cancer: analysis from the retroEMBRACE study. Radiother Oncol. 2016;120(3):434–40.
12. Nag S, Martínez-Monge R, Selman AE, Copeland LJ. Interstitial brachytherapy in the management of primary carcinoma of the cervix and vagina. Gynecol Oncol. 1998;70(1):27–32.
13. Toita T, Kitagawa R, Hamano T, Umayahara K, Hirashima Y, Aoki Y, et al. Phase II study of concurrent chemoradiotherapy with high-dose-rate intracavitary brachytherapy in patients with locally advanced uterine cervical cancer: efficacy and toxicity of a low cumulative radiation dose schedule. Gynecol Oncol. 2012;126(2):211–6.
14. Kirisits C, Lang S, Dimopoulos J, Berger D, Georg D, Potter R. The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: design, application, treatment planning, and dosimetric results. Int J Radiat Oncol Biol Phys. 2006;65(2):624–30.
15. Beriwal S, Demanes DJ, Erickson B, Jones E, De Los Santos JF, Cormack RA, et al. American Brachytherapy Society consensus guidelines for interstitial brachytherapy for vaginal cancer. Brachytherapy. 2012;11(1):68–75.
16. Mazeron R, Fokdal LU, Kirchheiner K, Georg P, Jastaniyah N, Segedin B, et al. Dose-volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: results from the prospective multicenter EMBRACE study. Radiother Oncol. 2016;120(3):412–9.
17. Ohno T, Noda SE, Okonogi N, Murata K, Shibuya K, Kiyohara H, et al. In-room computed tomography-based brachytherapy for uterine cervical cancer: results of a 5-year retrospective study. J Radiat Res. 2017;58(4):543–51.
18. Viswanathan AN, Creutzberg CL, Craighead P, McCormack M, Toita T, Narayan K, et al. International brachytherapy practice patterns: a survey of the Gynecologic Cancer Intergroup (GCIG). Int J Radiat Oncol Biol Phys. 2012;82(1):250–5.
19. Kuipersa T, Hoekstraa CJM, Rieta A, Maka ACA, Vonka EJA, Eldersa LH, et al. HDR brachytherapy applied to cervical carcinoma with moderate lateral expansion: modified principles of treatment. Radiother Oncol. 2001;58(1):25–30.
20. Liu Z-S, Guo J, Lin X, Wang H-Y, Qiu L, Ren X-J, et al. Clinical feasibility of interstitial brachytherapy using a 'hybrid' applicator combining uterine tandem and interstitial metal needles based on CT for locally advanced cervical cancer. Brachytherapy. 2016;15(5):562–9.
21. Dimopoulos JC, Kirisits C, Petric P, Georg P, Lang S, Berger D, et al. The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: clinical feasibility and preliminary results. Int J Radiat Oncol Biol Phys. 2006;66(1):83–90.
22. Kirchheiner K, Czajka-Pepl A, Ponocny-Seliger E, Scharbert G, Wetzel L, Nout RA, et al. Posttraumatic stress disorder after high-dose-rate brachytherapy for cervical cancer with 2 fractions in 1 application under spinal/epidural anesthesia: incidence and risk factors. Int J Radiat Oncol Biol Phys. 2014;89(2):260–7.
23. Leong YH, Tan KHS, Choo BA, Koh VY, Tang JI. Novel anesthetic technique for combined intracavitary and interstitial brachytherapy for cervix cancer in an outpatient setting. J Contemp Brachytherapy. 2017;9(3):236–41.
24. Watanabe Nemoto M, Nozaki-Taguchi N, Togasaki G, Kanazawa A, Kurokawa M, Harada R, et al. New approach to relieving pain and distress during high-dose-rate intracavitary irradiation for cervical cancer. Brachytherapy. 2015;14(5):642–7.
25. Tan LT. Implementation of image-guided brachytherapy for cervix cancer in the UK: progress update. Clin Oncol (R Coll Radiol). 2011;23(10):681–4.

26. Ohno T, Toita T, Tsujino K, Uchida N, Hatano K, Nishimura T, et al. A questionnaire-based survey on 3D image-guided brachytherapy for cervical cancer in Japan: advances and obstacles. J Radiat Res. 2015;56(6):897–903.
27. Dimopoulos JC, Petrow P, Tanderup K, Petric P, Berger D, Kirisits C, et al. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (IV): basic principles and parameters for MR imaging within the frame of image based adaptive cervix cancer brachytherapy. Radiother Oncol. 2012;103(1):113–22.
28. Cengiz M, Yildiz F, Selek U, Ozyigit G. Comment on "Computed tomography versus magnetic resonance imaging-based contouring in cervical cancer brachytherapy: results of a prospective trial and preliminary guidelines for standardized contours" by Viswanathan et al. (Int j radiat oncol biol phys 2007;68:491–498, 2007). Int J Radiat Oncol Biol Phys. 2007;69(3):963. author reply –4
29. Murakami N, Kasamatsu T, Wakita A, Nakamura S, Okamoto H, Inaba K, et al. CT based three dimensional dose-volume evaluations for high-dose rate intracavitary brachytherapy for cervical cancer. BMC Cancer. 2014;14:447.
30. Kato S, Tran DNL, Ohno T, Nakano T, Kiyohara H, Ohkubo Y, et al. CT-based 3D dose-volume parameter of the rectum and late rectal complication in patients with cervical cancer treated with high-dose-rate intracavitary brachytherapy. J Radiat Res. 2010;51(2):215–21.
31. Nomden CN, de Leeuw AA, Moerland MA, Roesink JM, Tersteeg RJ, Jurgenliemk-Schulz IM. Clinical use of the Utrecht applicator for combined intracavitary/interstitial brachytherapy treatment in locally advanced cervical cancer. Int J Radiat Oncol Biol Phys. 2012;82(4):1424–30.
32. Kirchheiner K, Nout RA, Tanderup K, Lindegaard JC, Westerveld H, Haie-Meder C, et al. Manifestation pattern of early-late vaginal morbidity after definitive radiation (chemo)therapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: an analysis from the EMBRACE study. Int J Radiat Oncol Biol Phys. 2014;89(1):88–95.
33. Kaidar-Person O, Abdah-Bortnyak R, Amit A, Nevelsky A, Berniger A, Bar-Deroma R, et al. Tolerance of the vaginal vault to high-dose rate brachytherapy and concomitant chemo-pelvic irradiation: long-term perspective. Rep Pract Oncol Radiother. 2014;19(1):56–61.
34. Jastaniyah N, Yoshida K, Tanderup K, Lindegaard JC, Sturdza A, Kirisits C, et al. A volumetric analysis of GTVD and CTVHR as defined by the GEC ESTRO recommendations in FIGO stage IIB and IIIB cervical cancer patients treated with IGABT in a prospective multicentric trial (EMBRACE). Radiother Oncol. 2016;120(3):404–11.
35. Murakami N, Kato S, Nakano T, Uno T, Yamanaka T, Sakurai H, et al. A phase I/II clinical trial for the hybrid of intracavitary and interstitial brachytherapy for locally advanced cervical cancer. BMC Cancer. 2016;16:640.

Interstitial Brachytherapy: Radical and Salvage

8

Ken Yoshida

Abstract

Interstitial brachytherapy (ISBT) is a useful treatment modality for gynecological cancer. Multiple treatment applicators can be implanted in and/or around clinical target volume (CTV); ISBT may achieve a better CTV coverage than an intracavitary brachytherapy and intracavitary/interstitial brachytherapy (ICISBT).

ISBT for gynecological tumor started since the 1910s, and its technique was a two-dimensional freehand implantation technique using low-dose-rate ISBT. The technique made progress in this century, and three-dimensional (3D) template/freehand image-guided implantation technique using high-dose-rate (HDR) ISBT has become mainstream. Image-guided technique made it possible to analyze a relationship between doses for CTV and local control rate and between doses for organs at risk and complication rates using dose-volume histogram (DVH) scientifically.

In this section, we introduce implantation technique, treatment outcome, and DVH analysis of ISBT, so-called "pure" ISBT, mainly for primary uterine cervical cancer, recurrent uterine cancer, and primary vaginal cancer. We also introduce our experience. We (Osaka National Hospital and Osaka Medical College) innovated our unique ambulatory implant technique for pelvic ISBT that patient could sit down and walk during treatment period. We performed 3D magnetic resonance image-assisted computed tomography-based treatment planning and measured applicator displacement with corrective action from a relatively early period of time in the world. In regard to follow-up, we introduce only vaginal washing.

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We exhibit many figures of our implantation technique and treatment planning method, and we hope this figures will help for readers to innovate more sophisticated ISBT method because we believe that ISBT is very valuable treatment modality and has potential for expansion.

Keywords
Interstitial brachytherapy · Gynecological tumor · Uterine cervical cancer Recurrent uterine cancer · Vaginal cancer · Image-guided · Displacement

8.1 Primary Uterine Cervical Cancer

8.1.1 Introduction

Interstitial brachytherapy (ISBT) is a useful treatment modality for gynecological cancer. Because multiple treatment applicators can be implanted in and/or around clinical target volume (CTV), ISBT may achieve a better CTV coverage than an intracavitary brachytherapy (ICBT).

ISBT for gynecological tumor started since the 1910s. Stevenson et al. reported their experience of radium implantation [1]. Pitts et al. reported that survival rate of stage III uterine cervical cancer was 30.9% for 110 cases treated by low-dose-rate (LDR) ISBT between 1926 and 1933 compared with 14% for 43 cases treated by other methods between 1921 and 1925 [2]. The implantation technique was a free-hand implantation without guidance of three-dimensional (3D) image and template.

The template technique was reported since the 1940s [3, 4] and progresses since the 1970s [5, 6]. Sophisticated transperineal templates (Syed-Neblett template, Martinez universal perineal interstitial template [MUPIT], and so forth) were developed and improved parallelism of applicators and reproducibility of implant quality. It improved the dose coverage to the CTV and spread the treatment indication. However, treatment planning of this method was still performed by two-dimensional (2D) X-ray films at that time. And so, dose prescription was not based on CTV, and dose-volume relationship of CTV was ambiguous.

Since the 1990s, 3D image-guided brachytherapy using computed tomography (CT) and magnetic resonance imaging (MRI) started [7–9]. This technique also spreads to pure ISBT [10–12]. Thanks to these imaging modalities, physicians could delineate the CTV and organs at risk (OARs) on isodose curve and evaluate how many doses were delivered to the CTV and the OARs. This second wind made it possible to deliver the prescribed doses to the CTV precisely. It also made it possible to analyze a relationship between doses for CTV and local control rate and between doses for OARs and complication rates using dose-volume histogram (DVH) scientifically. Japanese data is also reported since the middle of the 1990s. Terahara et al. showed the dose relationship between local control rate and DVH data on 1996 [13].

The introduction of high-dose-rate (HDR) brachytherapy is also important technical progress. LDR brachytherapy has been an important treatment and the best radiation modality for uterine cervical cancer on the first half of the twentieth century. However, it has a shortage of radiation exposure of medical staff. This is a big problem for our country because Japan is an only country to have experienced atomic bombs.

Osaka group has been achieved many contribution for development of HDR brachytherapy [14, 15]. Shigematsu et al. reported that the local control rate (LC) was higher in the high-dose-rate ICBT group and the complication rate was also higher in this group than in the low-dose-rate ICBT group [14]. The overall cumulative survival rate was nearly the same in both groups (55% at 5 years).

We (Osaka National Hospital and Osaka Medical College) also innovate our unique ambulatory implant technique for pelvic ISBT [12, 16] that patient could sit down and walk during applicator implantation. This technique allowed 3D image-guided ISBT using CT and MRI. In this section, we introduce not only common outcome of ISBT but also our experience of ISBT, so-called "pure" ISBT, except intracavitary/interstitial brachytherapy (ICISBT).

8.1.2 The Indication of ISBT

At present, there are four modalities of brachytherapy for previously untreated primary uterine cervical cancer. First modality is a classical conventional ICBT (ConvICBT) such as Manchester system. Second modality is an image-guided ICBT (IGICBT) that treatment planning was performed depending on CT/MR images. Third modality is a ICISBT that Kuipers et al. started primitive implantation method [17] and Medical University of Vienna progressed sophisticated image-guided method [18, 19]. Fourth modality is a classical pure ISBT. We often wondered which modality was the best choice for each patient.

American Brachytherapy Society (ABS) recommendations for HDR brachytherapy for cervical carcinoma revealed that the eligibility criteria for undergoing ISBT were bulky lesions, narrow vagina, and inability to enter the cervical os, lateral extension, and lower vaginal extension [20]. The indication of LDR-ISBT is almost same [21]. However, there is no definition about bulky lesion and lateral extension. How many sizes of CTV were adequate for ISBT? And so, we investigated simulation analysis using tumor models to clarify the indication for each brachytherapeutic modality [22].

We simulated a variety of sizes of high-risk (HR) CTV models using three types of applicator positions (ICBT, ICISBT, and ISBT). We calculated four treatment plans (ConvICBT, IGICBT, ICISBT, and ISBT) and compared DVH.

We evaluated eight types of HR CTV models. The smallest HR CTV was $2 \times 2 \times 2$ cm (mediolateral × ventrodorsal × craniocaudal) of rectangular shape, and the largest HR CTV was $7 \times 4 \times 4$ cm. Tandem was positioned at the center of the CTV. As a result, HR CTV size of $4 \times 3 \times 3$ cm seems to be a threshold volume in this simulation analysis, and IGICBT is a better choice for smaller HR CTV than the

threshold volume. On larger HR CTV, ICISBT or ISBT are the better choice. D_{2cm3}(OARs) of ISBT clearly revealed lower values than those of ICISBT for HR CTV sizes of 5 × 4 × 4 cm or larger. From this result, we considered that ISBT should be selected for HR CTV sizes of 5 × 4 × 4 cm or larger.

Liu et al. evaluated DVH for 58 patients treated by ICBT and ISBT and reported almost the same conclusion [23]. Thirty patients who received ICBT were treated before 2013, and 28 patients who received ISBT were treated after 2013 that ISBT was introduced in their hospital. All patients had large-volume tumors and/or parametrial extension with a remnant tumor of greater than 5 cm after EBRT of 45 Gy. Total D90(HR CTV) for ICBT was 76.9 ± 5.7 Gy, and total D90(HR CTV) for ISBT was 88.1 ± 3.3 Gy. Significant difference was observed. Furthermore, D_{2cm3}(OARs) of the bladder, rectum, and sigmoid for ISBT were less than those for ICBT.

8.1.3 Implantation and Treatment Planning

Common implant technique is a template-guided technique. Implantation is performed under spinal or general anesthesia. Basically, standard intracavitary implantation (tandem application) should be performed at first. After the implantation of tandem applicator, multiple needle applicators should be implanted at uterine and/or paracervical tissue to complement the doses for HR CTV. If tandem cannot be placed because of loss of the endocervical canal, positioning and loading of the central needles must be considered carefully to avoid a central cold spot. The ABS Committee commented that cure of cervical cancer requires some degree of inhomogeneity of dose at the center of both intracavitary and interstitial implants [24]. Attention to proper needle placement is necessary to fully encompass the tumor while avoiding the OARs. Ultrasonography (US), CT, or MRI guidance is desired. Sharma et al. visualized the tip of needle during implantation using transrectal ultrasonography (TRUS), and it makes easier to prevent from penetrating the gut wall [25].

Titanium or flexible plastic needles are preferred as they reduce CT simulation artifacts caused by stainless steel needles and also allow MRI-based planning. Perineal templates, such as Syed template and MUPIT, should be used as they help to maintain needle geometry and thus improve dose distribution.

The treatment planning is recently performed with 3D planning. CT is used for almost institutes. The HR CTV and the surrounding OARs, including the rectum, bladder, urethra, small bowel, etc., were contoured. The HR CTV was defined as the presumed residual gross tumor volume (GTV) with normal cervix. Fiducial marker seeds may be inserted at the edge of the HR CTV. Especially, it is effective to judge the distal edge of superficial vaginal invasion.

Erickson et al. reported a review of gynecological ISBT, and the prescribed doses to the tumor or reference point were 25–40 Gy for almost LDR-ISBT series [26]. ABS consensus guidelines recommended 35–45 Gy with 45 Gy of EBRT for LDR-ISBT. Total prescribed doses were 80–90 Gy [21].

Dose calculation is important issue for HDR-ISBT. The dwell times of the applicators those were implanted at central area (tandem and the needles near tandem) should be longer time because main tumor lesion is distributed in this area. The dwell times of the applicators those were implanted at the periphery should be dealt with different manner for each dose-rate ISBT because OAR is near. In LDR-ISBT, sparse implantation may be necessary because dose optimization cannot be performed. Against it, narrow implantation interval is desired for HDR-ISBT in order to optimize these dwell times precisely.

Dose optimization was performed using dose optimization software such as volume optimization, inverse optimization, manual optimization, etc. Prescribed isodose line was decided by the DVH result at 3D-planning era. The isodose that includes 90% of the target (D90) is mostly used for reference of the prescribed doses.

For HDR-ISBT, ABS consensus guidelines recommended 25–30.5 Gy in 5–9 fractions with 45 Gy of EBRT and 22.5–27 Gy in 5–9 fractions with 50.4 Gy of EBRT. Total EQD_2 doses were 70–80 Gy [27].

8.1.4 Experience of Osaka National Hospital and Osaka Medical College

We innovated unique ambulatory implant technique for HDR-ISBT in order to improve patient's activities of daily living during treatment and prevent from complication such as venous thrombosis [12, 16]. We use freehand implantation using plastic applicator needles. This technique enables us to take MRI, and we could register to planning CT images for the assistance of 3D image-guided planning.

Before implantation, we inserted a sounding tube and compared the position and the HR CTV by TRUS. We monitored and overlap the contour of the HR CTV for all craniocaudal level and finally delineate a maximum total contour of the HR CTV. Next, we measured the distance between sounding tube position and HR CTV. If the maximum distance between the sounding tube position and the edge of the HR CTV is more than 2–2.5 cm (Fig. 8.1a), we selected ISBT.

We made a vinyl template using above maximum contour of the HR CTV. We also made a silicone cylinder. The cylinder had five implant holes, and the center hole was used for the tandem needle. We change the diameter and length depending on the patient's vaginal cavity.

To decide implantation points, the most important thing is that physician's imagination about what kind of isodose shape is the best coverage for HR CTV without delivering excessive doses for OARs. After the physician decide the most desired isodose shape for each patient, we prepared a vinyl template that the implant points were punched.

1. HR CTV and OARs were monitored by TRUS.
2. Fiducial titanium marker seeds were inserted at the edge of the CTV.

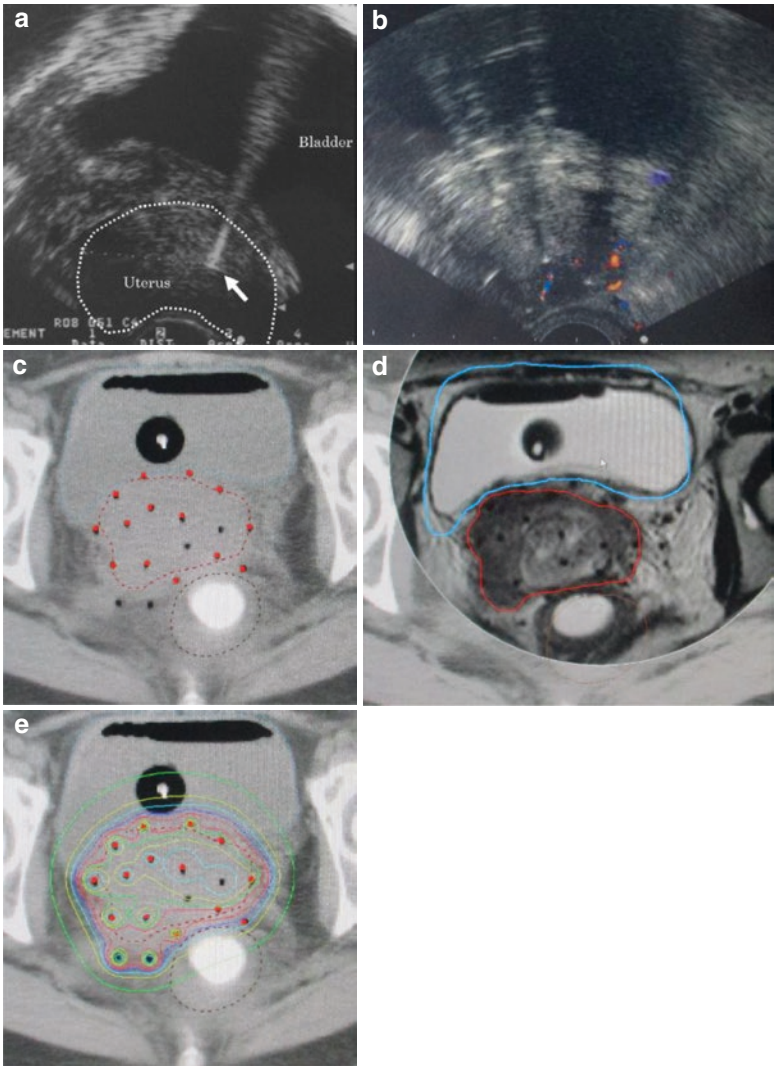

Fig. 8.1 (**a**) Transrectal ultrasonography (TRUS) image of uterine cervical cancer patient. Sounding tube was inserted into her uterine cavity, and the distance between sounding tube position (white arrow) and the lateral edge of high-risk clinical target volume (HR CTV) was calculated. The distance was 3 cm. Because it is larger than 2–2.5 cm, we selected interstitial brachytherapy for her. (**b**) TRUS image of the same patient as **a**. Doppler function is used to confirm the position of large vessel. (**c**, **d**) Planning computed tomography (CT) image of the same patient as **a** (**c**). Magnetic resonance imaging was overlapped to CT image (**d**). The contour of the CTV delineated with the assistance of the MRI image precisely (red line). However, MRI did not help to delineate the bladder (light blue line) and the rectum (brown line) because these organs changed their shape within short time between imaging time of CT and MRI. (**e**) Planning CT image of the same patient as **a**. Isodose curve was shown on the CT image. We prolonged the dwell times of applicator needles implanted into the uterine cavity (light-blue line, 200% planning aim isodose line). After enough CTV coverage was achieved, we reduced the dwell times of the needles near the bladder and the rectum with keeping enough dose coverage for the CTV

3. Flexible applicator needle with button stopper was inserted into the uterine cavity as a tandem needle. First 1–1.5 cm of needle tip was implanted into the uterine fundus in order to fix the needle position during the treatment.
4. Handmade silicone cylinder was inserted into the vagina and followed behind the tandem needle. The center hole of the cylinder was used for the tandem needle. As a result, the tandem needle was positioned at the center hole of the silicone cylinder.
5. Handmade vinyl template was contacted on the perineal skin surface. The tandem needle was positioned at the center hole of the vinyl template.
6. Flexible needles with button were implanted from the cylinder, vagina, and perineal skin under TRUS guidance. The needles were placed at the uterine, paravaginal tissue and paracervical tissue to complement the radiation doses to the region that becomes cold spot if we treat by intracavitary brachytherapy alone. Doppler TRUS is often convenient to confirm the large vessel position near the implantation points (Fig. 8.1b).

   The needle-needle interval should be shorter near the OARs because precise dose modification is necessary. It is a different manner from LDR-ISBT. In the case of LDR-ISBT, physician never does it if he uses treatment sources of same source strength.

   We implanted the needles to 1–1.5 cm beyond the HR CTV to be able to correct dwell positions if the needle were displaced caudally.
7. Button stoppers were sutured to the perineal skin. The protruded connector end of the applicator was cut down short enough to enable the patient to walk.

The CT-based planning was performed using MRI as a reference to contour the HR CTV and OARs (rectum, bladder) (Fig. 8.1c, d). The definition of these contours was based on the recommendation from the Gynecological GEC-ESTRO Working Group for reporting 3D-sectional image-assisted brachytherapy of cervix cancer [28, 29]. The treatment planning was performed using the computer volume optimization with manual modification [30].

Basically, we increased the dwell times of applicator needles to cover the CTV at first. At that time, we preferred to increase the dwell times of the needles implanted into the uterine cavity or muscle because radiation tolerance was higher in this area. After enough CTV coverage was achieved, we cut the isodose curve that protruded into OARs. At that time, we preferred to reduce the dwell times of the needles near the OARs. Because we implanted more needles near OARs showing above, such modification became easier (Fig. 8.1e). After we could modify the isodose curve to a certain extent, we checked the DVH. We modified furthermore with the completion of treatment planning while monitoring the DVH values.

Our planning aim was for the isodose that includes 100% of the target (D100) for HR CTV to be equal to the planning aim dose if D_{2cm3} for OARs did not become too high. If D_{2cm3} for OARs become too high, we compromised the dose for HR CTV. However, we kept D90 for HR CTV within the range of not less than planning aim dose. Our planning aim dose was 30 Gy in five fractions when center-shielded radiotherapy was used. When only whole-pelvic radiotherapy was used, we reduce the doses of ISBT to 25 Gy in five fractions.

8.1.5 External Beam Radiotherapy

External beam radiotherapy (EBRT) is combined for almost radical cases. Whole-pelvic radiotherapy (WPRT) of 45–50.4 Gy in 25–28 fractions was common. Center-shielded radiotherapy (CSRT) is combined in some countries. This technique is superior to reduce the irradiated doses for the rectal, urethra and bladder. However, calculation of total DVH for the CTV becomes difficult if the central shield only blocks a partially medial side of the CTV.

8.1.6 Treatment Results

Treatment results of selected series were shown in Table 8.1. Erickson et al. reported a review of ISBT data between the 1970s and the early 1990s [26]. Almost data was LDR-ISBT using template technique with 2D planning. Local control rates were 25–88%. Survival rates were 22–60%. Representative ISBT reports since the late 1990s to the early 2000s [31–36] were also shown in Table 8.1. Syed AMN et al. reported their treatment result of 185 patients (stage III–IV, 87 patients) treated between 1977 and 1997 [31]. Prescribed doses of EBRT were 39.6 Gy for WPRT and 10.8 Gy for CSRT. Prescribed doses of LDR-ISBT were 40–50 Gy to the implanted volume. Local control rate (LC) was 82%, and disease-free survival rate (DFS) was 58%. Three patients (2%) developed grade 3 (RTOG/EORTC late radiation morbidity scoring scheme) late bladder complication, and 15 patients (8%) developed grade 3 late gastrointestinal complication. Demanes et al. reported their treatment result of 62 patients (stage III–IV, 23 patients) treated by HDR-ISBT between 1991 and 1996 [32]. For example, the prescribed doses of WPRT, CSRT, and ISBT were 36 Gy, 14 Gy, and 33 Gy (six fractions). LC was 94% for all 62 patients, and overall survival rate (OS) was 52%. Four patients (6.5%) developed grade 3–4 late complication. Isohashi et al. reported their treatment result of 25 patients (stage III–IV, 20 patients) treated between 1995 and 2005 [33]. The median prescribed doses of EBRT were 30 Gy for WPRT and 20 Gy for CSRT. Prescribed doses of HDR-ISBT were 30 Gy in five fractions to 5 mm from applicators. For stage III disease, the 5-year LC was 73%, and progression-free survival rate was 51%. Two of all 25 patients (8%) developed grade 3 late complication.

Image-guided ISBT was reported since the 2000s [10–12, 37–40]. Beriwal et al. reported their CT-planning treatment result of 16 previously untreated patients (uterine cervix/vagina = 11:5) treated between 1998 and 2004 [10]. Seven of 11 uterine cervical cancer patients were stage III–IV. The median prescribed doses of EBRT were 45 Gy for WPRT and 9 Gy of parametrial boost. Prescribed doses of HDR-ISBT were 18.75 Gy in five fractions to the CTV. The 5-year LC was 75%, and cause-specific survival rate (CSS) was 64%. LC for uterine cervical cancer was 63%. The actuarial rate of grade 3–4 late complications was 7%. This group started dose escalation of ISBT since 2005. Kannan et al. reported their CT-planning treatment result of 47 previously untreated patients (stage III–IV, 41 patients) treated between 2005 and 2011 [37]. The median prescribed doses of HDR-ISBT increased

Table 8.1 Selected series of interstitial brachytherapy for previously untreated uterine cervical cancer

	Dose rate	Treatment duration	Patient's number	Imaging modality of treatment planning	ISBT[a] dose (median; range) (Gy)	Whole-pelvic EBRT[b] dose (median; range) (Gy) of {Beriwal et al.}	Whole-pelvic plus center-shielded EBRT dose (median; range) (Gy)	Local control rate (%)	Overall survival rate (%)	Severe complication (%)
2D dose calculation										
From table of review article of Erickson et al.	Mainly LDR	1974–1993		XP				33–88 (cervical cancer)	25–60 (cervical cancer)	3–37.5 (cervical cancer)
1997 [26]								17–100 (recurrent cancer)	26–36 (recurrent cancer)	11–86 (recurrent cancer)
								50–100 (vaginal cancer)	56–77 (vaginal cancer)	8–75 (vaginal cancer)
Prempree	LDR	1975–1977	49	XP				84	65	8
1983 [34]						–				
Gupta et al.	LDR	1985–1994	69	XP	32; 17–40		50.4; 30–59	44 (cervix)	27 (cervix)	14 (total)
1999 [35]			(30: cervix)							
Demanes et al.	HDR	1991–1996	62	XP	22–36	25–50	45–50	94	52	6.5

(continued)

Table 8.1 (continued)

	Dose rate	Treatment duration	Patient's number	Imaging modality of treatment planning	ISBT[a] dose (median; range) (Gy)	Whole-pelvic EBRT[b] dose (median; range) (Gy) of {Beriwal et al.}	Whole-pelvic plus center-shielded EBRT dose (median; range) (Gy)	Local control rate (%)	Overall survival rate (%)	Severe complication (%)
1999 [32]										
Syed et al.	LDR	1977–1997	185	XP	40–50	39.6	50.4	82	58 (disease-free survival)	10
2002 [31]										
Agrawal et al.	HDR	2000–2001	26	XP	16–24	40–50	40–50	77 (total)		4 (total)
2005 [36]			(17: cervix)							
Isohashi et al.	HDR	1995–2005	25	XP	30; 24–36	30	50	73 (stage III)	51 (stage III)	8
2009 [33]									54 (total)	
3D dose calculation										
Beriwal et al.	HDR	1998–2004	16	CT	18.75	45; 39.6–50.4	45; 39.6–50.4 + parametrial boost 9 Gy	75 (total)	64 (total; cause-specific survival)	7 (total)
2006 [10]			(11: cervix)					63 (cervix)		
Kannan et al.	HDR	2005–2010	47	CT	22.5; 18.3–25	45; 40.8–50.4	45; 40.8–50.4	61	59	10
2012 [37]										

Thibault et al.	HDR	2001–2009	43	CT/MRI	30; 18–35	45; 40–50.4	45; 40–50.4	87 (34 primary cancer)	86 (34 primary cancer)	28 (total)
2012 [11]			(12: cervix)							
Amsbaugh et al.	LDR	2009–2014	73	CT	LDR 40; 16–55	45	45	58.8 (locoregional)	48.2	39.7 (urinary, rectal, and vaginal toxicity)
2016 [38]	HDR		(36: cervix)		HDR 25; 12–29	45	45			21.9 (urinary and rectal toxicity)
Kamran et al.	HDR	2005–2015	56	CT/MRI	21.1–45.1	45; 45–57.6	45; 45–57.6	96 (MR-guided)	84 (MR-guided)	21 (MR-guided)
2017 [39]								87 (CT-guided)	56 (CT-guided)	19 (CT-guided)
Yoshida et al.	HDR	2005–2009	29	CT/MRI	30; 30–36	30; 30–45	50; 45–50.4	100 (T2)	100 (T2)	14
2015 [40]								95 (T3)	79 (T3)	
								83 (T4)	83 (T4)	

[a]Interstitial brachytherapy
[b]External beam radiotherapy

to 22.5 in five fractions, and the aim of total EQD_2 doses increased to 70–80 Gy. The median D90 was 76.25 (range, 59–87.9) Gy. The 2-year LC was 61% and OS was 59%. Grade ≥ 3 late complications was 10%.

Thibault et al. reported their CT/MRI-planning treatment result of 43 patients including 34 primary cancer patients treated between 2001 and 2009 [11]. Twelve of 34 primary cancer patients were previously untreated uterine cervical cancer patients. Eleven of 12 uterine cervical cancer patients were stage III–IV. The median prescribed doses of EBRT were 45 Gy for WPRT. The median planning aim doses of HDR-ISBT were 30 (range, 18–35) Gy in 4–6 fractions. The planning aim was to insure that 95% of the CTV received 100% of the planning aim dose (V100). The median D90 was 90.2 Gy. The 2-year LC was 87% and OS was 86% for 34 primary cancer patients. Twelve of 43 (28%) patients showed grade 3–4 late complications.

Kamran et al. compared the treatment outcome between MRI-guided ISBT and CT-guided ISBT [39]. They treated 56 locally advanced uterine cervical cancer patients (MRI-guided:CT-guided = 29:27). Two-year LC rates were 96% and 87% for MRI-guided ISBT and CT-guided ISBT (not significant difference was observed). Two-year Kaplan-Meier OS were 84% and 56% for MRI-guided ISBT and CT-guided ISBT, and significant difference was observed.

8.1.7 Experience of Osaka National Hospital and Osaka Medical College

Our experience showed their CT/MRI-planning treatment result of 29 patients (stage III–IV, 27 patients) treated between 2005 and 2009 [40]. Almost all treatment process (indication decision, implantation, planning, treatment, and follow-up) was done by a same physician (K.Y.). The median prescribed doses of EBRT were 30 Gy for WPRT and 20 Gy for CSRT. Planning aim doses of HDR-ISBT were 30 (range, 30–36) Gy in five fractions, and the aim of total EQD_2 doses increased to 70–80 Gy. The median D90 was 81.9 (range, 65.5–96.6) Gy. The 3-year LCs were 95% and 83% for T3 and T4. The 3-year OS was 79% and 83% for T3 and T4. Four of 29 (14%) patients showed grade 3–4 late complications.

8.1.8 Applicator Displacement

Compared with EBRT, ISBT has a merit that is less affected by motion of the tumor. Because the treatment applicators were implanted into the tumor, the positional relationship between the tumor and applicators is hard to change except the direction of needle implantation. However, there is a problem for this direction because applicator displacement may occur. The displacement may occur by the movement of the applicator or template. Edematous change and/or subcutaneous hematoma also become causes of applicator displacement. If the needle applicator displaces more than the cranial margin, it causes a loss of dose conformity and may lead to unexpected marginal recurrence and complications simultaneously.

This problem was pointed out in prostate ISBT at first [41, 42], and our group also verified it in prostate and gynecological cancer [43–45]. Mikami et al. reported that the median applicator displacement to caudal direction was 2 mm for 45 h after implantation calculated using daily CT measurement. It may be a first report for gynecological ISBT in the world [43]. There are some other reports about this at present [46–51]. All authors used CT for data calculation and compared applicator displacement using coordinates of the pelvic bone, the CTV, or the fiducial markers. The average or median displacement length of applicators was 0.3–19.1 mm for about 48 h. Applicator displacement influenced the DVH value of the CTV [45, 49–51]. The mean reductions of D90(CTV) were 0–6% compared with the values without displacement. However, more than 10% reduction of D90(CTV) was reported for some patients. And so, corrective actions of this dose delivery error will be necessary.

8.2 Local Recurrence of Uterine Cancer

8.2.1 Introduction

Recurrent uterine cancer of the vagina is usually not suitable for curative organ-sparing surgery because of the proximity of the tumor to the rectum, bladder, and urethra. Recurrent uterine cervical cancer after radical radiotherapy is also not suitable for curative surgery because of irradiation history. And so, ICBT and ISBT play an important role because curative dose is given to the CTV.

Recurrent uterine cancer is divided to two patterns. First is a vaginal recurrence after surgery. In this type, the small bowel is often located just above the recurrent tumor because the uterus is resected at the time of previous surgery. It means that physician must take care not to irradiate too much doses to the small bowel. We also take care a risk of bowel obstruction if EBRT is also delivered. Second is a vaginal/uterus recurrence after radical radiotherapy. In this type, the recurrent tumor may be a radioresistant if the tumor is a central recurrence of previous radiotherapy. Because second radiotherapy has a higher risk of complication, EBRT should not be performed, and CTV margin of brachytherapy must keep minimum level.

8.2.2 The Indication of ISBT

ABS consensus guidelines for ISBT for vaginal cancer show the treatment option of vaginal cancer [52]. It shows that primary stage I–IVA vaginal cancers or recurrent cervical, endometrial, or vulvar carcinoma in the vagina with residual vaginal lesions greater than 0.5 cm thick are potential candidates for ISBT.

Ito et al. reported their treatment result of 90 vaginal stump recurrence patients of uterine cervical cancer [53]. They divide 90 patients into 3 groups depending on the tumor size. Forty-three patients that the tumor was visible but not palpable belong to small group. Thirty-three patients that the tumor was palpable and its size

was less than 3 cm belong to medium group. Fourteen patients that the tumor size was equal to or more than 3 cm or extended to the pelvic cavity belong to large group. They performed ICBT with or without EBRT. The incidences of local failure were 10%, 49%, and 63% for small, medium, and large group. From this result, we considered that ICBT should be restricted for superficial tumor lesions.

8.2.3 Implantation and Treatment Planning

ABS consensus guidelines showed implantation technique for vaginal recurrence and primary vaginal cancer [52]. Before implantation, fiducial gold, platinum, or carbon fiber marker seeds should be inserted to delineate the residual GTV (and, if possible, its original extent). Titanium or flexible plastic needles reduce CT simulation artifacts caused by stainless steel needles, facilitate delineation of the target volume, and allow MRI-based planning, if available. For apical or upper vaginal lesions, a perineal template with a vaginal cylinder is recommended for implantation. Laparoscopy, laparotomy, transabdominal US, TRUS, CT, or MRI should be considered to help place the needles and avoid inadvertent placement of needles in OARs. For mid or distal vaginal lesions, either freehand techniques or template-based techniques can be used. Ideally, the CTV should be encompassed with a 1-cm margin beyond the GTV in the lateral, inferior, and superior margins unless limited by normal tissue constraints. This will often yield a peripheral set of catheters in the normal tissue just beyond the CTV. After implantation, a digital rectal examination should be performed to ensure that no catheters are perforating the rectum.

Charra et al. treated 78 vaginal stump recurrence of uterine cervical and corpus cancer by LDR-ISBT [54]. For the patients who did not have previous irradiation history, the mean prescribed doses of ISBT were 60.2 Gy as monotherapy or 27.2 Gy combined with 40.9 Gy of EBRT. For the patients who had previous irradiation history, the mean prescribed doses of ISBT were 46.4 Gy as monotherapy and 28.7 Gy combined with 30.8 Gy of EBRT.

ABS consensus guidelines showed that the recommended prescription dose for LDR brachytherapy were 25–40 Gy with EBRT, for a total dose of 70–85 Gy, depending on the tumor location, the extent of disease, and the response to EBRT [52]. The preferred dose rate for LDR brachytherapy is 35–70 cGy/h.

For HDR-ISBT, these guidelines showed 30–33 Gy in six fractions with 36 Gy of EBRT or 20–25 Gy in five fractions with 50.4 Gy of EBRT as recommended prescribed doses.

8.2.4 Experience of Osaka National Hospital and Osaka Medical College

Because uterine was already resected in case of vaginal stump recurrence, tandem applicator was not used. In case of uterine and/or vaginal recurrence after radical radiotherapy, it is also the same because uterine cavity was adhered as a late complication by previous radiotherapy.

A single flexible needle applicator was inserted into the center of the uterine cervix or vaginal stump. After implanting the first needle, a silicone cylinder was inserted into the vagina. The cylinder had five implant holes, and the center hole was used for the first needle. After inserting the cylinder, we attached a custom-made vinyl plate to the patient's perineum with holes for needle implantation. The vinyl plate had five holes for cylinder-guided implantation and several additional holes for freehand implantation. We implanted the needle applicators in and around the CTV with TRUS guidance and implanted 1–1.5 cm beyond the CTV to be able to correct dwell positions if the needle applicator was displaced caudally.

For the patients who had no irradiation history, the CTV is the GTV with 1 cm of margin around the GTV. Entire circumference of the vagina at the GTV level is also included in the CTV. If the tumor is located close to the cervix or vaginal stump, the mucosal surface of the cervix/vaginal stump is also included to the CTV.

For the patients who had irradiation history, the CTV is equal to the GTV.

The CT-based planning with the assistance of MRI is same as our planning for previously untreated uterine cervical cancer.

For the patients who had no irradiation history, we selected ISBT combined with EBRT for the patients who showed local recurrence within 2 years after previous surgery or showed nodal recurrence. The median single-fraction planning aim dose of HDR-ISBT was 6 Gy, and the median total planning aim doses were 30 Gy in five fractions for ISBT combined with 30–40 Gy of WPRT. We reduced the planning aim doses to 25 Gy in five fractions if WPRT is delivered to 50 Gy. We selected ISBT as a monotherapy for patients exhibiting local recurrence for more than 2 years after the previous treatment. The median total planning aim doses were 54 Gy in nine fractions for ISBT as a monotherapy.

For the patients who had irradiation history, we omitted EBRT and also reduced the total planning aim doses to 48 Gy in eight fractions for HDR-ISBT as a monotherapy.

8.2.5 External Beam Radiotherapy

EBRT may be combined for previously non-irradiated cases. WPRT of 45–50.4 Gy in 25–28 fractions were common. CSRT is combined in some countries. However, EBRT is not combined for almost patients who had previous irradiation history.

8.2.6 Treatment Results

Treatment results of selected series were shown in Table 8.2 [11, 54–71]. The LC and OS rates after ISBT ranged from 45–100% to 17–83%, respectively. Although the LC after 3D dose calculation with an image-guided system (60–100%) was theoretically superior to 2D dose calculation (45–85%), a wide variety of outcomes were observed, and image-guided ISBT did not provide a better LC result mainly because of the heterogeneous patient population, which featured selection bias. For example, Nag et al. [55] reported an LC rate of 100% in 13 favorable outcome

Table 8.2 Selected series of interstitial brachytherapy for local recurrence of uterine cancer

		Recurrent	Previously unirradiated	Imaging modality	ISBT[a]+EBRT[b]	ISBT dose	EBRT dose	Local control rate	Overall survival rate	Cause-specific survival rate	Severe complication
		Primary (no.)	Reirradiation (no.)	During implantation	ISBT alone (no.)	(Gy)	(Gy)	(%)	(%)	(%)	(%)
2D dose calculation											
Corn et al.	LDR	5	NA	Laparoscope	3	25–33.6	45–50.4	60	40	40	0
1995 [63]		0		CT	2	40–50	–				
				MRI							
Charra et al.	LDR	78	49	XP	34	15–55	20–60	70	56	62	10
1998 [54]		0	29		44	25–75	–				
Tewari et al.	LDR	30	17	XP		Mean 25.5	Mean 48	77		65	17
1999 [64]		0	13	Laparoscope							
Nag et al.	LDR	13	13	XP	11	18–35	45–50.4	100		77	15
2002 [55]		0	0	CT	2	40–50	–				
Badakh et al.	HDR	22	22	NA	0	12–45	–	NA	About 35 (2 years)		18
2009 [65]		0	0		22				(From figure)		
3D dose calculation											
Jensen et al.	PDR	22	32	CT	32	30	46	74	63		29
1998 [58]		12	2		2	NA	–	(CR)			
Eisburch et al.	LDR	14	20	Laparoscope		Total 69–87	40–45	55	40	40	18
1998 [66]		6	0	CT		70–80	–				
Popowski et al.	PDR	6	5	MRI	6	10–35	20–60	83	83	83	17
2000 [67]		0	1		0						

Viswanathan et al.	LDR	10	9	CT	9	HDR: median 24	30.6–50.4	NA	NA	NA	10
2006 [68]	HDR	0	1	MRI	1	LDR: median 35					
Weitmann et al.	PDR	23	12	US	8	14–21	43.2–50	47	38	43	9
2006 [56]	HDR	0	11	CT	15	28–42	–				
Beriwal et al.	HDR	17	25	CT	28	18.75–21.3	24–50.4	76 (primary)	70		7
2012 [69]		13	5		2			85 (recurrent)			
Thibault et al.	HDR	9	NA	CT	43	18–35	40–50.4	87 (primary)	86 (primary)		28
2012 [11]		34		MRI	0			45 (recurrent)	17 (recurrent)		
Lee et al.	LDR	6	31	CT	38	18–35	45–50.4	96 (unirradiated)	80 (unirradiated)		9
2013 [59]	HDR	38	13	MRI	6	12.5–48	45–50.4	61 (reirradiation)	55 (reirradiation)		
Mabuchi et al.	HDR	52	0	CT	0	42	–	77	About 50% (3 years)		25
2014 [57]		0	52		52			(CR)	(From figure)		
Mahantshetty et al.	HDR	94	113	CT	113	12–25	40–60	73 (cervical cancer: inadvertent surgery)	64 (cervical cancer: inadvertent surgery)		20.5
2014 [70]		19	0		0			70 (vault cancer)	64 (vault cancer)		
								84 (vaginal cancer)	56 (vaginal cancer)		

(continued)

Table 8.2 (continued)

		Recurrent	Previously unirradiated	Imaging modality	ISBT[a]+EBRT[b]	ISBT dose	EBRT dose	Local control rate	Overall survival rate	Cause-specific survival rate	Severe complication
		Primary (no.)	Reirradiation (no.)	During implantation	ISBT alone (no.)	(Gy)	(Gy)	(%)	(%)	(%)	(%)
Mahantshetty et al.	HDR	30	0	CT (for ISBT)	0	31.5–54.4 (EQD2)	–	44	52		23
2014 [71]			30	MRI (for ICISBT)	30						
Murakami et al.	HDR	26	16	CT	21	Single dose: 2.5–6	0–50	51	57		7
2016 [60]			10		5	Fraction size: 3–20					
Baek et al.	HDR	43	39	CT	17	30–60	30–50	78	84		16
2016 [62]			4	MRI	26	48–60	–				
Yoshida et al.	HDR	56	35	US	20	27–36	30–50	75	68		20
2015 [61]		0	21		36	42–54	–				

[a]Interstitial brachytherapy
[b]External beam radiotherapy

patients without 3D dose calculation. The 13 patients did not have previous irradiation, the tumor sizes were ≤2 and 2–4 cm for 7 and 3 patients, respectively, and the interval from hysterectomy to recurrence was more than 12 months for 9 patients. Because the tumor size [54, 56, 57] and recurrence interval [56–58] were important prognostic factors, the patient selection was biased toward a better outcome.

In contrast, Weitmann et al. [56] reported an LC rate of 47% for 23 patients, although 3D dose calculation had been performed. The authors of that study treated many higher-risk patients, 11 of whom had previous irradiation. Additionally, 8 had larger tumor sizes (35%), and 12 (52%) had shorter recurrence intervals.

Severe late complication rate was 0–29% (Table 8.2). We must take care for the reirradiation patients. Lee et al. reported that four patients (9%) experienced grade 3 late toxicity, including 3/13 patients (23%) treated in the reirradiation setting and 1/31 (3%) with no prior RT [59].

There are not so many reports about dose relationship between DVH and clinical result [56, 60, 61]. Weitmann et al. reported that a prescribed total dose of higher than 64 Gy with a coverage index higher than 0.8 yielded a better treatment outcome [56]. Murakami et al. reported that D90(CTV) was more than 65 Gy and single-fraction doses was more than 5 Gy as favorable factors of local control [60].

8.2.7 Experience of Osaka National Hospital and Osaka Medical College

We analyzed 56 patients to evaluate the effectiveness of image-guided HDR-ISBT for pelvic recurrence of uterine cancer [61]. The 3-year LC and OS were 75% and 68%. Pre-ISBT treatments included radical hysterectomy for 35 patients (Group A), radical hysterectomy with postoperative radiotherapy for 8 patients (Group B), and radical radiotherapy for 13 patients (Group C). The 3-year LC were 85%, 75%, and 46% for groups A, B, and C, respectively ($p = 0.017$).

The 3-year LC were 70% and 79% for a D90(CTV) of ≤85.7 and >85.7 Gy. The 3-year OS were 63% and 71% for a D90 (CTV) of ≤85.7 and >85.7 Gy. The D90(CTV) was 81.3 ± 8.1 Gy for patients with local central recurrence and 90.3 ± 23.6 Gy for all other patients ($p = 0.14$). The 3-year LC were 65% and 85% for a D100(CTV) of ≤67.1 and >67.1 Gy ($p = 0.098$). The 3-year OS were 67% and 69% for a D100 (CTV) of ≤67.1 and >67.1 Gy. The D100 (CTV) was 58.1 ± 15 Gy for patients with central recurrence and 70.3 ± 20.4 Gy for all other patients ($p = 0.07$). A total of 13 late complications of grades 3–5 occurred in 11 patients (20%).

Osaka group also reported 43 isolated vaginal recurrences of endometrial cancer including our 11 patients [62]. Thirty-four of 43 patients received ISBT. The treatment results for all patients were 78% and 84% for LC and OS.

We also investigated 48 patients of postoperative local recurrent uterine cancer and analyzed the treatment result depending on histology [72]. The 4-year LC and OS were 78% and 67% for all patients. The 4-year OS were 73%, 65%, 100%, and 20% for squamous cell carcinoma, endometrial adenocarcinoma, mucinous adenocarcinoma, and the others ($p = 0.06$). Grade ≥ 3 late complications occurred in 11 patients (23%). Ileus was only observed for patients receiving EBRT.

The median caudal needle applicator displacement was 3 mm (range, −4 to 16 mm) at the first 21 h, 2 mm (range, −7 to 19 mm) at 45 h, 4 mm (range, −2 to 23 mm) at 69 h, and 5 mm (range, −2 to 26 mm) at 93 h. Two of eight patients showed more than 10% reduction in D90(CTV) values [45].

8.3 Vaginal Cancer

8.3.1 Introduction

Vaginal cancer is also not suitable for curative organ-sparing surgery. And so, ISBT also play an important role.

8.3.2 The Indication of ISBT

ABS consensus guidelines showed the indication of ISBT showing above (see Sect. 2) [52].

Fine et al. reported their treatment indication [73]. For stage II–IV, they treated ISBT with EBRT (40–45 Gy). For stage I, they selected ICBT (15–20 Gy) with EBRT (45–50 Gy) if no palpable disease remained. And, ISBT (20–25 Gy) with EBRT (45–50 Gy) was selected if palpable disease remained.

8.3.3 Implantation and Treatment Planning

ABS consensus guidelines also showed the implantation technique of ISBT (see Sect. 2) showing below [52].

The dose should be optimized to the CTV with the goals of achieving a D90(CTV) ≥100% of the prescribed dose and minimizing the dose to normal organs.

8.3.4 Experience of Osaka National Hospital and Osaka Medical College

Implantation technique was almost same as our technique showing above (Fig. 8.2a–j).

For the patients who had no irradiation history, the CTV is the GTV with 1 cm of margin around the GTV. Entire circumference of the vagina on the GTV level is also included in the CTV. If the tumor is located close to the cervix, the mucosal surface of the cervix is also included to the CTV. For the patients who had irradiation history, the CTV is equal to the GTV.

There is a problem about CTV definition of vaginal cancer. If the tumor is confined to the vagina but located very close to the uterine cervix, the CTV definition

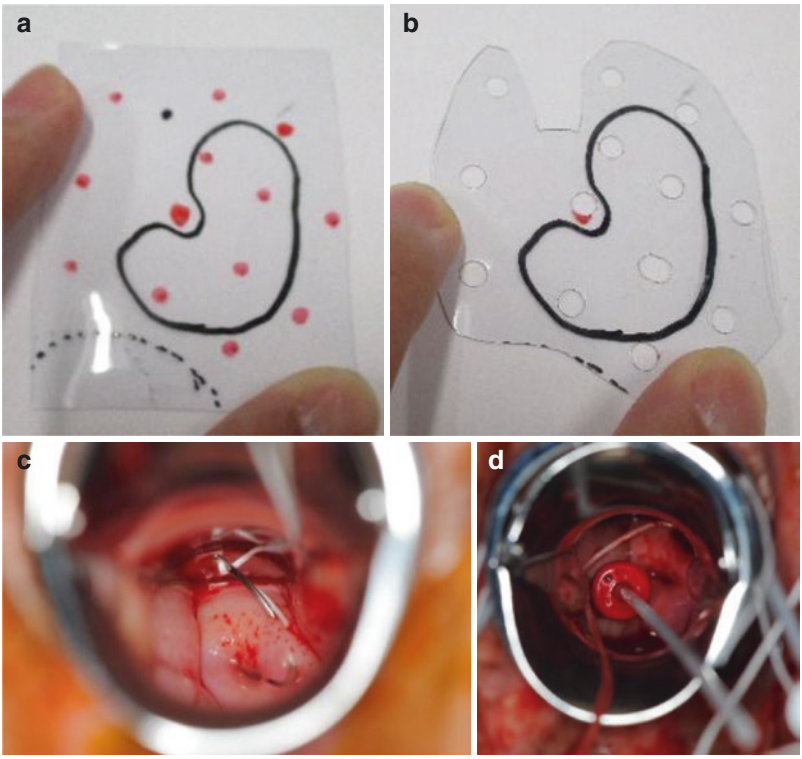

Fig. 8.2 (**a**, **b**) A photograph of a handmade vinyl template for a vaginal cancer patient. The maximum tumor contour was drawn by black line. The urethra (black dot) and the rectal contour (black-dotted line) were also drawn. After we decided the implant points (red dots), implantation points were punched. (**c**) We made a suture needle with silk thread to the uterine cervix to fix the tandem needle and handmade silicone cylinder. (**d**) Flexible applicator needle with button stopper was inserted into the uterine cavity as a tandem needle. (**e**, **f**) Handmade silicone cylinder was inserted into the vagina and followed behind the tandem needle. The cylinder was sutured by the silk thread. From this manipulation, the complex of the tandem, button stopper, and cylinder is fixed to the uterine cervix in order to reduce the risk of applicator displacement. Although we usually used silicone cylinder with 5 holes, we used smaller cylinder because the patient had large tumor in the vaginal cavity. (**g**) A photograph of sterilization tray for implantation. From left side, we put the button stoppers with silk thread, flexible applicator needle with button stopper with metal obturator, obturators and fiducial marker implantation device (we previously used as an Au-grain implantation device). (**h**) A photograph of flexible applicator needle with button stopper with metal obturator. (**i**) A photograph of the vinyl template with flexible applicator needle complex. (**j**) A photograph of the patient's perineum just after the implantation. (**k**) A photograph of the patient's planning computed tomography image. Applicator needles were shown as red dots. The clinical target volume (CTV) was delineated (red-dotted line), and the urethra is also delineated (blue-dotted line). The silicone cylinder was clearly visualized. (**l**) Planning CT image of the same patient as **k**. Isodose curve was shown on the CT image. The CTV was covered by 100% prescribed isodose line (red line). We tried to reduce the urethral dose (green line, 110% prescribed isodose line; pink line, 120% prescribed isodose line)

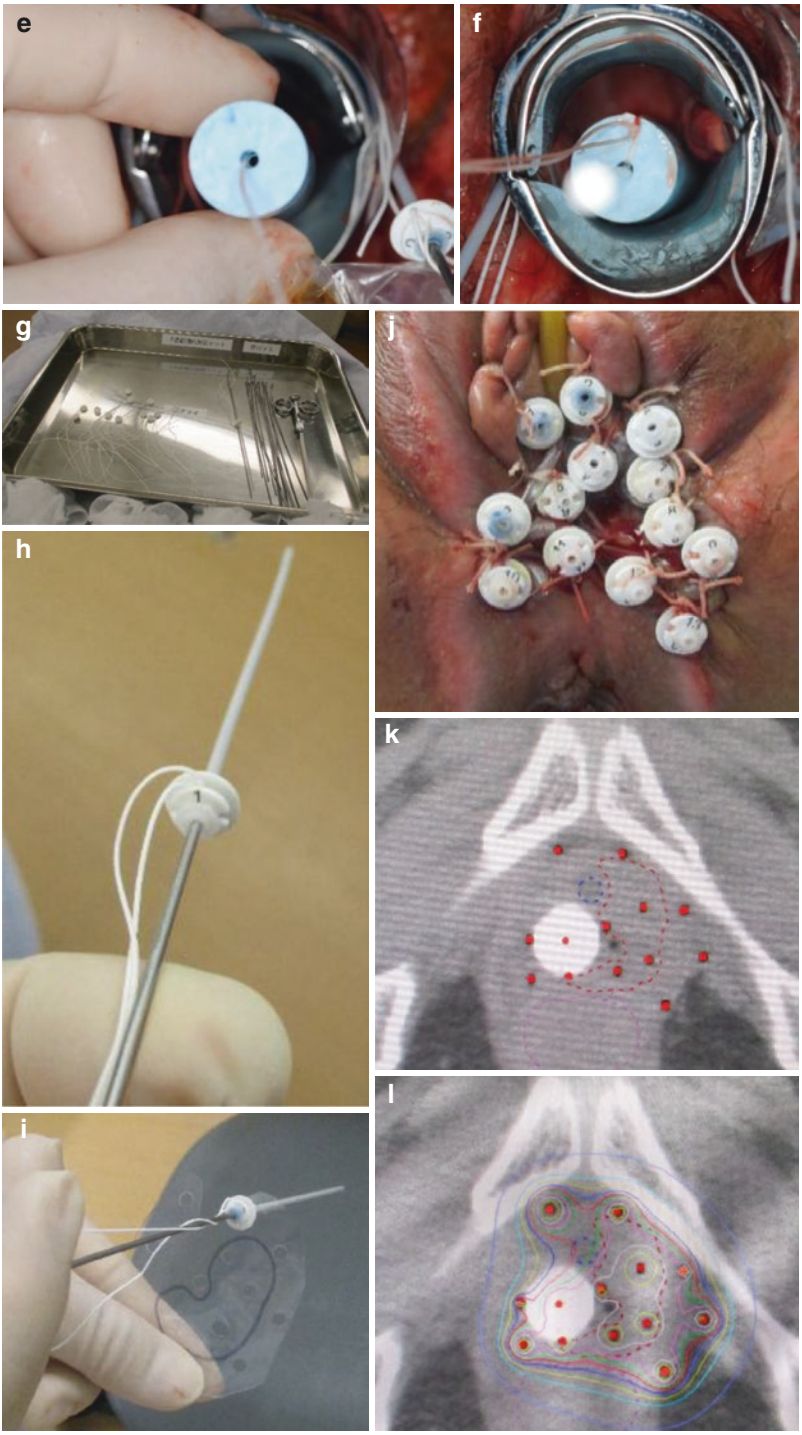

Fig. 8.2 (continued)

was shown above. However, if the tumor will grow and infiltrate into the uterine cervix, the disease changes to uterine cervical cancer. And so, the CTV of the tumor became larger (the GTV plus the normal uterine cervix) even if the cervical infiltration was very little. In such case, we always wonder how we should do it. We must define it depending on each patient's clinical situation.

The median single-fraction planning aim dose of HDR-ISBT was 6 Gy, and the median total planning aim doses were 30 Gy in five fractions for ISBT combined with 30–40 Gy of WPRT. We reduced the planning aim doses to 25 Gy in five fractions if the dose of WPRT is increased to 50 Gy.

8.3.5 External Beam Radiotherapy

EBRT should be combined for previously nonirradiated cases. WPRT of 45–50.4 Gy in 25–28 fractions were common. CSRT is combined in some countries. However, EBRT is not combined for the patients who had previous irradiation history or poor-risk diseases.

8.3.6 Treatment Results

8.3.6.1 LDR Brachytherapy

Fine et al. reported their treatment result of 55 patients [73]. The median total doses of ICBT/ISBT and EBRT were 70, 70.4, 90, and 51.75 Gy for stage I through IV. Local failure was observed 25%, 33%, and 62% for the administered dose of >75, 60–75, and <60 Gy. Eight of 55 patients showed severe complication.

Frank et al. reported 193 patients treated with the combination of EBRT and brachytherapy (including 32 patients treated with ISBT) [74]. The prescribed mean doses were 76 Gy (range, 65–90 Gy). Five-year pelvic disease control rates were 86% for stage I, 84% for stage II, and 71% for combined stages III and IVA. The 5- and 10-year risk of grade 3–4 (CTCAE ver.3.0) complications was 10% and 17%.

8.3.6.2 HDR Brachytherapy

There are some reports treated by HDR-ISBT [75–78]. The outcomes of these reports are 68.8–71% and 39.3–83% for LC and OS. Late complication rates are of 3–16.7%.

8.3.7 Experience of Osaka National Hospital and Osaka Medical College

Kanayama et al. reported the treatment results of 49 patients for Osaka group including our 12 patients [78]. They showed that 3-year locoregional control and OS were 71% and 83%. Late complication was observed 12% and 0% of grades 3 and 4–5 complication (CTCAE ver. 4.0).

8.4 Follow-Up: The Importance of Vaginal Washing

To keep better condition of vaginal mucosa, frequent vaginal washing during and after ISBT is important. Yellowish necrotic tissue appeared from tumor surface at first, and it also spreads to the normal mucosal surface of uterine cervix/vaginal. This yellowish tissue causes an adhesion. And so, we performed vaginal washing frequently and gently peeled the tissue to prevent adhesion (Fig. 8.3a–e). If the interval of follow-up is more than 2–3 weeks within 3–6 months after ISBT, vaginal

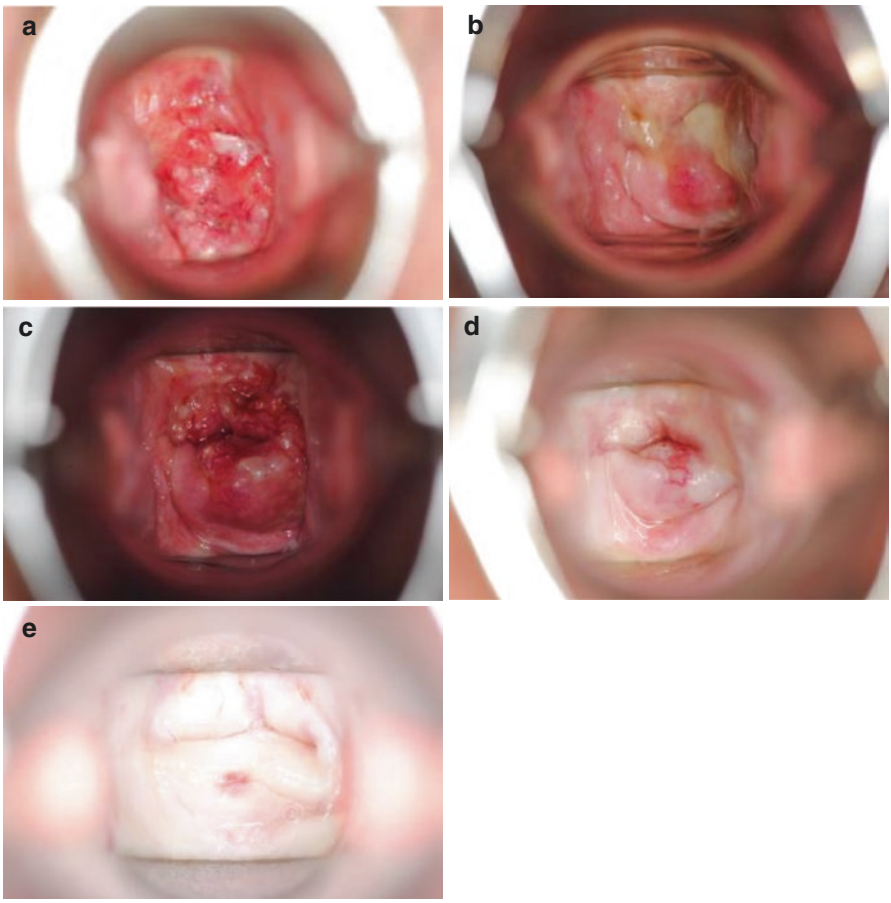

Fig. 8.3 (**a**) A photograph of pretreatment tumor status of the patient who had uterine cervical cancer histologically proven as squamous cell carcinoma categorized as T3b. (**b**) Photograph of 10 days after ISBT. Yellowish necrotic tissue was covered on the tumor surface. (**c**) Photograph of the same day as **b**. Necrotic tissue was peeled, and tumor surface was appeared. (**d**) Photograph of 357 days after ISBT. The uterine cervix changed pale by high doses of radiation. However, almost all mucosa surface was free from adhesion, and we could observe uterine cervical surface clearly. (**e**) Photograph of 2 years and 2 months after ISBT. The uterine cervix further changed pale. Fortunately, adhesive change did not progress

adhesion often occurred. In such case, we should peel off the adhered mucosa by manual and Cusco speculum very gently. This manipulation is useful for the patients who have a possibility to do sexual intercourse. Against it, we must take care of the patients if they had irradiation history. Because such patients have higher risk of severe complication such as fistula formation, we must manipulate it carefully. Rough manipulation may cause a mucosal injury, and it may develop infection and radiation necrosis.

Conclusion

Although ISBT is a relatively invasive method compared with ICBT and ICISBT, ISBT has an advantage that can achieve a better tumor coverage without increasing the doses for OARs, especially for large tumor. Recent technical progress such as our ambulatory technique will make it more comfortable method, and image-guided planning will improve the treatment outcome.

Applicator displacement is a certainly problem for pure ISBT. However, daily measurement of the distance of displacement will lead to adequate corrective action.

Finally, we are trying to spread the treatment indication of ISBT. With the advent of imaging modality, applicator needle implantation to deeper-seated tumor becomes safer and easier. For example, we performed an implantation to internal iliac lymph node by the guidance of color Doppler TRUS and virtual implantation [79]. Using Doppler TRUS, we could implant to the internal lymph node tumor while avoiding injury of nearest large vessel. Virtual implantation using preimplantation CT with template showed us the adequate needle length, adequate needle entry point of the skin.

If treatment isotope source will become thinner and smaller, thinner applicator may be developed, and it will make implantation safer. It will also lead to spread treatment indication. Anyway, we believe that ISBT is still valuable treatment modality and has potential for expansion.

References

1. Pitts HC, et al. Further report on the radium treatment of carcinoma of the cervix uteri. Am J Roentgenol. 1940;43:567–71.
2. Stevenson WC. Preliminary clinical report on a new and economical method of radium therapy by means of emanation needles. Br Med J. 1914;2:9–10.
3. Green A, et al. New techniques in radium and radon therapy. J Fac Radiol. 1951;2:206–33.
4. Morton JL, et al. Individualized interstitial irradiation of cancer of the uterine cervix using cobalt 60 in needles, inserted through a lucite template. Am J Roentgenol Radium Ther. 1951;65:737–47.
5. Martinez A, et al. A multiple-site perineal applicator (MUPIT) for treatment of prostatic, anorectal, and gynecologic malignancies. Int J Radiat Oncol Biol Phys. 1984;10:297–305.
6. Syed AMN, et al. Technique of after-loading interstitial implants. Radiol Clin. 1977;46:458–75.
7. Nakano T, et al. Clinical evaluation of the MR imaging for radiotherapy of uterine carcinoma. Nihon Igaku Hoshasen Gakkai Zasshi. 1987;47:1181–8.

8. Hatano K, et al. MRI-based intracavitary high dose rate brachytherapy for carcinoma of the uterine cervix: is the 'Manchester' system golden standard in the era of 3-D treatment planning and MRI? Int J Radiat Oncol Biol Phys. 1998;42(Suppl):316.
9. Pötter R, et al. Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. Radiother Oncol. 2007;83:148–55.
10. Beriwal S, et al. High-dose-rate interstitial brachytherapy for gynecologic malignancies. Brachytherapy. 2006;5:218–22.
11. Thibault I, et al. Inverse-planned gynecologic high-dose-rate interstitial brachytherapy: clinical outcomes and dose-volume histogram analysis. Brachytherapy. 2012;11:181–91.
12. Yoshida K, et al. A dose–volume analysis of magnetic resonance imaging-aided high-dose-rate image-based interstitial brachytherapy for uterine cervical cancer. Int J Radiat Oncol Biol Phys. 2010;77:765–72.
13. Terahara A, et al. Dose-volume histogram analysis of high dose rate intracavitary brachytherapy for uterine cervix cancer. Int J Radiat Oncol Biol Phys. 1996;35:549–54.
14. Shigematsu Y, et al. Treatment of carcinoma of the uterine cervix by remotely controlled afterloading intracavitary radiotherapy with high-dose rate: a comparative study with a low-dose rate system. Int J Radiat Oncol Biol Phys. 1983;9:351–6.
15. Teshima T, et al. High-dose rate and low-dose rate intracavitary therapy for carcinoma of the uterine cervix. Final results of Osaka University Hospital. Cancer. 1993;72:2409–14.
16. Yoshida K, et al. New ambulatory implant technique of high-dose-rate interstitial brachytherapy for prostate cancer. Radiat Med. 2006;24:595–9.
17. Kuipers T, et al. HDR brachytherapy applied to cervical carcinoma with moderate lateral expansion: modified principles of treatment. Radiother Oncol. 2001;58:25–30.
18. Dimopoulos JC, et al. The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: clinical feasibility and preliminary results. Int J Radiat Oncol Biol Phys. 2006;66:83–90.
19. Kirisits C, et al. The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: design, application, treatment planning and dosimetric results. Int J Radiat Oncol Biol Phys. 2006;65:624–30.
20. Nag S, et al. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. Int J Radiat Oncol Biol Phys. 2000;48:201–11.
21. Lee LJ, et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part III: Low-dose-rate and pulsed-dose-rate brachytherapy. Brachytherapy. 2012;11:53–7.
22. Yoshida K, et al. Simulation analysis of optimized brachytherapy for uterine cervical cancer: can we select the best brachytherapy modality depending on tumor size? Brachytherapy. 2016;15:57–64.
23. Liu ZS, et al. Computed tomography-guided interstitial brachytherapy for locally advanced cervical cancer: introduction of the technique and a comparison of dosimetry with conventional intracavitary brachytherapy. Int J Gynecol Cancer. 2017;27:768–75.
24. Viswanatha AN, et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: General principles. Brachytherapy. 2012;11:33–46.
25. Sharma DN, et al. Use of transrectal ultrasound for high dose rate interstitial brachytherapy for patients of carcinoma of uterine cervix. J Gynecol Oncol. 2010;21:12–7.
26. Erickson B, et al. Interstitial implantation of gynecologic malignancies. J Surg Oncol. 1997;66:285–95.
27. Viswanatha AN, et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: High-dose-rate brachytherapy. Brachytherapy. 2012;11:47–52.
28. Haie-Meder C, et al. Gynaecological (GYN) GEC-ESTRO Working Group. Recommendations from gynaecological (GYN) GEC-ESTRO working group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Oncol. 2005;74:235–45.

29. Pötter R, et al. Recommendations from gynecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol. 2006;78:67–77.
30. Yoshida K, et al. The usefulness of metal markers for CTV-based dose prescription in high-dose-rate interstitial brachytherapy. J Jpn Soc Ther Radiol Oncol. 2002;13:253–60.
31. Syed AMN, et al. Long-term results of low-dose-rate interstitial-intracavitary brachytherapy in the treatment of carcinoma of the cervix. Int J Radiat Oncol Biol Phys. 2002;54:67–78.
32. Demanes DJ, et al. High dose rate transperineal interstitial brachytherapy for cervical cancer: high pelvic control and low complication rates. Int J Radiat Oncol Biol Phys. 1999;45:105–12.
33. Isohashi F, et al. High-dose-rate interstitial brachytherapy for previously untreated cervical carcinoma. Brachytherapy. 2009;8:234–9.
34. Prempree T. Parametrial implant in Stage III B cancer of the cervix. III. A five-year study. Cancer. 1983;52:748–50.
35. Gupta AK, et al. Iridium-192 transperineal interstitial brachytherapy for locally advanced or recurrent gynecological malignancies. Int J Radiat Oncol Biol Phys. 1999;43:1055–60.
36. Agrawal, et al. The role of interstitial brachytherapy using template in locally advanced gynecological malignancies. Gynecol Oncol. 2005;99:169–75.
37. Kannan N, et al. High-dose-rate interstitial computed tomographybased brachytherapy for the treatment of cervical cancer: early results. Brachytherapy. 2012;11:408–12.
38. Amsbaugh MJ, et al. Computed tomography-planned interstitial brachytherapy for locally advanced gynecologic cancer: outcomes and dosimetric predictors of urinary toxicity. Brachytherapy. 2016;15:49–56.
39. Kamran SC, et al. Comparison of outcomes for MR-guided versus CT-guided high-dose-rate interstitial brachytherapy in women with locally advanced carcinoma of the cervix. Gynecol Oncol. 2017;145:284–90.
40. Yoshida K, et al. Preliminary results of MRI-assisted high-dose-rate interstitial brachytherapy for uterine cervical cancer. Brachytherapy. 2015;14:1–8.
41. Martinez AA, et al. Phase II prospective study of the use of conformal high-dose-rate brachytherapy as monotherapy for the treatment of favorable stage prostate cancer: a feasibility report. Int J Radiat Oncol Biol Phys. 2001;49:61–9.
42. Damore SJ, et al. Needle displacement during HDR brachytherapy in the treatment of prostate cancer. Int J Radiat Oncol Biol Phys. 2000;46:1205–11.
43. Mikami M, et al. Daily computed tomography measurement of needle applicator displacement during high-dose-rate interstitial brachytherapy for previously untreated uterine cervical cancer. Brachytherapy. 2011;10:318–24.
44. Yoshida K, et al. Needle applicator displacement during high-dose-rate interstitial brachytherapy for prostate cancer. Brachytherapy. 2010;9:36–41.
45. Yoshida K, et al. Daily CT measurement of needle applicator displacement during multifractionated high-dose-rate interstitial brachytherapy for postoperative recurrent uterine cancer. J Radiat Res. 2012;53:295–300.
46. Shukla P, et al. Quality assurance of multifractionated pelvic interstitial brachytherapy for postoperative recurrences of cervical cancers: a prospective study. Int J Radiat Oncol Biol Phys. 2012;82:617–22.
47. Chopra S, et al. Evaluation of quality indices during multifractionated pelvic interstitial brachytherapy for cervical cancer. Brachytherapy. 2013;12:156–61.
48. Pinnaduwage DS, et al. A dosimetric evaluation of using a single treatment plan for multiple treatment fractions within a given applicator insertion in gynecologic brachytherapy. Brachytherapy. 2013;12:487–94.
49. Rey F, et al. Dosimetric impact of interfraction catheter movement and organ motion on MRI/CT guided HDR interstitial brachytherapy for gynecologic cancer. Radiother Oncol. 2013;107:112–6.
50. Damato AL, et al. Characterization of implant displacement and deformation in gynecologic interstitial brachytherapy. Brachytherapy. 2014;13:100–9.

51. Onoe T, et al. High-dose-rate interstitial brachytherapy for gynecologic malignancies—dosimetric changes during treatment period. J Radiat Res. 2012;53:295–300.
52. Beriwal S, et al. American Brachytherapy Society consensus guidelines for interstitial brachytherapy for vaginal cancer. Brachytherapy. 2012;11:68–75.
53. Ito H, et al. Radiotherapy for centrally recurrent cervical cancer of the vaginal stump following hysterectomy. Gynecol Oncol. 1997;67:154–61.
54. Charra C, et al. Outcome of treatment of upper third vaginal recurrences of cervical and endometrial carcinomas with interstitial brachytherapy. Int J Radiat Oncol Biol Phys. 1998;40:421–6.
55. Nag S, et al. Interstitial brachytherapy for salvage treatment of vaginal recurrences in previously unirradiated endometrial cancer patients. Int J Radiat Oncol Biol Phys. 2002;54:1153–9.
56. Weitmann HD, et al. Ultrasound-guided interstitial brachytherapy in the treatment of advanced vaginal recurrences from cervical and endometrial carcinoma. Strahlenther Onkol. 2006;18:86–95.
57. Mabuchi S, et al. Reirradiation using high-dose-rate interstitial brachytherapy for locally recurrent cervical cancer. Int J Gynecol Cancer. 2014;24:141–8.
58. Jensen PT, et al. Pulsed dose rate (PDR) brachytherapy as salvage treatment of locally advanced or recurrent gynecologic cancer. Int J Radiat Oncol Biol Phys. 1998;42:1041–7.
59. Lee LJ, et al. Clinical outcomes following 3D image-guided brachytherapy for vaginal recurrence of endometrial cancer. Gynecol Oncol. 2013;131:586–92.
60. Murakami N, et al. Salvage high-dose-rate interstitial brachytherapy for pelvic recurrent cervical carcinoma after hysterectomy. Anticancer Res. 2016;36:2413–21.
61. Yoshida K, et al. Treatment results of image-guided high-dose-rate interstitial brachytherapy for pelvic recurrence of uterine cancer. Brachytherapy. 2015;14:440–8.
62. Baek S, et al. Salvage high-dose-rate brachytherapy for isolated vaginal recurrence of endometrial cancer. Brachytherapy. 2016;15:812–6.
63. Corn BW, et al. Improved treatment planning for the Syed-Neblett template using endorectal-coil magnetic resonance and intraoperative (laparotomy/laparoscopy) guidance: a new integrated technique for hysterectomized women with vaginal tumors. Gynecol Oncol. 1995;56:255–61.
64. Tewari K, et al. Interstitial brachytherapy for vaginal recurrences of endometrial carcinoma. Gynecol Oncol. 1999;74:416–22.
65. Badakh DK, et al. Reirradiation with high-dose-rate remote afterloading brachytherapy implant in patients with locally recurrent or residual cervical carcinoma. J Cancer Res Ther. 2009;5:24–30.
66. Eisbruch A, et al. Customized gynecologic interstitial implants: CT-based planning, dose evaluation, and optimization aided by laparotomy. Int J Radiat Oncol Biol Phys. 1998;40:1087–93.
67. Popowski Y, et al. Open magnetic resonance imaging using titanium-zirconium needles: improved accuracy for interstitial brachytherapy implants? Int J Radiat Oncol Biol Phys. 2000;47:759–65.
68. Viswanathan AN, et al. Magnetic resonance-guided interstitial therapy for vaginal recurrence of endometrial cancer. Int J Radiat Oncol Biol Phys. 2006;66:91–9.
69. Beriwal S, et al. Three-dimensional image based high-dose-rate interstitial brachytherapy for vaginal cancer. Brachytherapy. 2012;11:176–80.
70. Mahantshetty U, et al. Template-based high-dose-rate interstitial brachytherapy in gynecologic cancers: a single institutional experience. Brachytherapy. 2014;13:337–42.
71. Mahantshetty U, et al. Reirradiation using high-dose-rate brachytherapy in recurrent carcinoma of uterine cervix. Brachytherapy. 2014;13:548–53.
72. Yoshida K, et al. HDR image-guided interstitial brachytherapy for postoperative local recurrent uterine cancer. Radiother Oncol. 2017;123(Suppl 1):S518–9.
73. Fine BA, et al. The curative potential of radiation therapy in the treatment of primary vaginal carcinoma. Am J Clin Oncol. 1996;19:39–44.
74. Frank SJ, et al. Definitive radiation therapy for squamous cell carcinoma of the vagina. Int J Radiat Oncol Biol Phys. 2005;62:138–47.

75. Mock U, et al. High-dose-rate (HDR) brachytherapy with or without external beam radiotherapy in the treatment of primary vaginal carcinoma: long-term results and side effects. Int J Radiat Oncol Biol Phys. 2003;56:950–7.
76. Kushner DM, et al. High dose rate 192Ir afterloading brachytherapy for cancer of the vagina. Br J Radiol. 2003;76:719–25.
77. Murakami N, et al. Radiation therapy for primary vaginal carcinoma. J Radiat Res. 2013;54:931–7.
78. Kanayama N, et al. Definitive radiotherapy for primary vaginal cancer: correlation between treatment patterns and recurrence rate. J Radiat Res. 2015;56:346–53.
79. Yoshida K, et al. Interstitial brachytherapy using virtual planning and Doppler transrectal ultrasonography guidance for internal iliac lymph node metastasis. J Radiat Res. 2012;53:154–8.

Asian Cooperation and Global Trends in Brachytherapy for Cervical Cancer

9

Shingo Kato

Abstract

Brachytherapy plays an important role in the treatment of cervical cancer. Japan is a pioneer of high-dose-rate brachytherapy for cervical cancer and has made great contributions in the establishment of optimal therapy for this disease over the course of five decades. Japanese institutions have recently conducted several clinical studies of three-dimensional image-guided brachytherapy. Based on these experiences, several Japanese institutions have conducted international cooperative activities on radiotherapy for cervical cancer with other Asian countries for over 20 years.

Keywords

Cervical cancer · High-dose-rate brachytherapy · Three-dimensional image-guided brachytherapy · International cooperation · FNCA · IAEA/RCA

9.1 Introduction

The combination of external beam radiotherapy (EBRT) to the pelvis and brachytherapy (BT) to cervical tumors is the standard treatment for uterine cervical cancer. Traditionally, cervical cancer was treated with low-dose rate BT (LDR-BT) using Ra-226 or Cs-137. In 1964, Henschke et al. [1] and O'Connell et al. [2] reported on a high-dose rate (HDR) remote afterloading system (RALS)

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using Co-60. In Japan, an HDR-RALS was installed at the National Institute of Radiological Sciences (NIRS) in 1968. Since then, as pioneers of HDR-BT, several Japanese institutions have conducted clinical studies to establish the optimal dose and fractionation schedule of HDR-BT and appropriate combinations of EBRT and HDR-BT for treating cervical cancer. Following several clinical studies [3, 4], treatment guidelines of radiotherapy (RT) for cervical cancer were established in Japan in 1987 [5]. The NIRS has also conducted long-term follow-up studies to evaluate the efficacy and late toxicities of Japanese HDR-BT protocols for more than 20 years [6, 7]. Clinical studies comparing the outcomes of LDR- and HDR-BT have also been conducted by Japanese institutions [8, 9].

Based on these experiences, several Japanese institutions have been conducting international cooperative activities on RT for cervical cancer with other Asian countries, including the radiation oncology project of the Forum for Nuclear Cooperation in Asia (FNCA) and the International Atomic Energy Agency/Regional Cooperative Agreement for research, development, and training related to nuclear science and technology for Asia and Pacific (IAEA/RCA). These activities are briefly introduced in this chapter.

9.2 FNCA Radiation Oncology Project

The FNCA is a Japan-led cooperative framework for the peaceful and safe use of nuclear science and technology in Asia. Ten projects are currently ongoing under this framework, and the radiation oncology project is one of these. The project was launched in 1993, and 11 countries have been participating in the project recently, including Bangladesh, China, Indonesia, Japan, Kazakhstan, Korea, Malaysia, Mongolia, the Philippines, Thailand, and Vietnam. The project aims to establish optimal treatment protocols for RT and chemotherapy for predominant cancers in Asia, to improve the quality of RT in FNCA member countries, and to improve treatment outcomes for predominant cancers in Asia. Several activities are underway to this end, including international multi-institutional clinical studies of RT or chemoradiotherapy (CRT) for various cancers in Asia. Radiation oncologists involved in the project have organized a clinical study group and conducted clinical studies of RT or CRT for cervical cancer, nasopharyngeal cancer, and breast cancer. Another activity is aimed at securing physical quality assurance and quality control (QA/QC) of RT in Asia. Medical physicists involved in the project have conducted QA/QC audits of EBRT and BT at institutions participating in the clinical studies [10] (Fig. 9.1).

Japan has been playing a leading role in the project: (1) a Japanese delegate has been designated the project leader; (2) a number of Japanese radiation oncologists have been key members of FNCA clinical studies; (3) the NIRS has been the data center for all FNCA clinical studies; and (4) a number of Japanese medical physicists are key members involved in the QA/QC activities.

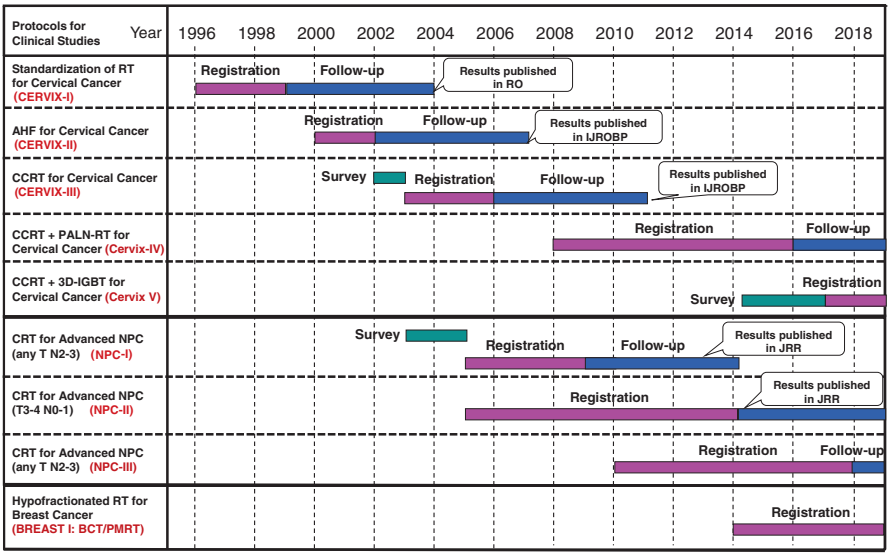
Fig. 9.1 Photograph of the FNCA workshop on radiation oncology held in Surabaya, Indonesia, in 2016, and the FNCA QA/QC audit of external beam radiotherapy

9.3 International Clinical Studies for Cervical Cancer in the FNCA Project

Cervical cancer is one of the most common types of cancer in Southeast Asia [11]. The mortality rate associated with the disease in the region is high, as many patients present at a relatively advanced stage of disease. Thus, developing and establishing effective treatment strategies against the disease are major public welfare issues. Since 1995, the FNCA radiation oncology project has been conducting international multi-institutional clinical studies to improve the treatment outcomes of cervical cancer. Table 9.1 provides a summary of past and ongoing clinical studies that have been conducted under the project.

When the project began, RT standards for cervical cancer varied widely across FNCA countries, given their diverse technical, cultural, and socioeconomic backgrounds. Several dose and fractionation schedules were being used for BT, and there was a lack of consensus regarding the optimal dose and fractionation schedule for BT and EBRT and BT combinations. Against this backdrop, the first clinical study (Cervix-I, 1996–2003) aimed to standardize RT for cervical cancer among FNCA countries. Treatment protocols for the combination of EBRT and either HDR- or LDR-BT for locally advanced cervical cancer were developed and standardized based on Japanese protocols [5–7], and patients with stage IIIB cervical

Table 9.1 International multi-institutional clinical studies in Asia under the FNCA Framework



RT radiotherapy, *AHF* accelerated hyperfractionation, *CCRT* concurrent chemoradiotherapy, *PALN* paraaortic lymph node, *3D-IGBT* three-dimensional image-guided brachytherapy, *NPC* nasopharyngeal carcinoma, *RO* radiotherapy and oncology, *IJROBP* International Journal of Radiation Oncology, Biology, and Physics, *JRR* Journal of Radiation Research

cancer were treated according to these protocols. The results of the study suggested that the standardized protocols provided favorable treatment outcomes with acceptable rates of late complications for Asian women with locally advanced cervical cancer [12]. This study was the first international multi-institutional clinical study of RT for cervical cancer conducted in both high- and low/middle-income countries in Asia.

In the second clinical study (Cervix-II, 1999–2006), the study group developed a protocol for accelerated hyperfractionated (AHF) RT to the pelvis and evaluated its toxicity and efficacy, given the difficulty of performing CRT in some of the low-income countries that suffer from technical and/or socioeconomic constraints. Patients with stage IIB or IIIB cervical cancer were treated with AHF RT, which consisted of 30 Gy/20 fractions/2 weeks (1.5 Gy/fraction, twice daily) of whole pelvic EBRT followed by 20 Gy/10 fractions/2 weeks (conventional 2 Gy daily fraction) of pelvic EBRT with central shielding. BT was performed in the same manner as in Cervix-I. The results of the study showed that AHF RT was feasible and achieved sufficient pelvic tumor control and overall survival without increasing severe toxicities. The study suggested that AHF RT could be an effective alternative for low/middle-income countries in Asia where CRT is not readily available [13].

Concurrent CRT has been the standard treatment for locally advanced cervical cancer based on results of several phase III clinical studies conducted in the United States [14–18] and meta-analyses [19–21]. However, whether CRT was really feasible and effective for patients in low/middle-income countries in Asia in early 2000 was a controversial issue. Therefore, in the third clinical study (Cervix-III, 2003–2010), the study group conducted a phase II study of concurrent CRT for locally advanced cervical cancer to evaluate its feasibility, safety, and efficacy in Asian countries. In the study, patients with stage IIB or IIIB cervical cancer were treated with concurrent CRT. The component of RT was similar to that of Cervix-I, and 40 mg/m^2 of cisplatin was administered weekly concurrently with EBRT. The results of the study showed that concurrent CRT achieved favorable treatment outcomes with acceptable toxicities [22]. Long-term follow-up results confirmed the feasibility and efficacy of concurrent CRT for locally advanced cervical cancer patients, even in low/middle-income countries in Asia [23]. Based on these results, the Cervix-III protocol has become a standard treatment protocol of CRT for cervical cancer in FNCA member countries.

In a fourth ongoing clinical study (Cervix-IV, 2009-), a phase II study of concurrent extended-field RT and weekly cisplatin chemotherapy is being conducted for lymph node-positive locally advanced cervical cancer to evaluate the feasibility, safety, and efficacy of the treatment.

In a fifth study scheduled to begin in 2017 (Cervix-V, 2017-), a prospective observational study of concurrent CRT with three-dimensional image-guided BT (3D-IGBT) will be conducted among FNCA countries. This study will evaluate the feasibility, safety, and efficacy of 3D-IGBT for locally advanced cervical cancer in Asian countries.

When conducting the first clinical study (i.e., Cervix-I), the study group encountered many problems and difficulties, including (1) wide differences in cultural and socioeconomic status among countries, which could have led to large imbalances in patient enrollment; (2) wide differences in cancer imaging capabilities among institutions, which could have resulted in staging error; (3) poor compliance with the treatment protocol; and (4) poor follow-up rates [12]. However, with the dedicated efforts of physicians of the study group, these problems have been solved, and the quality of the recent Cervix-III and Cervix-IV studies has improved, demonstrating excellent compliance with protocols and follow-up rates [22, 23].

Radiation oncologists and medical physicists in FNCA member countries have been trained through these numerous clinical studies. The knowledge acquired through these studies was reflected in training courses provided under IAEA/RCA radiation oncology projects. Moreover, networks established by the FNCA project have the potential to promote and strengthen further international cooperation in the field of radiation oncology in Asia, including collaborations with the South East Asia Radiation Oncology Group (SEAROG) [24] and the Federation of Asian Organization for Radiation Oncology (FARO) [25].

9.4 QA/QC Audits Within the FNCA Project

Medical physicists affiliated with the FNCA project have conducted QA/QC audits for BT and EBRT among institutions participating in FNCA clinical studies. For BT, source intensities have been measured, source activities calibrated, and source movement and positional accuracy checked at 12 institutions in eight FNCA member countries. For EBRT, 46 beams (4–18 MV) at 16 hospitals in 11 FNCA member countries were surveyed using radiophotoluminescent glass dosimeters [26]. The medical physicists also prepared handbooks for the QA/QC of EBRT and BT. FNCA QA/QC programs have contributed to improvements in the quality of RT in FNCA member countries.

9.5 IAEA/RCA Radiation Oncology Projects

The IAEA is an international organization within the United Nations that promotes the peaceful use of atomic energy and prohibits its use for any military purpose, including nuclear weapons. The RCA is an intergovernmental agreement that serves as a framework for Asian member states to intensify their collaboration through programs and projects focused on the specific shared needs of its members and to promote and coordinate cooperative research, development, and training projects in nuclear science and technology [27]. The RCA was developed in 1972 under the auspices of the IAEA. There are currently 21 member states in the RCA. Since 2000, the IAEA/RCA has implemented eight radiation oncology projects, including LDR- and HDR-BT, QA for RT, 3D-IGBT for cervical cancer, 3D conformal radiation therapy (3D-CRT), image-guided radiation therapy (IGRT), stereotactic body radiation therapy (SBRT), and intensity-modulated radiation therapy (IMRT) for predominant cancers in Asia in order to disseminate knowledge and treatment techniques to low/middle-income countries in Asia (Table 9.2). Japan has played a leading role in these efforts under the lead country coordinators Prof. Nakano of Gunma University (RAS6035-6053, 6072) and Prof. Kato of Saitama Medical University (RAS6062).

Each project had several activities, including regional training courses (RTCs), expert missions, and national training courses (NTCs). RTCs have been held several times for each project and attended by radiation oncologists and medical physicists from each member state. Lectures and hands-on training were also provided in RTCs (Fig. 9.2). Regarding expert missions, experts hired by the IAEA conducted missions aligned with the purpose of each project, such as lecturers for the RTCs. Experts also developed the curriculum for RTCs, published a technical document [28], and conducted QA audits of RT. Each country formed its national project team (NPT) consisting of, e.g., radiation oncologists, medical physicists, technologists, national radiation oncology societies, the Ministry of Health, and nuclear regulatory authorities. NPTs devised national work plans for project implementation domestically and organized NTCs. NTCs were often conducted by participants of RTCs using the provided training materials.

Table 9.2 List of IAEA/RCA radiation oncology projects since 2000

Project number	Duration	Lead country	Project title
RAS6035	2001–2003	Japan	LDR and HDR Brachytherapy in Treating Cervical Cancer (RCA)
RAS6037	2003–2004	Japan	Quality Assurance for Treatment of Cervix Cancer by Radiotherapy (RCA)
RAS6040	2005–2009	Japan	Improvement in Quality of Radiotherapy for Frequent Cancers in the Region (RCA)
RAS6048	2007–2009	Japan	Application of High-Precision 3D Radiotherapy for Predominant Cancers in the RCA Region (RCA)
RAS6053	2010–2014	Japan	Improving Image Based Radiation Therapy for Common Cancers in the RCA Region (RCA)
RAS6062	2012–2015	Japan	Supporting 3D Image-Guided Brachytherapy Services
RAS6065	2012–2015	Korea	Strengthening the Application of Stereotactic Body Radiation Therapy to Improve Cancer Treatment
RAS6072	2015–2017	Japan	Strengthening Intensity Modulated Radiation Therapy Capability in the Region (RCA)

Fig. 9.2 Photograph of the regional training course of RAS6062, held at Saitama Medical University (Saitama, Japan) in 2014

IAEA/RCA radiation oncology projects in the past have provided meaningful training to radiation oncology professionals in Asian countries. RAS6062 (2012–2015) provided four RTCs, and approximately 100 radiation oncologists and medical physicists from Asian countries were trained on treatment techniques of 3D-IGBT for cervical cancer. RAS6062 also published a technical document on 3D-IGBT [28] and provided safe and effective treatment protocols for 3D-IGBT. These RTCs, the technical document, and treatment protocols helped with the implementation of 3D-IGBT in Asian countries. In total, more than 700 radiation oncologists and medical physicists have been trained in these RTCs

Table 9.3 Achievements of IAEA/RCA radiation oncology projects since 2000

Project number	Regional training courses	RTC participants	Coordination meetings	Meeting participants	Expert missions	Experts
RAS6035	3	56	1	16		
RAS6037	2	44				
RAS6040	8	179	2	31	8	24
RAS6048	4	68	2	31		
RAS6053	6	134	4	58		
RAS6062	4	98	3	53	1	3
RAS6065 (ongoing)	4	105	2	39		
RAS6072 (ongoing)	1	23	1	7		
Total	32	707	15	235	9	27

RTC regional training course

(Table 9.3). IAEA/RCA radiation oncology projects also have contributed to the strengthening of the regional network of radiation oncology professionals in Asian countries including the SEAROG [24] and the FARO [25].

9.6 Global Trends

Ever since the Group Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) working group for gynecologic BT provided recommendations on 3D-IGBT planning in cervical cancer BT in 2005–2006 [29, 30], 3D-IGBT using computed tomography (CT) and/or magnetic resonance imaging (MRI) has been widely performed for cervical cancer BT. Many clinical studies have demonstrated that 3D-IGBT, according to GEC-ESTRO recommendations, improves target volume coverage and reduces doses to organs at risk, resulting in more favorable local tumor control and lower rates of late complications than conventional X-ray-based two-dimensional BT [31–44]. Based on the favorable results from these numerous studies, 3D-IGBT has become the standard treatment modality for cervical cancer. Recently, the International Commission on Radiation Units and Measurements published guidelines for prescribing, recording, and reporting on 3D-IGBT for cervical cancer [45].

There have been a number of obstacles in the implementation of 3D-IGBT, including (1) limited access to CT/MRI for BT, (2) shortage of CT/MRI-compatible applicators and/or 3D treatment planning systems, (3) lack of manpower, (4) limited time for 3D treatment planning, (5) poor knowledge of 3D-IGBT, and (6) poor cost remunerations. In several high-income countries, these obstacles have been overcome, and 3D-IGBT has rapidly spread [46–52] (Table 9.4). In low/middle-income Asian countries, however, these difficulties still exist due to technical and socioeconomic constraints. Notwithstanding, many radiation oncologists and medical physicists have been trained, and 3D-IGBT is being increasingly used in Asian countries [27].

Table 9.4 Imaging modalities of brachytherapy planning for cervical cancer in various countries

Study group	Year	X-ray	CT	MRI
ABS [46, 47]	2007 2014	43% 15%	55% 95%	2% 34%
Canada [48]	2009	50%	45%	5%
UK [49]	2008 2011	73% 26%	22% 53%	4% 21%
Australia and New Zealand [50]	2009	30%	65%	5%
Japan [51, 52]	2012 2016	84% 42%	15% 54%	1% 4%

ABS American Brachytherapy Society, *UK* United Kingdom, *CT* computed tomography, *MRI* magnetic resonance imaging

References

1. Henschke UK, Hilaris BS, Mahan GD. Remote afterloading with intracavitary applicators. Radiology. 1964;83:344–5.
2. O'Connell D, Howard N, Joslin CAF, Ramsey NW, Liversage WE. A new remotely controlled unit for the treatment of uterine carcinoma. Lancet. 1965;18:570–1.
3. Arai T, Morita S, Iinuma T, et al. Radiation treatment of cervix cancer using high dose rate remote after-loading intracavitary irradiation: an analysis of the correlation between optimal dose range and fractionation. Jpn J Cancer Clin. 1979;25:605–12.
4. Arai T, Morita S, Kutsutani Y, et al. Relationship between total iso-effect dose and number of fractionations for the treatment of uterine cervical carcinoma by high dose rate intracavitary irradiation. In: Bates TD, Berry RJ, editors. High dose rate afterloading in the treatment of cancer of the uterus. London: Br J Rad Special Report 17; 1980. p. 89–92.
5. Japan Society of Obstetrics and Gynecology, The Japanese Pathological Society, and Japan Radiological Society, editors. The general rules for clinical and pathological management of uterine cervical cancer. Tokyo: Kanehara Shuppan; 1987.
6. Arai T, Nakano T, Morita S, Sakashita K, Nakamura YK, Fukuhisa K. High-dose-rate remote afterloading intracavitary radiation therapy for cancer of the uterine cervix: a 20-year experience. Cancer. 1992;69:175–80.
7. Nakano T, Kato S, Ohno T, et al. Long-term results of high-dose rate intracavitary brachytherapy for squamous cell carcinoma of the uterine cervix. Cancer. 2005;103:92–101.
8. Teshima T, Inoue T, Ikeda H, et al. High-dose rate and low dose rate intracavitary therapy for carcinoma of the uterine cervix. Final results of Osaka university hospital. Cancer. 1993;72:2409–14.
9. Hareyama M, Sakata K, Oouchi A, et al. High-dose-rate versus low-dose-rate intracavitary therapy for carcinoma of the uterine cervix: a randomized trial. Cancer. 2002;94:117–24.
10. FNCA - Forum for Nuclear Cooperation in Asia. Available at: http://www.fnca.mext.go.jp. Accessed on 1 Oct 2017.
11. International Agency for Research on Cancer. GLOBOCAN 2012. Estimated Incidence, Mortality and Prevalence Worldwide in 2012. Available at: http://globocan.iarc.fr/. Accessed on 1 Oct 2017.
12. Nakano T, Kato S, Cao J, et al. A regional cooperative clinical study of radiotherapy for cervical cancer in east and southeast Asian countries. Radiother Oncol. 2007;84:314–9.
13. Ohno T, Nakano T, Kato S, et al. Accelerated hyperfractionated radiotherapy for cervical cancer: multi-institutional prospective study of forum for nuclear cooperation in Asia among eight Asian countries. Int J Radiat Oncol Biol Phys. 2008;70:1522–9.

14. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stages IIB-IVA carcinoma of the cervix with negative Para-aortic lymph nodes: a gynecologic oncology group and southwest oncology group study. J Clin Oncol. 1999;17:1339–48.
15. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med. 1999;340:1144–53.
16. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and Para-aortic radiation for high-risk cervical cancer. N Engl J Med. 1999;340:1137–43.
17. Rose PG, Ali S, Watkins E, et al. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a gynecologic oncology group study. J Clin Oncol. 2007;25:2804–10.
18. Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and Para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. J Clin Oncol. 2004;22:872–80.
19. Green JA, Kirwan JM, Tierney JF, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. Lancet. 2001;358:781–6.
20. Lukka H, Hirte H, Fyles A, et al. Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer-a meta-analysis. Clin Oncol. 2002;14:203–12.
21. Vale C, Tierney JF. Stewart LA, et al. for chemotherapy for cervical Cancer meta-analysis collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systemic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol. 2008;26:5802–12.
22. Kato S, Ohno T, Thephamongkhol K, et al. Multi-institutional phase II clinical study of concurrent chemoradiotherapy for locally advanced cervical cancer in east and south-East Asia. Int J Radiat Oncol Biol Phys. 2010;77:751–7.
23. Kato S, Ohno T, Thephamongkhol K, et al. Long-term follow-up results of a multi-institutional phase 2 study of concurrent chemoradiation therapy for locally advanced cervical cancer in east and Southeast Asia. Int J Radiat Oncol Biol Phys. 2013;87:100–5.
24. The south east Asian radiation oncology group - SEAROG Available at: http://www.searog.net/. Accessed on 1 Oct 2017.
25. Federation of Asian Organizations for Radiation Oncology – FARO Available at: http://faroac.org/. Accessed on 1 Oct 2017.
26. Mizuno H, Fukuda S, Fukumura A, et al. Multicentre dose audit for clinical trials of radiation therapy in Asia. J Radiat Res. 2017;58:372–7.
27. International Atomic Energy Agency The Regional Cooperative Agreement for research, development and training related to nuclear science and technology for Asia and Pacific - IAEA/RCA Available at: https://www.iaea.org/technicalcooperation/Regions/Asia-and-the-Pacific/RCA/. Accessed on 1 Oct 2017.
28. The Transition from 2-D Brachytherapy to 3-D High Dose Rate Brachytherapy Available at: http://www-pub.iaea.org/books Accessed on 1 Oct 2017.
29. Haie-Meder C, Pötter R, Limbergen EV, et al. Recommendations from Gynaecological (GYN) GEC-ESTRO working group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Oncol. 2005;74:235–45.
30. Pötter R, Haie-Meder C, Limbergen EV, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy - 3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol. 2006;78:67–77.
31. Kirisits C, Pötter R, Lang S, et al. Dose and volume parameters for MRI-based treatment planning in intracavitary brachytherapy for cervical cancer. Int J Radiat Oncol Biol Phys. 2005;62:901–11.

32. Georg P, Pötter R, Georg D, et al. Dose effect relationship for late side effects of the rectum and urinary bladder in magnetic resonance image-guided adaptive cervix cancer brachytherapy. Int J Radiat Oncol Biol Phys. 2012;82:653–7.
33. Pötter R, Dimopoulos J, Bachtiary B, et al. 3D conformal HDR-brachy- and external beam therapy plus simultaneous cisplatin for high-risk cervical cancer: clinical experience with 3 year follow-up. Radiother Oncol. 2006;79:80–6.
34. Dimopoulos J, Lang S, Kirisits C, et al. Dose-volume histogram parameters and local tumor control in magnetic resonance image-guided cervical cancer brachytherapy. Int J Radiat Oncol Biol Phys. 2009;75:56–63.
35. Georg P, Kirisits C, Goldner G, et al. Correlation of dose-volume parameters, endoscopic and clinical rectal side effects in cervix cancer patients treated with definitive radiotherapy including MRI-based brachytherapy. Radiother Oncol. 2009;91:173–80.
36. Kato S, Tran DNL, Ohno T, et al. CT-based 3D dose-volume parameters of the rectum and late rectal complications in patients with cervical cancer treated with high-dose-rate intracavitary brachytherapy. J Radiat Res. 2010;51:215–21.
37. Isohashi F, Yoshida Y, Koizumi M, et al. Rectal dose and source strength of the high-dose-rate Iridium-192 both affect late rectal bleeding after intracavitary radiation therapy for uterine cervical carcinoma. Int J Radiat Oncol Biol Phys. 2010;77:758–64.
38. Yoshida K, Yamazaki H, Takenaka T, et al. A dose-volume analysis of magnetic resonance imaging-aided high-dose-rate image-based interstitial brachytherapy for uterine cervical cancer. Int J Radiat Oncol Biol Phys. 2010;77:765–72.
39. Pötter R, Georg P, Dimopoulos J, et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. Radiother Oncol. 2011;100:116–23.
40. Wakatsuki M, Ohno T, Yoshida D, et al. Intracavitary combined with CT-guided interstitial brachytherapy for locally advanced uterine cervical cancer: introduction of the technique and a case presentation. J Radiat Res. 2011;52:54–8.
41. Oike T, Ohno T, Noda S, et al. Can combined intracavitary/interstitial approach be an alternative to interstitial brachytherapy with the Martinez universal perineal interstitial template (MUPIT) in computed tomography-guided adaptive brachytherapy for bulky and/or irregularly shaped gynecological tumors? Radiat Oncol. 2014;9:222–8.
42. Murakami N, Kasamatsu T, Wakita A, et al. CT based three dimensional dose-volume evaluations for high-dose rate intracavitary brachytherapy for cervical cancer. BMC Cancer. 2014;14:447–53.
43. Sturdza A, Pötter R, Fokdal LU, et al. Image guided brachytherapy in locally advanced cervical cancer: improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. Radiother Oncol. 2016;120:428–33.
44. Fokdal L, Sturdza A, Mazeron R, et al. Image guided adaptive brachytherapy with combined intracavitary and interstitial technique improves the therapeutic ratio in locally advanced cervical cancer: analysis from the retroEMBRACE study. Radiother Oncol. 2016;120:434–40.
45. International Commission on Radiation Units and Measurements (ICRU) Report 89. Prescribing, recording, and reporting brachytherapy for cancer of the cervix. J ICRU. 2013;13
46. Viswanathan AN, Erickson BA. Three-dimensional imaging in gynecologic brachytherapy: a survey of the American brachytherapy society. Int J Radiat Oncol Biol Phys. 2010;76:104–9.
47. Grover S, Harkenrider MM, Cho LP, Erickson B, Small C, Small W Jr, et al. Image guided cervical brachytherapy: 2014 Survey of the American Brachytherapy Society. Int J Radiat Oncol Biol Phys. 2016;94:598–604.
48. Pavamani S, D'Souza DP, Portelance L, Craighead PS, Pearce AG, Traptow LL, et al. Image-guided brachytherapy for cervical cancer: a Canadian Brachytherapy Group survey. Brachytherapy. 2011;10:345–51.

49. Tan LT. Implementation of image-guided brachytherapy for cervix cancer in the UK: progress update. Clin Oncol. 2011;23:681–4.
50. van Dyk S, Byram D, Bernshaw D. Use of 3D imaging and awareness of GEC-ESTRO recommendations for cervix cancer brachytherapy throughout Australia and New Zealand. J Med Imaging Radiat Oncol. 2010;54:383–7.
51. Ohno T, Toita T, Tsujino K, et al. A questionnaire-based survey on 3D image-guided brachytherapy for cervical cancer in Japan: advances and obstacles. J Radiat Res. 2015;56:897–903.
52. Toita T, Ohno T, Ikushima H, et al. JASTRO Brachytherapy Group 19th meeting abstract. 2017; 54.

Part III

Prostate

Prostate Brachytherapy: Clinical Efficacy and Future Trends

10

Peter F. Orio III, Katelyn A. Crouse, Paul L. Nguyen, and Martin T. King

Abstract

Low-dose rate (LDR) prostate brachytherapy is a highly efficacious and cost-effective treatment with a very favorable side effect profile and has a role in the treatment paradigm of low-, intermediate-, and high-risk prostate cancers. Brachytherapy is typically an outpatient procedure where tiny radioactive "seeds" are implanted in the prostate to eradicate the cancer right where it has grown. Brachytherapy has a long and proven track record with data demonstrating it to be extremely effective when used alone in low and favorable intermediate-risk prostate cancer. Brachytherapy also shows significantly higher rates of cancer control and tumor eradication in the higher-risk setting when used in combination with external beam radiation therapy (EBRT) as compared to surgery or EBRT alone.

Despite its efficacy, brachytherapy utilization rates are declining secondary to competing treatment options, to include a shift to active surveillance. With prostate cancer diagnosis on the rise, and prospective and randomized trials showing brachytherapy's superior efficacy over other modalities such as radical prostatectomy and EBRT, it is important to put corrective actions in place to ensure that brachytherapy is available to patients across the globe.

Keywords

Prostate cancer · Brachytherapy · Low risk · Intermediate risk · High risk Outcomes

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10.1 Low-Dose Rate Prostate Brachytherapy Efficacy Analysis and Trends

Prostate cancer accounts for approximately 8% of all newly diagnosed cancer cases worldwide and 15% of cancer diagnoses in men, with more than 1.1 million new cases being recorded in 2012 across the globe [1]. In the United States and many other countries, prostate cancer is most frequently diagnosed in older men, with the highest probability of diagnosis being between ages 65 and 74 [2]. With projections of the male population ages 55–84 showing a significant increase for the United States over the next four decades, prostate cancer diagnoses will likely simultaneously rise [2]. Screening for prostate cancer in most developed countries allows for the disease to be caught before it spreads, increasing the likelihood of providing curative treatment options to newly diagnosed men. Increasing diagnoses, however, also require careful medical research, knowledge, and availability of efficacious and cost-effective treatment regimens for these patients.

Prospective randomized comparisons of prostate cancer treatment options are largely limited by physician biases, difficulty in patient recruitment, and the long natural history of prostate cancer, making survival endpoints difficult to attain. As such, researchers are often left to interpret single-institution retrospective and single-modality prospective studies to formulate comparisons between treatment outcomes and use of biochemical control as a surrogate endpoint for study design.

With results published in 2012, the Prostate Cancer Results Study Group (PCRSG) undertook a Herculean effort with the goal of distilling studies into clinically useful comparisons and completed the first large-scale comprehensive review of the literature comparing risk-stratified patients with long-term follow-up by treatment option [3]. The literature review demonstrated that brachytherapy provides superior outcomes in patients with low-risk disease in terms of biochemical prostate-specific antigen (PSA) free progression [3]. Additionally, the combination of EBRT and brachytherapy was shown to be superior to EBRT or surgery alone for intermediate-risk disease. Combination therapies involving EBRT and brachytherapy plus or minus androgen deprivation therapy (ADT) appear superior in terms of biochemical control as compared to more localized treatments such as brachytherapy alone, surgery alone, or EBRT alone for high-risk patients [3].

In 2017, the American Brachytherapy Society (ABS) formed a committee of clinical experts in brachytherapy to update existing, but outdated, guidelines to articulate the intricacies as well as new advances for the delivery of brachytherapy as well as to highlight its efficacy in treating prostate cancer. Utilizing previously published guidelines, clinical trial results, literature, and the experience of the committee members, the results outlined patient selection criteria and delivery guidelines for patients in both the brachytherapy monotherapy and brachytherapy boost setting [4]. Evidence that was reviewed was similar to the findings of the PCRSG, demonstrating that low-risk disease can be treated with brachytherapy alone

without the need for EBRT or ADT [4]. Additionally, intermediate-risk patients with favorable features can be treated with brachytherapy monotherapy in the appropriate setting, and the guidelines outline that some high-intermediate- and high-risk patients should receive EBRT with a brachytherapy boost, plus or minus ADT as needed based on specific patient risk factors [4].

The National Cancer Database, representing an estimated 60–70% of newly diagnosed cancers in the United States, has shown over the past 15 years a trend in the increased utilization of prostatectomy, largely motivated by robotic-assisted radical prostatectomy, which was FDA approved for use in 2000 in the United States [5]. This has come at the cost of a decline in brachytherapy despite its proven clinical efficacy, as well as EBRT [5]. With a greater number of surgeries being performed, the use of ADT has also declined as it is not utilized with initial surgical removal of the prostate but used in combination with radiation techniques in the treatment of select higher-intermediate- and most high-risk and metastatic cancers [5].

Factors negatively impacting brachytherapy are multifactorial, some of which can be attributed to changes in screening, monitoring, and financial incentives for physicians [6]. The United States has seen a decrease in PSA screening which has resulted in a decrease in prostate cancer diagnosis due to the US Preventive Services Task Force discouraging the use of the service beginning in 2012 up until a change in 2017 [6]. Beginning in 2017, it is now recommended that PSA screening be offered based on individual circumstance [6]. This, with a simultaneous increase in patients electing active surveillance, has decreased treatment rates in recent years [6]. Additionally, an increase in the number of robotic prostatectomy as mentioned and the increased technical sophistication of EBRT technologies such as intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy, and proton beam therapies have resulted in a decrease in patients being referred for brachytherapy [6].

Radiation oncology practices in the United States have demonstrated a significant reduction in the use of brachytherapy from 2004 to 2012 [7]. Considering the superior results demonstrated for brachytherapy from multiple trials [3, 8], the future of brachytherapy's role in treating prostate cancer needs to be considered carefully or a proven technology will be in jeopardy, and patients may not be granted access to a highly effective treatment which has minimal side effects [7]. Suboptimal volume of brachytherapy procedures has resulted in less training opportunities, leaving a question as to whether future physicians can be trained in this procedure [7]. Lack of knowledge of brachytherapy's efficacy also remains widespread across the globe despite the ABS and other radiation therapy organizations offering schools and other opportunities for physicians to learn brachytherapy delivery techniques [7]. Simulation-based trainings at academic society organization's annual meetings, creation of centers of excellence for training of residents and attending physicians, as well as worldwide collaboration in providing educational opportunities in the future could remedy the downward trend of brachytherapy's utilization.

10.2 Brachytherapy in Low-Risk Prostate Cancer

Results of phase II/III clinical trials and large observational studies demonstrate brachytherapy is a highly efficacious and cost-effective treatment of low-risk prostate cancer. Studies have shown that brachytherapy as monotherapy is appropriate in low-risk prostate cancer, without the need for it to be combined with EBRT or ADT [3].

The American College of Surgeons Oncology Group's phase III Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial (SPIRIT) studied men with low-risk prostate cancer who attended a multidisciplinary education session through the University of Toronto Health Network and either elected to be randomized to radical prostatectomy or brachytherapy (n = 34 randomized) or chose to elect either radical prostatectomy (n = 62) or brachytherapy (n = 94) and assessed quality of life following treatment with a median follow-up of 5.2 years [8]. Although the trial closed secondary to poor accrual, men treated with brachytherapy scored better on health-related quality of life surveys for urinary (91.8 vs 88.1; P = 0.02) and sexual (52.5 vs 39.2; P = 0.001) areas as well as in overall patient satisfaction (93.6 vs 76.9; $P < 0.001$) as compared to patients who received radical prostatectomy [8].

In a similar study comparing brachytherapy for organ-confined disease to historical data of prostatectomy and EBRT, researchers on RTOG 98-05 study found that brachytherapy resulted in only 3 of 98 patients (3%) having maximum late toxicities of grade 3, all of which were genitourinary (GU), with no grade 4 or 5 toxicities [9]. The 8-year overall survival (OS) rate was 88%, with no patients having died of prostate cancer or toxicities related to care [9].

Research into the late effects of brachytherapy as monotherapy shows that results in terms of biochemical failure and toxicity compare very favorably to other treatment modalities [10]. The rates of biochemical relapse-free survival (bRFS), distant metastasis-free survival (DMFS), OS, and prostate cancer-specific mortality (PCSM) were studied in a cohort of 1989 low-, intermediate-, and high-risk patients treated from 1996 to 2007 by Kittel et al. [10]. The overall 10-year rates for bRFS, DMFS, OS, and PCSM were recorded as 81.5%, 91.5%, 76.1%, and 2.5%, respectively [10]. The overall rates of late grade $\geq$ 3 GU and gastrointestinal (GI) toxicity were 7.6% and 0.8%, respectively, which are comparable to results of other studies on brachytherapy as monotherapy in the United States [10]. Additionally, a study looking at biochemical relapse in brachytherapy published in 2015 showed that at a median follow-up of 5 years, 108 of 2223 patients (4.8%) treated with brachytherapy had developed either local or distant recurrence, proving lower rates of recurrence than most studies reviewed that reported on rates of distant recurrence following prostatectomy [11].

Long-term toxicities impacting quality of life are rare when brachytherapy is performed as monotherapy for patients with low-risk disease. Randomized evidence [8] suggests a favorable side effect profile, subsequent patient satisfaction, and durable urinary and sexual quality of life with brachytherapy as compared to other treatment modalities as well as good long-term survival outcomes.

10.3 Brachytherapy in Intermediate-Risk Prostate Cancer

Intermediate-risk patients can be candidates for brachytherapy monotherapy when their specific risk factors are considered by their physician. However, most often these patients are treated with brachytherapy in combination with EBRT and/or ADT [3]. Recent phase II/III evidence demonstrates brachytherapy provides excellent biochemical control for selected patients with intermediate-risk prostate cancer when utilized in combination with EBRT.

As with many treatment techniques, the quality of a brachytherapy implant and patient-specific disease characteristics are highly linked to rates of cancer control. Eleven American institutions combined data on 2693 patients diagnosed with low- and intermediate-risk disease that were treated with brachytherapy monotherapy between 1988 and 1998 [12]. With a median follow-up of 63 months, it was found that outcomes after brachytherapy relate to tumor stage, Gleason score (GS), pretreatment PSA, year of brachytherapy implant, and post-brachytherapy dosimetric quality, highlighting the importance of patient-specific risk factors when determining treatment recommendations for low-intermediate- and high-intermediate-risk prostate cancers [12]. PSA nadir ≤0.5 ng/mL was particularly associated with durable long-term PDFS [12].

RTOG 0232 compared EBRT followed by brachytherapy boost and brachytherapy alone in patients with intermediate-risk disease at 68 participating centers throughout the United States and Canada from 2003 to 2012 (Prestidge, 13). Patients GS 2–6 and PSA ≥10 but <20 or GS 7 and PSA <10 received either EBRT 45 Gy/25 + brachytherapy or brachytherapy monotherapy (I125; Pd103) [13]. Freedom from progression (FFP) was studied, and it was found that the addition of EBRT to brachytherapy in men with intermediate-risk disease, stratified by GS, PSA, and ADT utilization, did not statistically improve outcomes [13]. At the fifth interim analysis, of the required 443 patients with 5 years of follow-up, 5-year PFS (95% CI) was 85% (80, 89) for the EBRT plus brachytherapy arm and 86% (81, 90) for the brachytherapy arm (HR Z 1.02, futility P Z 0.0006) [13].

An estimate of toxicities following EBRT (45 Gy in 25 fractions), followed 2–6 weeks later by brachytherapy to a delivered dose of 108 Gy, was published by Lee et al. in 2006 [14]. Patients were analyzable for acute and late toxicities [14]. Acute grade 3 toxicity was documented in 10 of 131 patients (7.6%), and no grade 4 or 5 acute toxicities were observed [14]. The estimate of late grade 3 GU and GI toxicity at 18 months was 3.3%, and no late grade 4 or 5 toxicities were observed [14].

Memorial Sloan Kettering Cancer Center studied the toxicities and outcomes of patients being treated with 45 Gy EBRT to the prostate and seminal vesicles, followed by brachytherapy boost with I^{125} (100 Gy) or Pd^{103} (90 Gy) [15]. At a median follow-up of 73 months, late GI and GU toxicity grade 2 and 3 occurred in 20% and 3% of patients, respectively [15]. The OS at 72 months was 96.1% [15].

10.4 Brachytherapy in High-Risk Prostate Cancer

The standard recommendation for patients with high-risk disease is EBRT and ADT as "multimodality" therapy. Recent studies have shown that the addition of brachytherapy to EBRT, however, improves biochemical control long-term, and therefore, patients with high-intermediate- or high-risk disease receiving EBRT +/− ADT should also be offered brachytherapy as a dose escalation or "trimodality" technique.

The Canadian Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) trial studied patients with intermediate- or high-risk prostate cancer who had negative metastatic work-up with GS 8–10 or initial PSA (iPSA) 20–40 ng/mL [15]. Patients who had iPSA >40, cT-Stage ≥T3b, prior TUPR, and TRUS prostate volume > 75 cm^3 or were unfit for general or spinal anesthesia were excluded per protocol [16]. The randomized study assigned men to either traditional dose-escalated EBRT in combination with ADT or EBRT plus a brachytherapy boost [16]. The study followed these patients in follow-up for a median of 6.5 years, and results demonstrated men who received a brachytherapy boost were nearly twice as likely to be free of biochemical failure [16].

A phase II study of men with high-risk prostate cancer found that a trimodality approach involving 2 years of ADT, EBRT, and brachytherapy and the addition of upfront docetaxel is well tolerated in patients and results in limited side effects while producing good long-term control results [17]. Eligibility for this study included PSA >20 ng/mL or GS 7 and a PSA >10 ng/mL, any GS 8–10, or stage T2b–T3 regardless of GS or PSA [17]. Patients received 45 Gy EBRT to the pelvis, followed 1 month later by brachytherapy with either I^{125} or Pd^{103} [17]. One month after brachytherapy, patients received three cycles of docetaxel and completed 2 years of ADT [17]. The median follow-up was 5.6 years [16]. Grade 2 and 3 acute GU and GI toxicities were 50.0% and 14.2%, respectively, with no grade 4 toxicities [17]. The 5- and 7-year actuarial rates of late grade 2 GI/GU toxicity, with no grade 3–5 toxicities reported, were 7.7% [17]. The 5- and 7-year FFBF rates were 89.6% and 86.5%, and corresponding rates for disease-free survival were 76.2% and 70.4% with 5- and 7-year OS rates being 83.3% and 80.1% [17].

10.5 The Future of Prostate Brachytherapy

It is recommended by both the American Association of Physicists in Medicine (AAPM) and ABS that a robust quality assurance program is key to ensure successful patient care [18]. Quality assurance is key in brachytherapy as factors such as inadequate training of physicians, physicist, dosimetrists, and therapists can lead to incorrect seed placement, program structure deficiencies, inadequate procedures, and poor management oversight of program and contractors [18]. The lack of a peer review process or lack of a culture of safety can lead to underutilization or improper utilization of brachytherapy to treat prostate cancer. As discussed, the development of centers of excellence, taking advantage of organizational training

opportunities across the globe, and the consultation of organizations such as AAPM and ABS are critical in the creation and maintenance of a high-quality brachytherapy program [6].

Adoption of programs such as the design and implementation of a training program utilizing phantom-based simulators to teach the process of brachytherapy at The University of Texas MD Anderson Cancer Center will advance brachytherapy techniques worldwide [19]. The MD Anderson program focuses on teaching practicing oncologists, fellows, and resident physicians to focus on quality assurance through hands-on education for the simulation, treatment planning, implant technique, treatment evaluation, and outcome assessment of brachytherapy procedures [19]. Analysis of the program's participants for brachytherapy implants showed a high degree of consistency between trainees as compared to implants in clinical practice, highlighting the potential opportunities to train brachytherapists in the skills necessary to safely perform and ensure quality assurance across the globe in the future [19].

Despite brachytherapy's low rate of toxicity to organs at risk, toxicities overall remain a concern to radiation oncologists when prescribing radiation dose delivery. Although rectal injury is uncommon with advanced imaging, technologies developed to assist in the protection of organs at risk such as hydrogel spacers have been shown to greatly reduce toxicities such as grade 1–2 proctitis, which is reported in between 1 and 21% of prostate cancer patients and can potentially prevent severe rectal complications such as grade 3 ulcers and grade 4 fistulas. A key motivation in the utilization of rectal spacers is the higher risk of grade 3 rectal toxicity on EBRT + brachytherapy arm of the ASCENDE-RT trial [16].

By placing a hydrogel spacer between the Denonvilliers' fascia and the rectal wall, space is created to protect the rectal wall from radiation delivered with both EBRT and brachytherapy. A randomized controlled trial recently looked at the dosimetry and clinical effects of perirectal hydrogel spacer application for patients undergoing EBRT and found that late rectal toxicity was 2.0% (all grade 1) in the spacer and 7.0% (up to grade 3) in the control group [20]. A long-term follow-up study completed by Hamstra et al. showed grade 1+ rectal toxicity at 3 years decreased by 75% in the spacer arm (control 9% vs spacer 2% $p < 0.03$), and no grade 2+ rectal toxicity was observed in patients who received a perirectal hydrogel spacer ($p < 0.015$) [21]. American institutions are beginning to incorporate rectal spacers into brachytherapy workflows as well, placing the spacer in the operating room immediately following radioactive seed implantation. Utilization of these advanced technologies, which are currently in the process of becoming widely available across the globe, can spare normal tissues from being negatively affected by radiation delivered to eradicate nearby tumors.

Another advancement for brachytherapy in the future is the integration of magnetic resonance imaging (MRI) technologies into treatment delivery. MRI is the standard imaging tool for staging of prostate cancer in much of the world, and the next step in the integration process for MRI technologies is its utilization in the planning and delivery of brachytherapy, which has grown in investigational and clinical use over the past decade [22]. Several advantages to MRI integration

into brachytherapy treatment delivery include soft tissue resolution, localization of the disease within the prostate, visualization of the prostate's apex, as well as localization of the bladder, rectum, and neurovascular bundles in relation to the prostate [22].

Lack of widespread utilization of MRI technologies can be attributed to access to these technologies, economic considerations and reimbursement, the learning curve associated with utilization of this technology in the operating room, reproducibility issues between treatment planning and delivery, as well as the favorable results of brachytherapy utilizing the current standard of CT-based planning and TRUS-based treatment delivery [22]. Investigational research in the United States has focused on the advancement of MRI in brachytherapy treatment planning and delivery, and it is believed that once operational costing and training opportunities are remedied, these technologies will be more utilized globally as MRI-based treatment planning and delivery has the potential to allow physicians to better define the prostate and the disease within, decreasing side effects for patients and increasing clinical outcomes.

Significant research has gone into costing analysis to define the value of brachytherapy as a treatment modality both with standard utilization of CT planning and TRUS-based treatment delivery as well as with the utilization of MRI in the workflow. Time-driven activity-based costing analysis demonstrated low resource utilization for brachytherapy overall, with 41% and 10% of costs occurring in the operating room and with the MRI scan, respectively, with no large increase in the cost of providing brachytherapy with utilization of an MRI as compared to the standard treatment regime of CT and TRUS-based care [23].

Conclusion

Research shows that brachytherapy is a cost-effective treatment modality with outcomes as good, if not superior, to other modalities. Regardless, data shows varying degrees of utilization across economic and geographic landscapes, and the application of this technique has seen a decline at academic centers, comprehensive community centers, and community cancer centers alike [6]. Given the increasing pressures facing radiation therapy centers across the globe, consideration needs to be given to the utilization of brachytherapy as a form of conformal therapy because of its ability to safely deliver high doses of radiation for disease control and cost-effectiveness both for implementation and long-term program sustainability [24].

References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.1, Cancer incidence and mortality worldwide: IARC CancerBase no. 11 [internet]. Lyon, France: International Agency for Research on Cancer; 2014.
2. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer

Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.
3. Grimm P, Billiet I, Bostwick D, et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the prostate Cancer results study group. BJU Int. 2012;109(Suppl 1):22–9.
4. Bittner NH, Orio PF, Merrick GS, Prestidge BR, Hartford AC, Rosenthal SA. The American College of Radiology and the American Brachytherapy Society practice parameter for transperineal permanent brachytherapy of prostate cancer. Brachytherapy. 2017;16(1):59–67.
5. Martin JM, Handorf EA, Kutikov A, Uzzo RG, Bekelman JE, Horwitz EM, Smaldone MC. The rise and fall of prostate brachytherapy: use of brachytherapy for the treatment of localized prostate Cancer in the National Cancer Data Base. Cancer. 2014;120:2114–21.
6. Orio PF, Nguyen PL, Buzurovic I, Cail DW, Chen YW. Prostate brachytherapy case volumes by academic and non-academic practices: implications for future residency training. Int J Radiat Oncol Biol Phys. 2016;96(3):624–8.
7. Orio PF, Nguyen PL, Buzurovic I, Cail DW, Chen YW. The decreased use of brachytherapy boost for intermediate and high-risk prostate cancer despite evidence supporting its effectiveness. Brachytherapy. 2016;15(6):701–6.
8. Crook JM, Gomez-Iturriaga A, Wallace K, Ma C, Fung S, Alibhai S, Jewett M, Fleshner N. Comparison of health-related quality of life 5 years after SPIRIT: surgical prostatectomy versus interstitial radiation intervention trial. J Clin Oncol. 2011;29(4):362–8.
9. Lawton CA, Hunt D, Lee WR, Gomella L, Grignon D, Gillin M, Morton G, Pisansky TM, Sandler H. Long-term results of a phase II trial of ultrasound-guided radioactive implantation of the prostate for definitive management of localized adenocarcinoma of the prostate (RTOG 98-05). Int J Radiat Oncol Biol Phys. 2011;81(1):1–7.
10. Kittel JA, Reddy CA, Smith KL, Stephans KL, Tendulkar RD, Ulchaker J, Angermeier K, Campbell S, Stephenson A, Klein EA, Wilkinson DA, Ciezki JP. Long-term efficacy and toxicity of low-dose-rate ^{125}I prostate brachytherapy as monotherapy in low-, intermediate-, and high-risk prostate Cancer. Int J Radiat Oncol Biol Phys. 2015;92(4):884–93.
11. Lo AC, Morris WJ, Pickles T, Keyes M, McKenzie M, Tyldesley S. Patterns of recurrence after low-dose-rate prostate brachytherapy: a population-based study of 2223 consecutive low- and intermediate-risk patients. Int J Radiat Oncol Biol Phys. 2015 Mar 15;91(4):745–51.
12. Zelefsky MJ, Kuban DA, Levy LB, Potters L, Beyer DC, Blasko JC, Moran BJ, Ciezki JP, Zietman AL, Pisansky TM, Elshaikh M, Horwitz EM. Multi-institutional analysis of long-term outcome for stages T1-T2 prostate cancer treated with permanent seed implantation. Int J Radiat Oncol Biol Phys. 2007 Feb 1;67(2):327–33.
13. Prestidge BR, Winter K, Sanda MG, Amin M, Bice WS, Michalski J, Ibbott GS, Crook JM, Catton CN, Gay HA, Donavanik V, Beyer DC, Frank SJ, Papagikos MA, Rosenthal SA, Barthold HJ, Sandler HM RM. Initial report of NRG oncology/RTOG 0232: a phase III study comparing combined external beam radiation and transperineal interstitial permanent brachytherapy with brachytherapy alone for selected patients with intermediate risk prostatic carcinoma. Int J Radiat Oncol Biol Phys. 2016;96(2):S4.
14. Lee WR, DeSilvio M, Lawton C, Gillin M, Morton G, Firat S, Baikadi M, Kuettel M, Greven K, Sandler H. A phase II study of external beam radiotherapy combined with permanent source brachytherapy for intermediate-risk, clinically localized adenocarcinoma of the prostate: preliminary results of RTOG P-0019. Int J Radiat Oncol Biol Phys. 2006 Mar 1;64(3):804–9.
15. Hurwitz MD, Halabi S, Archer L, McGinnis LS, Kuettel MR, DiBiase SJ, Small EJ. Combination external beam radiation and brachytherapy boost with androgen deprivation for treatment of intermediate-risk prostate Cancer. Cancer. 2011;117(24):5579–88.
16. Morris WJ, Tyldesley S, Roda S, Halperon R, Pai H, McKenzie M, Duncan G, Morton G, Hamm J, Murray N. Androgen suppression combined with elective nodal and dose escalated radiation therapy (the ASCENDE-RT Trial): an analysis of survival endpoints for a randomized

trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiation Oncol Biol Phys. 98:275–85.
17. Dibiase SJ, Hussain A, Kataria R, Amin P, Bassi S, Dawson N, Kwok Y. Long-term results of a prospective, phase II study of long-term androgen ablation, pelvic radiotherapy, brachytherapy boost, and adjuvant docetaxel in patients with high-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2011 Nov 1;81(3):732–6.
18. Pfeiffer D, Sutlief S, Feng W, Pierce HM, Kofler J. AAPM task group 128: quality assurance tests for prostate brachytherapy ultrasound systems. Med Phys. 2008 Dec;35(12):5471–89.
19. Thaker NG, Kudchadker RJ, Swanson DA, Albert JM, Mahmood U, Pugh TJ, Boehling NS, Bruno TL, Prestidge BR, Crook JM, Cox BW, Potters L, Moran BJ, Keyes M, Kuban DA, SJ F. Establishing high-quality prostate brachytherapy using a phantom simulator training program. Int J Radiat Oncol Biol Phys. 2014 Nov 1;90(3):579–86.
20. Mariados NM, Sylverseter J, Shah D, et al. Hydrogel spacer prospective multicenter randomized controlled pivotal trial: dosimetric and clinical effects of perirectal spacer application in men undergoing prostate image guided intensity modulated radiation therapy. Int J Radiation Oncol Biol Phys. 2014;92(5):971–7.
21. Hamstra DA, et al. Continued benefit to rectal separation for prostate radiation therapy: final results of a phase III trial. Int J Radiation Oncol Biol Phys. 2017;97(5):976–85.
22. Pugh TJ, Pokharel SS. Magnetic resonance imaging in prostate brachytherapy: evidence, clinical end points to data, and direction forward. Brachytherapy. 2017;16:659–64.
23. Thaker NG, Pugh TJ, Mahmood U, Choi S, Spinks TE, Martin NE, Sio TT, Kudchadker RJ, Kaplan RS, Kuban DA, Swanson DA, Orio PF, Zelefsky MJ, Cox BW, Potters L, Buchholz TA, Feeley TW, Frank SJ. Defining the value framework for prostate brachytherapy using patient-centered outcome metrics and time-driven activity-based costing. Brachytherapy. 2016 May-Jun;15(3):274–82.
24. Orio PF, Durkee B, Lanni T, Lievens Y, Petereit D. Is brachytherapy cost effective? In: William Y, Tanderup K, Pieters B, editors. Emerging Technologies in Brachytherapy. Boca Raton: CRC Press; 2017.

How We Led the Japanese Low-Dose-Rate Brachytherapy to Successful Practice (Urologist Perspective)

11

Shiro Saito

Abstract

Permanent seed implantation brachytherapy (PB) with iodine-125 (I-125) seed was first performed in Japan in September 2003. Even taking into account the good feature of the treatment, PB in Japan had not been allowed because of the country's strict laws on radiation safety. However, after a long period of discussion between Japanese medical associations and the government, PB was finally approved in Japan in July 2003. The guidelines for this treatment include several restrictions that should be followed by each institution that is to perform the treatment. Approximately 40,000 cases are treated around the country at 118 institutes during the past 14 years without major troubles or accidents because all institutes performing PB are following the guidelines carefully and all members related to this treatment are trained to be highly skillful by attending training course of PB. Numerous data have been reported from institutes performing PB in Japan and all of them prove that PB is clinically effective with excellent cancer control and maintenance of quality of life (QOL).

Japanese Prostate Permanent Seed Implantation Study Group (JPSS) was established in 2004 and holds annual conference and technical training course for PB. Most of the medical staffs involved in PB are attending the conference and training course. JPSS are supporting three nationwide multi-institutional clinical studies that the results would be dispatched worldwide.

Keywords

Prostate cancer · Brachytherapy · Iodine-125 · Permanent seed implantation Guideline

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11.1 Introduction

Permanent seed implantation brachytherapy (PB) using iodine-125 (I-125) seed was first performed in Japan in September 2003. In spite of new appearance in Japan, this treatment has a long history in the United States (USA). Whitmore et al. first reported the use of I-125 seeds for the prostatic interstitial irradiation in 1972, and this treatment had been commonly performed for a decade [1]. As the procedure was mostly based on an open retropubic freehand approach, postimplantation evaluation often revealed a nonuniform distribution of the seeds, which resulted in inadequate radiation dose coverage. With a median follow-up of 11 years, the overall local recurrence-free survival rates at 5, 10, and 15 years were 59%, 36%, and 21%, respectively. And even among node-negative stage T2a patients, the 10- and 15-year local control rates were only 56% and 34%, respectively [2]. It was concluded that retropubic I-125 PB was less effective than other modalities in its eradication of localized prostate cancer [3].

The subsequent development of ultrasound technique made it possible to obtain clear images of the prostate through transrectal ultrasound (TRUS). With the ability to introduce a seed transperineally into the prostate under the guidance of TRUS [4], RB became more accurate and less invasive. Adequate seed distribution and radiation dose coverage in the prostate led to good clinical outcomes, and the brachytherapy becomes a common treatment option for localized prostate cancer after 1990 in the USA. The number of procedures performed around the country grew rapidly (Fig. 11.1) until around 2010, and over 80,000 cases were treated with PB each year at that time. In spite of multiple reports of excellent cancer control and maintenance of quality of life (QOL) by RB, numbers of treatment

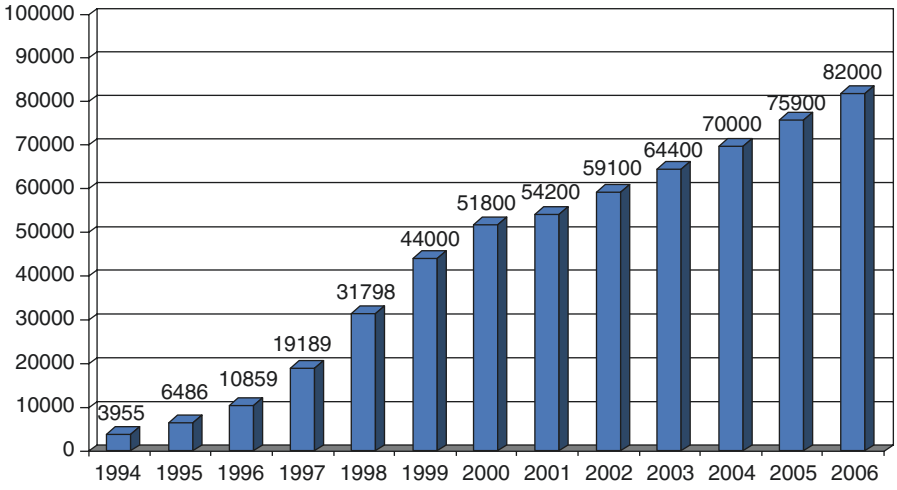

Fig. 11.1 Number of PB cases each year in the USA. It rapidly grew until 2006 but reduced after that. Data were provided by the industry

cases are reducing after 2010 in USA. Cases of other treatment options such as robotic prostatectomy and intensity-modulated radiation therapy (IMRT) might be increasing.

11.2 Starting Permanent Seed Implantation Brachytherapy in Japan

Before PB was performed in Japan, temporary placement of iridium (Ir-192) had been performed for treating localized or locally invasive prostate cancer at about ten institutes around the country. Mostly they were using high-dose-rate (HDR) Ir-192 based on remote-controlled afterloading system (RALS). According to numerous data from the USA, PB seemed to be a highly expected treatment for localized prostate cancer; however, it was restricted under the laws in Japan. The establishment of guidelines based on law related to radioisotope handling and safety was dispensable to lead to the treatment being permitted by the government. To obtain permission for performing PB in Japan, members from the Japanese Society for Therapeutic Radiology and Oncology (JASTRO) and Japanese Urological Association (JUA) spent a long time discussing with the Ministry of Health, Labor, and Welfare as well as the Ministry of Education and Science. With the accomplishment of the Japanese guideline for PB, the treatment finally became available in July 2003. Even after the admission in Japan, a limited number of institutes had started the treatment because the medical cost was fixed very low by Japanese health insurance system. In April 2006, the medical cost for this treatment was revised and set higher, and many institutes have started the treatment.

I-125 as well as palladium (Pd-103) seeds are commonly used in the USA for PB; only I-125 seed is available in Japan. All seeds are imported from the USA and sold by two different companies. Seeds are ordered for each patient a few weeks ahead of the treatment and delivered from the Japan Radioisotope Association.

11.3 Guidelines for Permanent Seed Implantation Brachytherapy in Japan [5]

The procedure for permanent seed implantation performed in Japan should follow the guideline of the JASTRO, JUA, and Japan Radiological Society (ARS). This guideline mainly consists of radiation safety parameters, including the qualifications of the institutions and physicians to perform this treatment. The treatment should be done at radiation treatment room registered for brachytherapy or in a room registered for HDR Ir-192 treatment. The institution should have a radiation oncologist approved by the JASTRO and a urologist approved by the JUA in full-time employment. Physicians and all other staff members involved in this treatment should attend the education course held by the Japan Radioisotope Association.

The maximum radiation activity allowed to be internally remaining at the time of the patient leaving hospital is 1300 MBq (35.1 mCi), or the 1-cm dose equivalent

rate should be lower than 1.8 μSv/h at a 1-m distance from the surface of the body if total internally placed activity is over 1300 MBq. Patients should spend at least overnight at the radiation-controlled room after the seed implantation to check the seed expulsion, which may occasionally be seen through the urine. The annual dose to each member of the family should be below 5 μSv, and to children and others besides the family, the annual dose should be less than 1 μSv. If a patient dies within 1 year of seed implantation, the prostate should be taken out with the seeds by performing an autopsy before cremation.

11.4 Recent Situation of Permanent Seed Implantation Brachytherapy in Japan

The prostate cancer population is rapidly multiplying in Japan; it became the third cancer of Japanese men in 2017, and about 86,100 patients are newly diagnosed every year [6]. According to the increase of prostate-specific antigen (PSA) screening, those with localized stage are growing, and a number of the patients who are receiving curative treatments, such as surgery or radiation therapy, are increasing.

Various kinds of radiation therapies are performed for the treatment of prostate cancer such as external beam radiotherapy (EBRT) including three-dimensional conformal radiation therapy (3D-CRT), and IMRT, PB, HDR brachytherapy or particle therapy such as proton or carbon-ion therapy. People who receive radiation therapies as initial treatments for cancer are increasing in Japan; however, still more people choose surgery than radiation therapy. According to the data of JASTRO, 12.3% of whole radiation therapy are for prostate cancer, and about three-quarters of prostate radiation therapy are performed by EBRT in Japan [7] (Fig. 11.2).

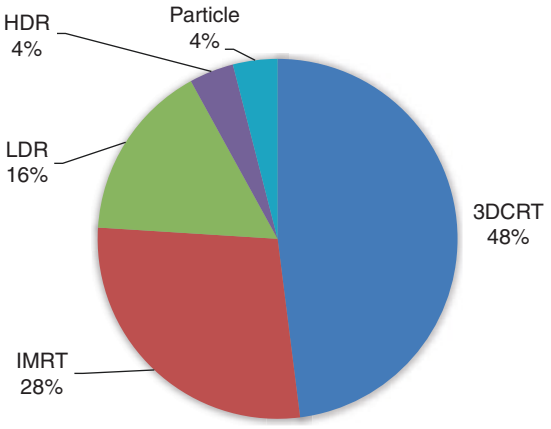

Fig. 11.2 Treatment modalities of radiation therapy for prostate cancer in Japan. Estimated from 2012 annual report of JASTRO [7] (https://www.jastro.or.jp/aboutus/child.php?eid=00048). Particle (proton and carbon ion). *3D-CRT* three-dimensional conformal radiation therapy, *IMRT* intensity-modulated radiation therapy, *LDR* low dose rate, *PB* permanent brachytherapy, *HDR* high-dose-rate; Ir-192 brachytherapy

At the time PB has been permitted in Japan in 2003, the limited numbers of qualified institutes have received the permission. But until the end of 2016, 118 institutes have performed PB, and over 37,000 cases have been treated with this manner around the country (Fig. 11.3). The first case of PB in Japan was performed at Tokyo Medical Center in September 2003, and the treatment became common option for treating localized prostate cancer. The number of institutes performing PB and the number of cases rapidly increased until 2011; however, it had been reducing after that. The major reason of this reduction is that robotic-assisted radical prostatectomy became common in Japan, and this surgery became able to be covered by the national insurance. Even though, cases treated with PB are slowly recovering these years, and approximately 3300 cases were treated around the country in 2016.

Tokyo Medical Center is the leading institute for PB in Japan, and they treated over 3000 cases during these 14 years. Figure 11.4 shows the numbers of cases treated each year in this institution. Same as total cases around the country, the number of cases reached peak at 2011, and reduced after that, however, it recovered in 2014 and increased for 2 years until it reached its maximum in 2016 (271 cases). What is interesting is that numbers of cases treated with combination of EBRT are increasing these few years. It means higher-risk cases are recently treated more because for numerous articles [8, 9] that present higher-risk cases which are also

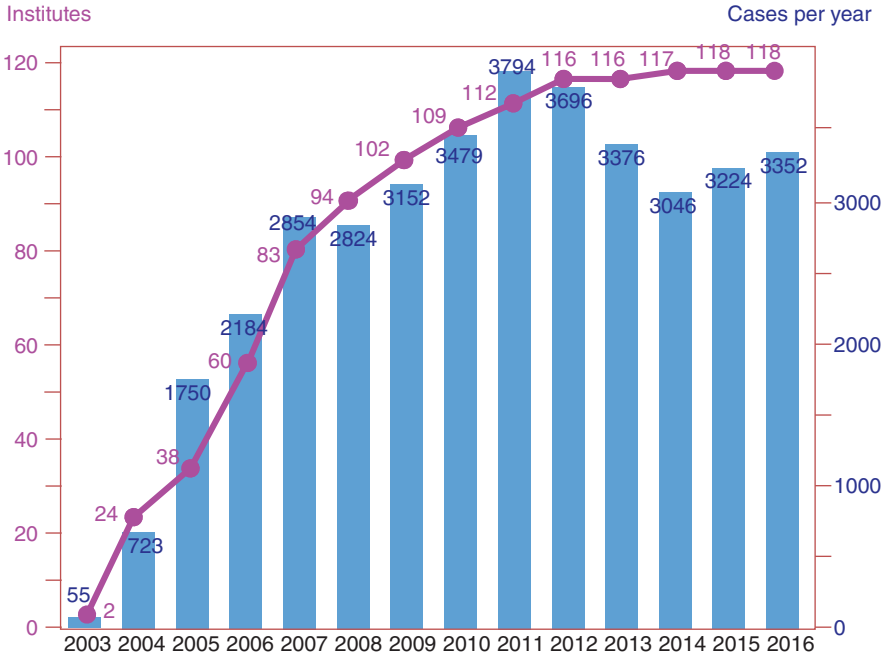

Fig. 11.3 Number of PB cases performed each year in Japan and total number of institutes that experienced PB until each year. A total of 37,509 cases were treated until the end of 2016 in 118 institutes

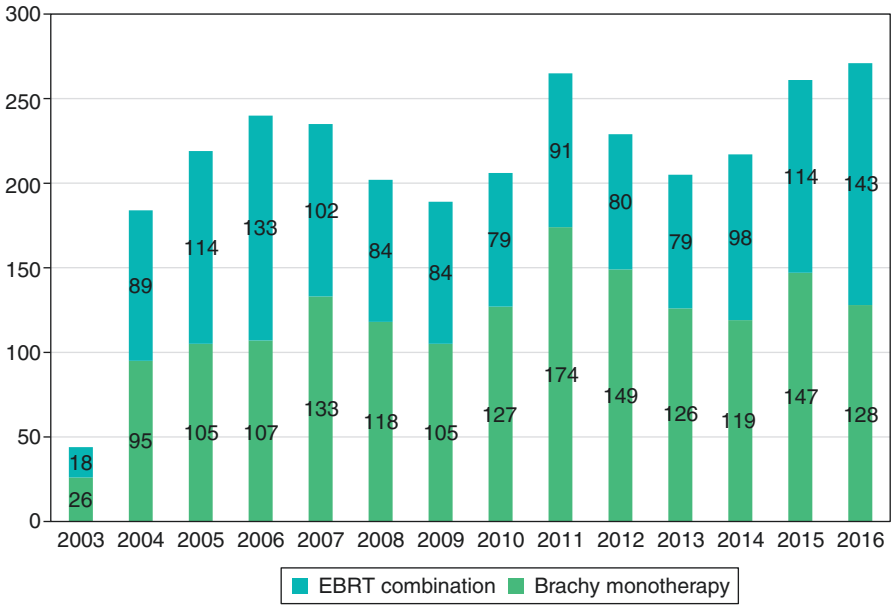

Fig. 11.4 Number of PB cases performed each year in Tokyo Medical Center. Lower part is cases treated with PB alone, and upper part is cases treated with a combination of EBRT. A total of 2962 cases were treated from 2003 to 2016

well treated by PB when they are combined with EBRT or short-term androgen-deprivation therapy (ADT).

11.5 Activity of Academic Study Group JPSS for the Development of Seed Implantation Brachytherapy in Japan

As for the restriction of performing PB by the guideline in Japan, all PB cases are able to be taken in only at major institutes. All physicians involved in PB are well trained, and the treatments will be performed safely with high technique. In most of the institutes, radiation oncologists sit in the front of computer for planning, while urologists do needle insertion and seed placement.

For the purpose of sharing the information of PB and improving its technique in Japan, the Japanese Prostate Permanent Seed Implantation Study Group (JPSS) was established in 2004 and holds annual conference every year. Technical training course is also held every year and shows the live surgery to the audience and educate treatment techniques to urologists, radiation oncologists, nurses, and physicists. All medical staffs involved in PB are asked to attend these meetings and train themselves for performing PB safely and with high technique.

Multi-institutional studies are organized by JPSS to investigate Japanese outcomes of PB and dispatch the data to the world. The Japanese Prostate Cancer Outcome Study of Permanent I-125 Seed Implantation (J-POPS) [10] is multi-institutional cohort study enrolling 7200 PB cases from July 2004 to December 2012, which is approximately 40% of the entire cases treated during that period of the time around the country. Background of cases enrolled in this study may enhance situation of PB in Japan, and its outcomes will create evidence for establishing a guideline of the treatment.

The Study of Seed and Hormone for Intermediate-risk Prostate Cancer (SHIP) [11] is a multi-institutional randomized clinical trial (RCT) to compare short-term (3 months) and long-term (9 months) effects of ADT combined with PB for treating intermediate-risk cases of localized prostate cancer. Three hundred and seventy cases had been enrolled in this study until July 2011 and would be followed at least 5 years.

The trimodality with brachytherapy, EBRT, and hormonal therapy for high-risk prostate cancer (TRIP) [12] study is also a multi-institutional RCT to investigate the effect of trimodality treatment, such as PB, EBRT, and ADT, for high-risk cases. Two hundred and seventy cases are enrolled and randomized into two groups having only neoadjuvant and concurrent ADT for 6 months or having continuous long-term adjuvant ADT for another 2 years. The results from this study will show the effect of ADT in treating high-risk prostate cancer with PB combined with EBRT, which is not previously revealed. SHIP and TRIP studies are expected to present tremendously important results for establishing evidence of PB for intermediate- and high-risk prostate cancer.

11.6 Clinical Outcomes of Permanent Seed Implantation Brachytherapy in Tokyo Medical Center

Between September 2003 and December 2015, 2680 patients underwent PB for cT1-3N0M0 prostate cancer at Tokyo Medical Center. In National Comprehensive Cancer Network (NCCN) classification, low-risk and part of intermediate-risk (Gleason score 3 + 4 with positive biopsy core rate < 34%) cases were treated with PB alone, and their prescription dose was 145–160 Gy. Other intermediate-risk and high-risk cases were treated with combination of PB and EBRT, and their prescription dose was 100–110 Gy for PB and 45 Gy (1.8GyX25) for EBRT. In this analysis, median follow-up period is 6.6 years, and backgrounds of the patients analyzed were shown in Table 11.1. Kaplan-Meier analysis was performed to evaluate their overall survival rate (OS), disease-specific survival rate (DSS), and biochemical progression-free survival rate (BPFS). The Phoenix definition was used to determine biochemical failure after the treatment. However, clear PSA bounce cases were excluded from failure for the analysis. The OS, DSS, and BPFS at 10 years were 88.7% (Fig. 11.5a), 99.3%, and 91.4%, respectively. Of 2680 patients, 972 (36.3%) were low-risk cases, 1362 (50.8%) were intermediate-risk cases, and 346 (12.9%) were high-risk cases. BPFS of each risk classification was 95.9%, 91.0%,

Table 11.1 Backgrounds of the patients of the analysis (n = 2680)

Follow-up years median (range)	6.6 (0.1–14.0)
Age (year) Median (range)	68 (38–90)
Initial PSA (ng/ml) Median (range)	7.6 (1.0–96.8)
Gleason score Cases(%)	≤6: 1206 (45.0) 7: 1299 (48.5) 8≤: 175 (6.5)
Clinical stage Cases (%)	T1c: 1670 (64.8) T2: 828 (32.2) T3: 78 (3.0)
Bx positive care rate (%) Median (range)	25.0 (1.3–100)
EBRT combination Cases (%)	+: 1162 (43.4) –: 1518 (56.6)
Neoadjuvant hormone Tx Cases (%)	+: 1359 (50.7) –: 1321 (49.3)
Risk classifications Cases (%)	Low risk: 972 (36.3) Intmed risk: 1362 (50.8) High risk: 346 (12.9)

and 78.6% at 10 years in the order of low, intermediate, and high risk (Fig. 11.5b). Toxicities were scored by the criteria of Common Terminology Criteria for Adverse Events v.4.0, and genitourinary and gastrointestinal toxicities of grade 3 or more were 1.5% and 0.2%, respectively.

11.7 Discussion

Prostate cancer is classified into three risk groups, low, intermediate, and high. Initially, BP was believed to be effective for lower-risk cases but not for higher risk. However, according to the clinical outcomes at Tokyo Medical Center shown in Fig. 11.5b, PB seems to be effective in all risk groups including high-risk cases. Many articles reported that PB achieved better cancer control compared with surgery or EBRT [13, 14]. Permanent brachytherapy, even performed alone or combined with EBRT, can provide high biologically effective dose (BED) [15] to the cancer tissue compared to high-dose EBRT. A randomized clinical trial named ASCENDE-RT [16] was reported recently which compared PSA outcomes between PB-based treatment and high-dose EBRT in higher-risk cases. It resulted in the PB group having significantly greater PSA control both in intermediate- and high-risk cases.

These data suggests that the future goal for PB is to achieve better cancer control than other treatment options for high-risk cases. Combination with ADT must be necessary, but the question is how long it should be used. In NCCN guidelines [17], EBRT requires long-term (2–3 years) ADT, but it is not requested for PB. The TRIP study may clarify the answer in a few years.

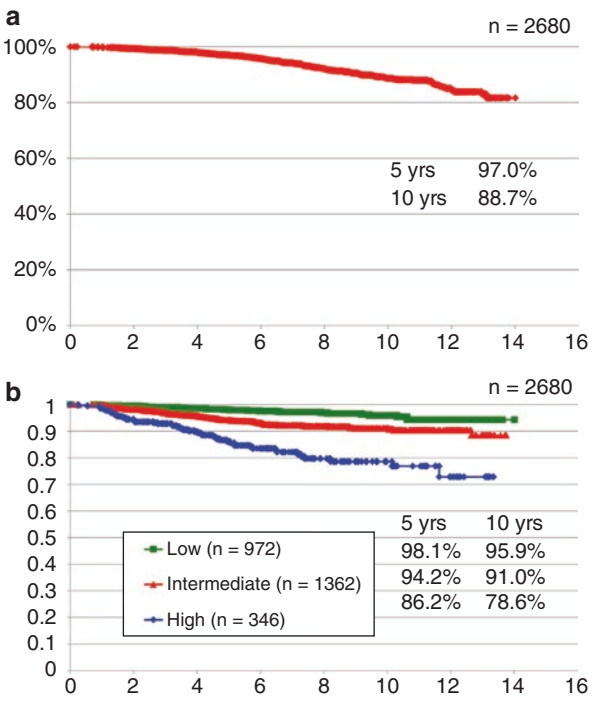

Fig. 11.5 (**a**): Overall survival rate of all 2960 cases. (**b**) PSA relapse-free survival rate in low- (—), intermediate- (—), and high-risk (—) group

One other field for PB is focal therapy [18]. Focal PB is surely effective for maintaining better QOL, but there is not enough evidence for cancer control.

Further investigation is necessary in this field.

11.8 Conclusion

The beginning of PB in Japan was in 2003, but there were already prior experiences in the USA, and numerous evidences had been shown at that time. We established our own guidelines according to previous foreign experiences and followed the recommendations. The academic study group JPSS was established immediately after the permission from the government to start this treatment. JPSS held annual educational meetings and technical courses to educate medical staffs who were involved in PB program in each institute. These backgrounds and efforts made it possible to start PB safely and also in high level at each institute from the beginning. Finally, PB has been established as one of the options for treating localized prostate cancer in Japan.

With various investigations of PB, it has become increasingly apparent that its efficacy and morbidity depend on implantation quality. Much data shows that cure rate, urinary and rectal complications, and maintenance of sexual potency are related to specific source distribution. So it is widely expected that all medical staffs who are involved in providing PB will make continuous efforts to refine planning

philosophies, intraoperative techniques, and postimplantation evaluation for the improvement of treatment quality.

Appendix

Tokyo Medical Center is a leading institute of PB in Japan, and numerous medical staffs were involved in this program. All of them supported the development of this treatment not only in a single institute but also in whole country. The author presents a great appreciation for their efforts and wishes to maintain their spirits in the program forever. The author is especially thankful to all physicians who are recently involved in the program. Toru Nishiyama M.D.; Yasuto Yago M.D.; Masanori Hasegawa M.D.; and Ken Nakamura M.D. are urologists, and Yutaka Shiraishi M.D.; Kazuhito Toya M.D.; and Atsunori Yorozu M.D. are radiation oncologists. Yasuto Yagi M.D. made an effort in analyzing statistical data of PB.

References

1. Whitmore WF, Hilaris BS, Grabstold H. Retropubic implantation of iodine-125 in the treatment of prostatic cancer. J Urol. 1972;108:918–20.
2. Zelefsky MJ, Whitmore WF. Long-term results of retropubic permanent I-125 implantation of the prostate for clinically localized prostate cancer. J Urol. 1997;158:23–9.
3. Zelefsky MJ. Three-dimensional conformal brachytherapy for prostate cancer. Current Urol Reports. 2004;5:173–8.
4. Holm HH, Juul N, Pedersen JF, et al. Transperineal Iodine-125 seed implantation in prostatic cancer guided by transrectal ultrasonography. J Urol. 1983;130:283–6.
5. Saito S, Nagata H, Kosugi M, et al. Brachytherapy with permanent seed implantation. Int J Clin Oncol. 2007;12:395–407.
6. Statistic of cancer in Japan; presented by National Cancer Center. 2017. http://ganjoho.jp/reg_stat/statistics/stat/short_pred.html.
7. Treatment modalities of radiation therapy for prostate cancer in Japan. Estimated from 2012 annual report of JASTRO. https://www.jastro.or.jp/aboutus/child.php?eid=00048.
8. Jackson MW, Amini A, Jones BL, et al. Prostate brachytherapy, either alone or in combination with external beam radiation, is associated with longer overall survival in men with favorable pathologic group 4 (Gleason score 8) prostate cancer. Brachytherapy. 2017;16:790–6.
9. Spratt DE, Soni PD, McLaughlin PW, et al. American brachytherapy society task group report: combination of brachytherapy and external beam radiation for high-risk prostate cancer. Brachytherapy. 2017;16:1–12.
10. Saito S, Ito K, Yorozu A, et al. Nationwide Japanese prostate cancer outcome study of permanent iodone-125 seed implantation (J-POPS). Int J Clin Oncol. 2015;20:375–85.
11. Miki K, Kiba T, Sasaki H, et al. Transperineal prostate brachytherapy, using I-125 seed with or without adjuvant androgen deprivation, in patients with intermediate-risk prostate cancer: study protocol for a phase III, multicenter, randomized, controlled trial. BMC Cancer. 2010;10:572–8.
12. Konaka H, Egawa S, Saito S, et al. Tri-Modality therapy with I-125 brachytherapy, external beam radiation therapy, and short- or long-term hormone therapy for high-risk localized prostate cancer (TRIP): study protocol for a phase III, multicenter, randomized, controlled trial. BMC Cancer. 2012;12:110–9.

13. Grimm P, Billiet I, Bostwick D, et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the prostate Cancer results study group. BJU Int. 2012;109(Suppl 1):22–9.
14. Ciezki JP, Weller M, Reddy CA, et al. A comparison between low-dose-rate brachytherapy with or without androgen deprivation, external beam radiation therapy with or without androgen deprivation, and radical prostatectomy with or without adjuvant or salvage radiation therapy for high-risk prostate Cancer. Int J Radiat Oncol Biol Phys. 2017;97:962–75.
15. Stock RG, Stone NN, Cesaretti JA, et al. Biologically effective dose values for prostate brachytherapy: effects on PSA failure and posttreatment biopsy results. Int J Radiat Oncol Biol Phys. 2006;64:527–33.
16. Morris WJ, Tyldesley S, Rodda S, et al. Androgen suppression combined with elective nodal and dose escalated radiation therapy (the ASCENDE-RT trial): an analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate Cancer. Int J Radat OncolBiol Phys. 2017;98:275–85.
17. National Comprehensive Cancer Network(NCCN)Cancer Network, NCCN Guideline, Prostate Cancer Ver 2, 2017. http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
18. Valerio M, Ahmed HU, Emberton M, et al. The role of focal therapy in the management of localized prostate cancer: a systemic review. Eur Urol. 2014;66:732–51.

A Review of Permanent Prostate Brachytherapy as Practiced in Japan

12

Atsunori Yorozu and Shiro Saito

Abstract

Iodine-125 permanent prostate brachytherapy (PPB) was introduced in Japan in 2003. The Japanese guidelines of radiation safety control for PPB regulate radiation safety parameters including the qualifications of the institutions and doctors to perform this treatment. To evaluate the safety and efficacy of PPB for localized prostate cancer, the nationwide Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 Seed Implantation (J-POPS) was conducted between 2005 and 2010. The J-POPS study is the largest multi-institutional prospective cohort study to achieve state-of-the-art clinical outcomes for localized prostate cancer treated using PPB. This study, along with regular training courses and joint radiation oncology-urology conferences, has promoted and achieves quality PPB. Every year, 3000 patients are treated with this modality in Japan. In this article, the early results of J-POPS and many clinical investigations are reviewed to provide the current status of PPB as practiced in Japan. This review covers planning techniques, postimplant dosimetry, toxicity, clinical outcomes, and special issues of radiation safety control.

Keywords

Prostate cancer · Permanent brachytherapy · Low-dose-rate · Iodine-125 Safety control

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12.1 Introduction

Since 2015, prostate cancer has been the most common malignancy in men in Japan. It is estimated that in 2015, nearly 98,400 men were diagnosed. Current common treatment options for early stage prostate cancer include radical prostatectomy, external beam radiation therapy (EBRT), low-dose-rate (LDR) and high-dose-rate brachytherapy, androgen deprivation therapy (ADT), and active surveillance. Transrectal ultrasound (TRUS)-guided permanent prostate brachytherapy (PPB), also known as LDR brachytherapy, is a short-time procedure associated with a rapid recovery and return to normal activity. Until 2002, a sealed radioactive source of I-125 had not been approved in Japan. To obtain permission from the government for this treatment in Japan, a task force for the promotion of PPB from the Japan Radioisotope Association in cooperation with the Japanese Society for Radiation Oncology (JASTRO) and the Japanese Urological Association (JUA) discussed the issue extensively with representatives from the Ministry of Health, Labor, and Welfare and the Ministry of Education and Science. With the establishment of the Japanese guidelines for radiation safety control of PPB, the treatment finally became available in June 2003 [1]. In September of that year, PPB with I-125 was performed at Tokyo Medical Center for the first time in Japan [2]. In 2004, 269 patients were treated with brachytherapy at two hospitals. In 2006, the medical cost for this treatment was revised by government reimbursement regulations. A total of 1412 patients were treated at 23 hospitals in 2005, 2783 patients were treated at 83 hospitals in 2008, and 3793 patients were treated at 109 hospitals in 2011. It is estimated that over 30,000 patients in Japan have been treated with this modality as of 2016. Subsequently, PPB has produced excellent clinical outcomes associated with a relatively low toxicity. Only the I-125 isotope is available for PPB in Japan and is supplied by two radiation source supply companies to medical institutions via the Japan Radioisotope Association, imported from the United States.

TRUS-guided PPB has evolved for decades since its introduction into clinical practice in the United States. The Japanese Brachytherapy Group of JASTRO made radiotherapy planning guidelines for PPB in 2012 [3], basically following American Brachytherapy Society (ABS) recommendations [4, 5]. Joint radiation oncology-urology conferences, regular technical training courses, and multi-institutional clinical trials have also been carried out countrywide to improve the quality of PPB, which may lead to better clinical outcomes and radiation safety.

Over 100 articles in English have been published in the last decade from Japan, and the techniques, planning, methods of dosimetry, and outcomes are reviewed to provide timely updated recommendations for PPB in Japan. This review has been categorized into six areas: (1) summary of the Japanese guidelines for radiation safety control; (2) treatment methods, planning, and technical issues; (3) postimplant dosimetry; (4) toxicity and management; (5) clinical outcomes and trials; and (6) radiation safety issues.

12.2 Special Issues of Japanese Guidelines for Radiation Safety Control of PPB

The procedure for permanent seed implantation performed in Japan should follow the guidelines of JASTRO, JUA, and the Japan Radiological Society [1]. This guideline mainly consists of radiation safety parameters including the qualifications of the institutions and doctors to perform this treatment. The treatment should be done in a radiation treatment room registered for brachytherapy. The institution should have a radiation oncologist approved by JASTRO and a urologist approved by JUA, both in full-time employment. Doctors and all other staff members, such as nurses, radiation therapists, or medical physicists, involved in this treatment should attend the education course held by the Japan Radioisotope Association. To avoid unnecessarily high radiation exposure to the public, the International Commission on Radiological Protection recommends that a medical facility may authorize release from its control any individual who has been administered a by-product material if the effective dose to any other persons from exposure to this individual is not likely to exceed 5 mSv and the effective dose to a member of the public is not likely to exceed 1 mSv [6]. The guideline introduced the regulation of two types of release criteria, not exceeding the measured radiation dose rate of 1.8 μSv/h at 1 m from the patient or not exceeding the administered radionuclide activity of 1300 MBq for I-125. These release criteria will be deregurated soon. Patients should spend at least overnight in the radiation controlled room after seed implantation to check for seed expulsion, which may occasionally be seen through the urine. If a patient dies within 1 year of the seed implantation, the prostate should be taken out with the seeds by performing an autopsy before cremation [1, 7].

12.3 Treatment Methods, Planning, and Technical Issues

12.3.1 Recommended Treatment Protocol in a Large Cohort Study in Japan (J-POPS)

To evaluate the safety and efficacy of PPB for localized prostate cancer, the nationwide Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 Seed Implantation (J-POPS) was initiated in July 2005, and registration continued until December 2010 [8]. The J-POPS study is the largest multi-institutional prospective cohort study to achieve state-of-the-art clinical outcomes for localized prostate cancer treated using PPB, which has become a common treatment option in Japan. Recruitment for the J-POPS study began in July 2005 and continued until December 2010. Initially, the study aimed to enroll 2000 participants within 2 years (cohort 1), extending the period of enrollment until December 2010 (cohort 2). Among 72 hospitals performing PPB around the country until June 1, 2007, 46 (64%) provided cohort 1 of the J-POPS.

Each participant is treated with PPB in accordance with the ABS recommendation. All participants were treated with loose seeds, which were available in Japan at

that time, using a specific applicator (Mick Applicator) as a seed insertion instrument. I-125 seed activity specified from 0.2 to 0.4 mCi/seed is only available in Japan. Modified peripheral loading or modified uniform loading is recommended for seed placement. Treatment with PPB alone (monotherapy) is usually performed in low-risk cases (PSA < 10 ng/ml, GS < 7, and clinical T stages T1–T2a), and combined treatment with PPB and EBRT is recommended for intermediate-risk (PSA 10–20 ng/ml or GS = 7 or clinical T stages T2b–T2c) and high-risk cases (PSA 20 ng/ml or GS > 7 or clinical T stages T3a). Neoadjuvant ADT is recommended for patients with a prostate volume >40 ml of short duration and for those who have had high-risk diseases for several months as an adjuvant. It is difficult to treat a large prostate with seed implantation alone because the upper limit of total activity is 1300 MBq. According to initial experiences, 40 ml is the prostate size that requires 1300 MBq to cover 90% of the prostate volume (D90) with at least 144 Gy. This means that a prostate size over 40 ml probably needs ADT to reduce the size. The median prostate volume was 25.2 mL in this cohort. Alpha-1 blockers are recommended for postoperative use to reduce adverse voiding events, such as voiding difficulty, urinary retention, or voiding irritability.

The gross target volume (GTV) is defined as the prostate volume visualized on images. The clinical target volume (CTV) is determined from the GTV with an added treatment margin of 3–5 mm in all directions, except for <2 mm in the posterior direction. Using online in vivo 3-D dosimetry, fluoroscopy, and sonography to eliminate errors due to seed placement, there is no need for an expansion from the CTV to define the PTV, i.e., PTV = CTV. A dose of 144 Gy is prescribed for the PTV as PPB monotherapy. It is recommended that the percentage volume of the prostate receiving 100% (V100) for PTV should be >90% or that the minimal dose received by 90% of the prostate volume (D90) should be 144–180 Gy for planning goals. The maximum urethral dose is <200 Gy, and that for the rectum is <200 Gy in any slice. The prescribed dose for PPV should be 100–110 Gy for combination therapy with EBRT and 40–50 Gy for EBRT with a 1.8–2.0 Gy/fraction. EBRT is performed either before PPB or approximately 1 month after PPB. It is recommended that the EBRT radiation field should be set for both the prostate and seminal vesicles for intermediate-risk and high-risk cases. Irradiation of the pelvis is optional for those classified as intermediate or high risk. The maximum urethral and rectal dose for PPB should be <150% of the prescribed dose for combination therapy with EBRT. A CT scan is obtained approximately 1 month after implantation for the postimplant dosimetric assessment. The calculated dosimetry parameters are the prostate V100, V150, and D90. Additionally, the rectal dose, expressed as the rectal volume (ml) which received 100% and 150% of the prescribed dose (R100 and R150, respectively), and the urethral dose, expressed as the values of the minimal dose received by 90%, 30%, 10%, and 5% of the urethral volume (urethral D90, D30, D10, and D5, respectively) and the volume of the urethra receiving 200% of the prescribed dose (U200), are assessed from the dose-volume histogram (DVH) obtained at post-planning. Urethral D30 and D10 were not included at first but are recommended in the JASTRO guideline today. The urethral dose is defined by the urinary catheter dose or by the dose at the center of the prostate when a catheter has

Table 12.1 Recommended dose prescriptions and dose constraints in the planning from JASTRO guidelines

Prescription dose	144 Gy/160 Gy as monotherapy 110 Gy as combined with EBRT of 40–50 Gy (1.8–2 Gy/fraction)
PTV	D90 between 100% and 130% of the prescription dose V100 > 98%, V150 < 50%
Urethra	UD10 < 150% of the prescription, UD30 < 125% of the prescription
Rectum	RV100 < 0.1 cc

EBRT external beam radiation therapy, *PTV* planning target volume, *D90* the minimal dose received by 90% of the PTV, *V100, V150* the percentage volume of the PTV receiving 100%, 150% of the prescription dose, *UD10, UD30* the dose to 10% and 30% of the urethral volume, *RV100* the volume of rectal wall in cubic centimeters receiving 100% of the prescribed dose

not been inserted. The DVH of all enrolled cases were analyzed at the committee and presented every year to all institutes attending J-POPS for treatment quality assurance. This kind of feedback may be related to the improvement in treatment quality of PPB around the country. Recommended dose prescription and dose constraints in JASTRO guidelines are listed in Table 12.1 [3].

The CTV for preimplant dosimetry should be the prostate gland with a margin in the preplanning method. In contrast, the CTV in intraoperative planning is usually the gland without a margin. Stock recommends 160 Gy as a prescription dose for the CTV, the prostate gland without a margin in the intraoperative planning technique [9].

12.3.2 Preplanning Versus Interactive/Intraoperative Planning Technique

There are currently two major planning approaches to brachytherapy: preplanning and intraoperative planning [4, 9–11]. Traditionally, PPB implants are preplanned. With this technique, the patient is implanted with a predetermined arrangement of seeds based on an ultrasound volume study performed several weeks in advance. Creation of a plan well before the actual procedure allows ample time to perform the necessary optimizations and enables precise ordering of the seeds. However, factors such as neoadjuvant hormonal therapy, difficulty in replication of the patient setup, relaxation of the pelvic musculature during anesthesia, and edema subsequent to needle and seed insertion can all lead to alterations of prostate volume and shape. While advocates of the preplanning method assert that these are nominal obstacles easily overcome with experience and minor intraoperative adjustments, some investigators have moved toward developing a single-step procedure, bringing the entire planning and implantation process into the operating room. The intraoperative method is supported by those who claim facilitated and enhanced accuracy in plan execution [9]. However, it has drawbacks, as the need for a preoperative volume study is not eliminated and costly operating room time may be prolonged. Numerous institutions specializing in either the preplanning or the intraoperative method have demonstrated similar postimplantation dosimetry and excellent biochemical results [10, 11]. Yoshida compared preplanning and

intraoperative planning, based on postimplant dosimetry, toxicity, and biochemical outcomes for 665 patients at Tokyo Medical Center, and found similar clinical outcomes [12]. However, urethral doses and rectal doses were significantly lowered in the intraoperative planning technique when prescribed dose is equivalent. Therefore, dose escalation could be easier with the intraoperative plan. In the J-POPS study, intraoperative or interactive planning in EBRT combination therapy group was effective in decreasing the incidence of rectal toxicity [13]. Ishiyama reported the intraoperative interactive plan showed a significant reduction of the seed migration rate compared to the preplanning group [14]. Moreover, posttraumatic swelling following implantation is increased by cessation of hormone therapy and may reduce D90; however, the intraoperative plan technique overcomes this disadvantage of hormone therapy. At present, the intraoperative or interactive planning method is preferred in Japan.

12.3.3 Seed Migration with Loose Seeds

Until 2010, only loose seeds were available in Japan, and seed migration was unavoidable. The incidence and associated factors of loose-seed migration were investigated in cohort 1 of J-POPS, consisting of 1641 patients treated with monotherapy and 519 patients treated with PPB combined with EBRT [15]. Seed migration was observed in 22.7% of monotherapy and 18.1% of combination. Migration to the lungs and abdominal/pelvic region was observed in 14.6% and 11.1% of PPB patients, respectively. This large-scale analysis showed no difference in D90 or V100 between seed migration and the absence. The migrated seeds have been reported to be in the heart, mediastinum, kidney, inguinal canal, liver, sacrum, vertebral venous plexus, and even in varicoceles [15–17].

12.3.4 Loose Seeds Versus Intraoperatively Built Custom-Linked Seeds

Stranded or linked seeds were introduced to Japan in 2012. The push-button seed delivery system allows the user to create intraoperatively built custom-linked (IBCL) seeds, using a combination of seeds, connectors, and spacers. IBCL seeds combine the benefits of loose and stranded seeds including intraoperative customization, reduced migration, and stabilization due to linking. Ishiyama conducted a prospective quasirandomized control trial to compare dosimetric parameters, seed migration rates, operation times, and acute toxicities of IBCL seeds with those of loose seeds in 140 patients [18]. They showed seed migration rate was significantly lower in the IBCL-seed group (0%) than in the loose-seed group (55%). Mean operation time was slightly but significantly longer in the IBCL-seed group (57 min) than in the loose-seed group (50 min). No significant differences in acute toxicities were seen. In the multi-institutional retrospective analysis including 854 patients in 13 Japanese centers, the learning curve for the dosimetric parameters

and operation times were analyzed [19]. Prostate V150 and rectal V150 were significantly higher in the loose-seed group than in the IBCL-seed group. The percentage of patients with seed migration in the IBCL-seed group was one-tenth that in the loose-seed group. They revealed no dosimetric demerits, no learning curve for dosimetry, and a slightly extended operation time for IBCL seeds. A significant reduction in the rate of seed migration was identified in the IBCL-seed group. Katayama showed more dose coverage postoperatively in the anterior base prostate sector in IBCL-seed implantation compared with loose-seed implantation, while other postimplant DVH parameters and toxicities did not differ significantly between the two groups [20].

12.4 Postimplant Dosimetry

12.4.1 Evaluation of Postimplant Dosimetry

The ABS recommends that CT-based postoperative dosimetry be performed within 60 days of the implant [1, 2]. Postimplant dosimetry is mandatory for good clinical practice and quality assurance. The interval between the implant and CT will produce differing results in postimplant dosimetry because of varying degrees of edema. Postimplant CT obtained within 24 h of the procedure is more convenient for the patient and allows early identification of dosimetric problems; however, undertaking dosimetry at this time will underestimate dosimetric parameters because of edema. The optimum CT timing to minimize edema-derived dosimetry error is radionuclide specific, 30.7 days for I-125. We compared the results of intraoperative dosimetry with those of postimplant CT-based dosimetry on day 1 and day 30 in 412 patients [21]. The mean intraoperative D90 was 118.8% of the prescribed dose versus 106.4% for day 1 ($p < 0.01$) and 119.2% for day 30 ($p = 0.25$). There were no significant correlations between the intraoperative D90 and the postimplant D90 values. Prostatic edema at day 1 had the largest effect on the day 1 D90. The factor significantly affecting the day 30 D90 was neoadjuvant ADT. The intraoperative and postimplant dosimetric values differed significantly for the urethra and rectum. Consistency in timing and postimplant segmentation is favored.

It is well known that there is inter- and intraobserver variability in postimplant CT contouring of the prostate, which results in differences in computed doses. Therefore, methods for improving reproducibility of postimplant dosimetry such as MR-CT image fusion are encouraged. MRI-based dosimetry using contrast-enhanced T1WI appears to be acceptable by Ohashi. Their results suggest that MRI-based dosimetry is a practical method for estimation of the higher dose distribution, especially if seeds are clustered together or close to calcifications [22]. Katayama presented a novel method for postimplant dosimetry using T2*-WI/T2-weighted image fusion. They reported that in T2*-weighted image (T2*-WI), seeds can be easily detected without the use of an intravenous contrast material [23].

12.4.2 Dose-Response Issues

Whereas no prospective dose escalation clinical trials have been conducted on PPB for prostate cancer, numerous studies support a dose-response relationship of biochemical control associated with increasing doses or biological effective doses (BED) [9, 24]. The optimal D90 cutoff for postimplantation dosimetry remains a debated issue. The Mount Sinai group prescribe 160 Gy for their real-time planning, and they recommend D90 values of 180 Gy [9]. Morris reported that D90 was not predictive of disease-free survival [25]. They caution that these important dosimetric parameters are not surrogates of oncologic endpoints. Ohashi analyzed 663 patients with low-risk and low-tier intermediate-risk prostate cancer treated with I-125 PPB in two centers between 2003 and 2009 [26]. They concluded prostate D90 was the only significant independent predictor of biochemical failure-free survival. We analyzed low-risk and low-tier intermediate-risk prostate cancer patients of Tokyo Medical Center to define the optimal dose for I-125 prostate implants by correlating postimplantation dosimetry findings with biochemical failure and toxicity [27, 28]. Between 2003 and 2009, 683 patients with prostate cancer were assessed and followed up for a median time of 80 months by Shiraishi [28]. Implant dose was defined as the D90 on days 1 and 30 after implantation. A multivariate analysis found day 1 D90 and day 30 D90 to be the most significant factors affecting the 7-year biochemical failure-free rate. We found that day 30 D90 cutoff points from 130 to 180 Gy appeared to be good for the entire cohort. Greater D90s were associated with an increase in late genitourinary or gastrointestinal toxicity less than grade 2, but the increase was not statistically significant. High prostate D90s, even with doses exceeding 180 Gy, achieve better treatment results and are feasible.

In practice, many brachytherapists plan a dose higher than 144 Gy to compensate for edema, seed placement uncertainty, and other factors. In the J-POPS study, the median D90 was 160.6 Gy in Japanese multi-institutions [13]. At Tokyo Medical Center, the median D90 was 184.7 Gy [27]. Based on the published literature, an acceptable dose range for postimplant D90 for I-125 may be 130–180 Gy if normal structures are not overdosed. D90s from 180 to 200 Gy seem to be well tolerated without increased incidence of severe toxicity [8, 11–13, 25, 27, 28]. Tanaka assessed the biochemical recurrence (BCR)-free rate in patients who underwent PPB, using two different definitions (Phoenix definition and PSA $\geq$ 0.2 ng/mL as in the definition for radical prostatectomy) in 203 patients [29]. A higher BED $\geq$180 Gy2 promises a favorable BCR-free rate, even if the strict definition is adopted. These Japanese results are comparable with reports of favorable oncologic results of the prostate D90 of $\geq$180 Gy. Higher-risk patients may benefit from a D90 $\geq$ 180 Gy. Recently, Ishiyama evaluated the current variability of treatment planning of seed implantation in Japanese centers [30]. Twelve Japanese radiation oncologists were asked to make treatment plans with the data as they would in their own practice. A relatively high dose with a small deviation was irradiated to the prostate (mean D90 = 188 Gy; SD = 10 Gy). Then, five radiation oncologists were asked to participate in two virtual trials in which the D90 was (1) required to be set at just 180 Gy and (2) increased as much as possible without violating other

limitations. In the virtual trials, all five physicians could achieve 180 Gy for the D90 with a very small deviation, although the urethral dose showed relatively large deviations. Dose escalation without increase of urethral dose or V150 was difficult, although the rectum could be spared by most of the physicians. An addition, Okamoto reported feasibility and an excellent outcome of high-dose (BED ≥ 220 Gy) radiotherapy by LDR in combination with EBRT in 60 patients with high-risk and very high-risk cancer [31]. These recommended BED values by Stock and Stone are supported in many Japanese institutions.

12.5 Toxicity and Management

12.5.1 GU Toxicity

Baseline data for 2339 out of 2354 patients in J-POPS were analyzed for toxicities using the National Cancer Institute's Common Terminology Criteria for Adverse Events and the International Prostate Symptom Scores (IPSS) recorded prospectively until 36 months after radiation therapy [32]. Grade 2+ acute urinary toxicities developed in 7.36%. Grade 2+ late urinary developed in 5.75% of the patients. A higher incidence of grade 2+ acute urinary toxicity occurred in the monotherapy group than in the PPB boost group (8.49% versus 3.66%; $p < 0.01$). The 3-year cumulative incidence rates for grade 2+ late urinary toxicities were 6.04% versus 4.82% for the monotherapy and PPB boost groups, respectively, with no significant differences between the treatment groups. The mean of the postimplant IPSS peaked at 3 months, but it decreased to a range that was within two points of the baseline score, which was observed in 69.47% at the 1-year follow-up assessment. The acute urinary toxicities observed were acceptable given the frequency and retention. Tanaka evaluated the chronologic changes in IPSS, uroflowmetric parameters, and prostate volume (PV) in 110 patients who received PPB [33]. The maximal flow rate, voided volume, and postvoid residual urine volume showed transient deterioration at 1 and 6 months after seed implantation and had returned to the baseline 12 months later. The mean PV compared with the baseline PV showed a significant 3.8 cc decrease (11.2%) at 12 months after implantation. The patients who did not receive neoadjuvant hormonal therapy had a 5.9 cc decrease in PV (20.2%) 12 months later. In contrast, those who received neoadjuvant hormonal therapy had no change in PV after seed implantation. The change in the PV was different after seed implantation in patients with or without neoadjuvant hormonal therapy. Tanaka also summarized chronologic changes of urinary toxicity in Japan experiences [34].

12.5.1.1 Acute GU Toxicity and Management

Alpha 1-adrenoceptor blocker may improve lower urinary tract symptoms after PPB. Oyama retrospectively assessed changes in lower urinary tract symptoms (LUTS) within 1 year after brachytherapy in 116 patients receiving alpha 1-adrenoceptor antagonists [35]. Alpha 1-adrenoceptor antagonists (tamsulosin, silodosin, and naftopidil) were given to all patients for up to 6 months after seed implantation.

In the management of LUT after brachytherapy, silodosin may provide a more favorable improvement. Silodosin and tamsulosin may have an advantage in improving not only voiding but also lower urinary tract storage symptoms after brachytherapy. Tanaka reported that approximately 70% of patients experience urinary frequency during the first 6 months after seed implantation [34]. The incidence of urinary retention was approximately 2–4%. A high IPSS before seed implantation was an independent predictor of acute urinary toxicity of grade 2 or higher. The incidence of urethral toxicity after LDR brachytherapy in a Japanese patient series is similar to that reported recently in the United States. Tanaka conducted a randomized controlled trial of silodosin versus naftopidil, two different alpha-1 adrenoceptor antagonists, on the lower urinary tract symptoms of 141 patients who underwent PPB [36]. Patients were randomized and allocated to two groups (silodosin 8 mg versus naftopidil 75 mg). The primary endpoint was a change in the IPSS at 3 months after seed implantation. The mean change in the IPSS at 3 months after seed implantation in both groups was 10.6 (naftopidil) and 10.4 (silodosin), respectively ($p = 0.728$). An increase in urinary frequency and a decrease in total urinated volume and mean voided volume were observed in frequency volume chart for 12 months after seed implantation. Multivariate analysis revealed that the urethral dose (UD30) was an independent predictive parameter of IPSS recovery. Patients with UD30 < 200 Gy showed a higher recovery rate of IPSS at 12 months after seed implantation. A lower dose on the urethra was an independent predictor of IPSS recovery in this important study.

12.5.1.2 Late GU Toxicity and Urinary Symptom Flare

Several predictive factors for urinary toxicities have been reported, such as urinary symptom flare, which is a late transient worsening of urinary symptoms described by Cesaretti [37]. In some large series, baseline IPSS, larger prostate volumes, lack of ADT, and higher radiation doses were revealed as factors associated with late urinary toxicity [38]. Sakayori analyzed genitourinary toxicity by follow-up of the IPSS and Overactive Bladder Symptom Score (OABSS) after PPB for 680 patients, with the median follow-up of 54 months [39]. The IPSS and OABSS showed similar patterns of change. Urinary symptoms improved more rapidly in those with high baseline IPSS levels. Age, ADT use, preimplant prostate volume, and BED were significantly associated with urinary outcomes. From experiences of 1313 patients in Tokyo Medical Center, Eriguchi examined the factors associated with long-term urinary toxicities after PPB with or without EBRT [40]. Time to IPSS resolution was not associated with BED, but baseline IPSS, total needles, and urethra D30 had the greatest effect. Urinary symptom flare was associated with baseline IPSS, age, BED, and EBRT. Urinary G2+ toxicity was associated with baseline IPSS, neoadjuvant ADT, and seed density. ADT use was associated with urinary G2+ toxicity. Higher dose and supplemental EBRT did not appear to increase moderate to severe urinary toxicities or time to IPSS resolution; however, it influenced urinary symptom flare. Miyake also showed that patients treated with higher BED had higher risks of urinary flare [41]. They revealed that persistent lower urinary tract symptoms after seed implantation were attributed to storage rather than voiding issues.

12.5.2 GI Toxicity and Management

Rectal toxicity of PPB is variable in its presentation and can range in severity from mild, self-limited proctitis to more severe cases of ulceration and fistula formation. Rectal dose-volume analysis is a practical method for predicting the risk of development of rectal toxicities. Katayama evaluated the associated factors of rectal toxicity in 2339 patients after PPB in J-POPS [13]. The 3-year cumulative incidence for grade 2+ rectal toxicity was 2.88%, 1.76%, and 6.53% in all subjects, the monotherapy group and PPB boost group, respectively. In the multivariate analysis, among all subjects, grade 2+ rectal toxicity was associated with rectal V100 and PPB boost. R100 in the monotherapy and R100 and interactive planning in the PPB boost group were also associated with grade 2+ toxicity. Rectal toxicity was relatively rare in this study compared with previous reports. For Japanese prostate cancer patients, R100 < 1 mL in both monotherapy and PPB boost groups and interactive planning in the PPB boost group may be effective in decreasing the incidence of rectal toxicity. Nakamura examined intraoperative rectal dose-volume constraints to prevent grade 2+ rectal bleeding in 197 patients treated with monotherapy using real-time intraoperative planning [42]. Postimplant dosimetry was performed on days 1 and 30 after implantation using CT imaging. The differences in R100s were compared among intraoperative, day 1 and day 30 dosimetry. The mean values of R100us, R100CT_1, and R100CT_30 were 0.31, 0.22, and 0.59 cc, respectively. These values temporarily decreased on day 1 and increased on day 30. The maximum bleeding odds ratio was identified among patients with an R100us value above 0.1 cc, an R100CT_1 value above 0.3 cc, and an R100CT_30 value above 0.5 cc. R100 should be less than 0.1 cc intraoperatively for preventing rectal bleeding. Shiraishi determined the rectal tolerance to grade 2 rectal bleeding after the PPB boost, based on a rectal dose-volume histogram from 458 patients with stages T1 to T3 prostate cancer who received combined modality treatment consisting of I-125 seed implantation followed by EBRT to the prostate and seminal vesicles [43]. The prescribed doses of brachytherapy and EBRT were 100 and 45 Gy in 25 fractions, respectively. The rectal dosimetric factors were analyzed for rectal V100 and V150 during brachytherapy and for rectal volumes receiving >30–40 Gy (V30–V40) during EBRT therapy. As a result, 9.7% of patients developed grade 2 rectal bleeding. In the multivariate analysis, age, R100, and V30 were identified as risk factors for grade 2 rectal bleeding. The rectal bleeding rate increased as the R100 increased: 5.0% for 0 ml; 7.5% for >0 to 0.5 ml; 11.0% for >0.5 to 1 ml; 17.9% for >1 to 1.5 ml; and 27.3% for >1.5 ml. Grade 2 rectal bleeding developed in 6.4% of patients with a V30 < =35% and in 14.1% of patients with a V30 > 35%. When these dose-volume parameters were considered in combination, the grade 2 rectal bleeding rate was 4.2% for a R100 < =0.5 ml and a V30 < =35%, whereas it was 22.4% for R100 > 0.5 ml and V30 > 35%. The risk of rectal bleeding was found to be significantly volume-dependent in patients with prostate cancer who received combined modality treatment. Now these dose constraints are used in the IMRT protocol of Tokyo Medical Center and TRIP study (described later).

12.5.3 Erectile Function

In administering a radical treatment for prostate cancer, the preservation of male sexual function is one of the important factors for determining the therapeutic plan. However, cultural and racial backgrounds in relation to the age of onset and sexual function are not necessarily the same throughout the world. The median age of onset in Japanese prostate cancer patients is 72 years, which is older than that in Europe and the United States [8]. Nishimura evaluated long-term erectile function following PPB in 665 men at the Tokyo Medical Center [44]. Erectile function was assessed before treatment and at 6 months, 1, 2, 3, 4, and 5 years after implantation using the Mount Sinai Erectile Function Score 4-point scale. In patients who were potent before treatment, the actuarial potency preservation rate fell to 46.2% at 6 months after brachytherapy and then slowly recovered reaching 52.0% at 5 years after brachytherapy. Patient age at implantation and pretreatment erectile function are predictive factors for the development of erectile dysfunction following PPB. Neoadjuvant hormone therapy affected potency preservation only at 6 months after brachytherapy. Recently, Okihara explored sexual function after PPB in J-POPS [45]. A total of 482 patients were selected, and Expanded Prostate Cancer Index Composite questionnaires were given before and at 3, 12, 24, and 36 months after the PPB. Furthermore, changes over time in their answers to Q18 (usual quality of your erections) were analyzed. Regarding Q18, 232 patients (48.2%) selected either "There was no sexual activity" or "There was no desire for erection" before receiving permanent brachytherapy. Of the 482 patients, sexual function was preserved in 138 patients (28.7%) 3 years after PPB. Considering the baseline proportion of potent patients was 41.3%, approximately 30% of potent patients had become impotent. Overall satisfaction significantly improved without regard for the deterioration of sexual function. Significant factors for maintaining sexual activity were patient age and sexual activity before PPB. In Japanese patients undergoing PPB alone for prostate cancer, sexual function may not be as well preserved as patients in western countries. However, decreased sexual function does not seem to be a major factor determining patients' overall satisfaction. These findings might be specific to Japanese patients, in whom elderly subjects account for the majority. Tanaka assessed the variations in HRRQOL in 109 patients who underwent PPB [46]. Sexual function showed a significant deterioration in Japanese men after seed implantation.

12.5.4 Follow-Up and PSA Bounce

Follow-up of definitively treated cancer patients is important for the practice of radiation oncology. Postoperative follow-up should consist of sufficient visits within the first 3 months and then every 3–12 months subsequently. The radiation oncologist should try to obtain a long-term follow-up of patient status. To check for biochemical or clinical failure, consideration should be given to the PSA bounce or spike phenomenon in cases of spurious PSA elevation following implantation.

Satoh examined the incidence, timing, and magnitude of the PSA "bounce" in 388 consecutive Japanese patients with T1-T2N0M0 prostate cancer treated with PPB with no ADT or EBRT in a multi-institutional pooled analysis [47]. PSA bounce is a common phenomenon after PPB and occurs at a rate of 19–51% in Japanese men who underwent PPB, depending on the definition used. The median time to develop PSA bounce was 12–18 months. There was a PSA bounce magnitude of 2 ng/mL in 5.3% of patients, and 95.3% of PSA bounces occurred within 24 months after PPB. It is more common in younger patients, and early PSA bounce should be considered when assessing a patient with a rising PSA level after PPB, before implementing salvage interventions. Furthermore, PSA bounce magnitude might be lower in Japanese than in Caucasian patients. Tanaka found that D90 of the urethra was the most significant predictor of PSA bounce in hormone-naïve patients treated with PPB alone [48].

12.5.5 Quality of Life (QOL)

It is important that treatment selection includes patient preferences and balance of predicted clinical outcomes over time versus potential impairment of QOL. Health-related quality of life (HRQOL) may vary among countries and people. Namiki investigated HRQOL in Japanese men with localized prostate cancer who underwent PPB or retropubic radical prostatectomy (RRP) [49]. A total of 70 patients who underwent PPB and 67 who underwent RRP were enrolled. The Medical Outcomes Study 36-Item Short Form (SF-36), University of California, Los Angeles; Prostate Cancer Index; and the IPSS were administered before and 1, 3, 6, and 12 months after treatment. No patients received neoadjuvant or adjuvant therapy. The PPB patients reported no significant changes in any of the general HRQOL domains throughout the follow-up period. However, the PPB patients experienced a significantly delayed recovery of the urinary bother score. The data from the IPSS showed adverse effects from PPB on voiding symptoms for the initial 6 months after treatment. No differences were found in bowel symptoms. RRP was associated with worse sexual function than PPB. Tanaka assessed the variations in HRRQOL in 109 patients who underwent PPB. The general HRQOL in the patients who underwent seed implantation was well preserved during the first year after seed implantation, whereas the urinary, bowel, and sexual function and bother scores showed transient deterioration during the first year after PPB [46].

12.6 Clinical Outcomes

12.6.1 Mid- and Long-Term Results

Table 12.2 shows the results of brachytherapy-based treatment regimens from Japanese institutions for prostate cancer risk categories. The biochemical disease-free rates ranged between 87% and 98% at 5–7 years for low-risk, between 88% and

Table 12.2 Results of PPB in Japan

Authors	Reference	Year	Risk	*N*	Median follow-up (year)	bNED	Treatment
Uesugi	[50]	2012	Low and intermediate	414	3	87% at 6 year	PPB ± NADT
Ohashi	[26]	2013	Low	488	5	98% at 7 year	PPB ± NADT
			Intermediate	175		92% at 7 year	PPB ± NADT
Yorozu	[27]	2013	Low	462	5.5	98% at 7 year	PPB ± NADT
			Intermediate	704		93% at 7 year	PPB ± RT ± NADT
			High	145		81% at 7 year	PPB ± RT ± NADT
Tanaka	[29]	2014	Low	93	6	93% at 5 year	PPB ± NADT
			Intermediate	92		92% at 5 year	PPB ± RT ± NADT
			High	18		94% at 5 year	PPB ± RT ± NADT
Ohashi	[51]	2014	High	206	5	85% at 5 year	PPB + RT ± NADT
Sekiguchi	[52]	2014	Low	175	5.5	94% at 5 year	PPB ± NADT
			Intermediate	130		97% at 6 year	PPB ± NADT
Tabata	[53]	2016	Intermediate	292	5.5	88% at 7 year	PPB ± RT + ADT
Okamoto	[31]	2017	High	143	5	95% at 5 year	PPB + RT + ADT

PPB permanent prostate brachytherapy, *NADT* neoadjuvant androgen deprivation therapy, *ADT* androgen deprivation therapy, *RT* external beam radiotherapy, *bNED* biochemically non-evidence of disease

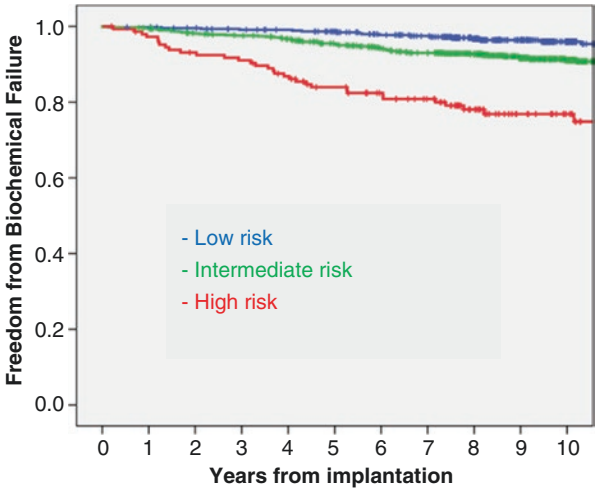

Fig. 12.1 Long-term follow-up of 1313 patients according to risk groups at Tokyo Medical Center

97% for intermediate-risk, and between 81% and 95% for high-risk prostate cancer. We reassessed 1313 patients treated with PPB at Tokyo Medical Center [27] for long-term outcomes and show 10-year biochemical disease-free rates in Fig. 12.1. A biochemical failure was defined by the Phoenix definition. With a median follow-up of 9.3 years, the 10-year biochemical disease-free rate was 91% (low risk 96%, intermediate risk 91%, and high risk 77%). A Japanese multimodality approach for each risk prostate cancer combining PPB with or without EBRT with or without

ADT seems to provide favorable freedom from biochemical failure compared with excellent results reported from western countries. However, one must acknowledge the many factors that can influence reported outcomes.

12.6.2 Salvage PPB and Focal Salvage

PPB is a good option for the treatment of the prostate cancer patient who experiences a local failure after definitive radiotherapy. Shimbo evaluated the effects and side effects of PPB for patients with postradiation local failure [54]. For 15 patients who received salvage brachytherapy, 144 Gy was given. The biochemical relapse-free survival rate was 100% at 1 year, 91.7% at 2 years, and 60.2% at 3 years. All acute genitourinary and gastrointestinal adverse events were in grades 1–2. As for late adverse events, one patient (6.7%) developed grade 3 hematuria at 17 months post-salvage. Although careful patient selection is needed, salvage PPB appears to provide good prostate cancer control with an acceptable rate of complications for patients with a local recurrence of prostate cancer after initial radiotherapy. Hori reported a patient who was successfully treated with salvage brachytherapy for a seminal vesicle recurrence [55]. Hosogoe reported a case of salvage PPB for a castration-resistant and EBRT-resistant local recurrence after radical prostatectomy [56].

The focal salvage PPB used to treat local recurrence after PPB is anticipated. This treatment is a method to delay chemical castration and a curative treatment option in cases of local recurrence of prostate carcinoma after PPB. Sasaki reported salvage partial PPB for eight cases of biopsy-proven localized prostate cancer recurrence appeared rational, technically feasible, and safe [57]. Kunogi investigated the treatment results of 12 patients for focal partial salvage re-implantation against local recurrence after PPB [58]. The focal clinical target volume (F-CTV) was delineated on positive biopsy areas in a mapping biopsy, combining the cold spots on the postimplant dosimetry for initial brachytherapy. The F-CTV was expanded by 3 mm to create the planning target volume (PTV) as a margin to compensate for uncertainties in image registration and treatment delivery. The prescribed dose to the PTV was 145 Gy. The median follow-up time was 56 months, and the median RD2cc and UD10 were 63 and 159 Gy, respectively. The 4-year biochemical disease-free rate was 78%. No patients had grade 3 GU/GI toxicities or died after salvage re-implantation.

12.6.3 Clinical Trials

Three large-scale clinical trials are ongoing in Japan. The first is the J-POPS mentioned earlier. The second is the Seed and Hormone for Intermediate-risk Prostate Cancer (SHIP) 0804, which is a phase III, multicenter, randomized, controlled study that investigates the impact of adjuvant ADT following neoadjuvant ADT and PPB [59]. A total of 420 patients with intermediate-risk, localized prostate cancer were

enrolled and randomized to one of two treatment arms before 2011. The patients initially underwent 3-month ADT prior to PPB. Those randomly assigned to adjuvant therapy subsequently underwent 9 months of adjuvant ADT. The primary endpoint is biochemical progression-free survival. The correlative study (SHIP36B) also evaluates biopsy results at 36 months following treatment to examine the relationship between the results and the eventual recurrence after completion of radiotherapy. The third trial is a phase III, multicenter, randomized controlled trial (RCT) of trimodality with BT, EBRT, and ADT for high-risk prostate cancer (TRIP) that investigates the impact of adjuvant ADT following PPB and supplemental EBRT with neoadjuvant and concurrent ADT [60]. Until 2012, a total of 340 patients with high-risk cancer were enrolled and randomized to one of two treatment arms. The patients commonly underwent 6-month ADT with combined androgen blockade before and during PPB and supplemental EBRT. Those randomly assigned to the long-term ADT group will subsequently undergo two years of adjuvant ADT with luteinizing hormone-releasing hormone agonist. The primary endpoint is biochemical progression-free survival. The present RCT is expected to provide additional insight regarding the potency and limitations of the addition of 2 years of adjuvant ADT to this trimodality approach and to establish an appropriate treatment strategy for high-risk prostate cancer.

12.7 Radiation Safety Issues

In accordance with the Nuclear Regulatory Commission's recommendation that radiation exposures to others be kept as low as reasonably achievable, prostate brachytherapy patients are given instructions against unnecessarily exposing others [61, 62]. Instructions are left to the discretion of the facility. Therefore, radiation safety instructions given to patients have relied on a community consensus developed from the literature and actual practice. The Japanese Guidelines for Safety Control of Brachytherapy with PPB recommend a strict and sophisticated approach [1]. This special situation arises from a general anxiety about radiation risks among the Japanese population. Published data have been limited to Europeans and North Americans who are physically different from Asian populations; thus, those data do not provide peace of mind for Asian patients. So, Hanada expanded the radiation dose rate measurement data set by measuring radiation under various brachytherapy situations to revise our guidelines [63]. Radiation exposure varies according to the patient's body posture, with results differing as much as approximately 40% in measured radiation dose rates at 30 cm from the anterior skin surface. Weight, body mass index, and tissue thickness showed good correlations with measured radiation dose rates. The magnitude of radiation exposure attenuation by shielding was approximately 95%, similar to the attenuation ratio based on tissue measurements made in the lateral direction. The respective mean times required to reach 1 mSv were 1.2, 7.6, and 65.4 days in the standing position and 0.6, 4.6, and 40.4 days in the supine position at the site of contact and at 30 and 100 cm from the anterior skin surface. Moreover, direct radiation exposure measurements were obtained from dosimeters provided to 25 patients who underwent PPB, along with their family

members [63]. The estimated lifetime exposure dose and the precaution time for holding children near the patient's chest were calculated. The mean estimated lifetime exposure doses were 7.61 (range: 0.45–20.21) mSv for patients and 0.19 (range: 0.02–0.54) mSv for family members. Assuming a dose limit of 1 mSv, the precaution times for holding a child every day were 250.9 (range: 71.3, 849.4) min. We now recommend a more sophisticated approach, considering attenuation by a possible protective device, such as lead-lined underwear, the duration of wearing such an undergarment, and the contact time of the involved person per day at given distances. Under these data and circumstances, the Japanese guidelines will deregulate release criteria permitting administered radionuclide activity up to 2,000 MBq from 1300 MBq today, or dose rate of 2.8 μSv/h at 1m from the patient.

If a prostate cancer patient treated with I-125 brachytherapy dies within 12 months of treatment, prostate removal before cremation is recommended to avoid problems related to radioactivity in the ashes, such as inhalation of airborne particulate matter by crematorium staff or nearby residents. The cremation of bodies is already common in countries and is increasing in others such as the United States. Therefore, a manual prepared under the editorial supervision of several professional associations was issued in 2008 in Japan [7]. Satoh investigated the incidence and causes of death and the actions taken subsequent to death, among prostate cancer patients who died within 12 months after PPB over a 10-year period in Japan [64, 65]. From 2003 to 2013, of the 27,976 patients who underwent PPB during the specified period, 79 died within 12 months of implantation. The prostate and brachytherapy source were retrieved at autopsy from 69 of the 79 patients. Autopsies could not be performed on the other ten patients, two of whom died in the earthquake.

Conclusions

Since 2003, PPB has been a good treatment option for localized prostate cancer in Japan. With implantation techniques maturing in the last decade and regular interactive education, PPB and EBRT have evolved steadily. We should pursue better long-term clinical outcomes while maintaining quality of life for patients and collaborate with brachytherapists worldwide.

References

1. Guideline for safety control of permanent implantation brachytherapy of prostate cancer. Editorial supervision by the Japanese Society for Therapeutic Radiology and Oncology/ Japanese Urological Association/Japan Radiological Society; 2003.
2. Saito S, Nagata H, Kosugi M, Toya K, Yorozu A. Brachytherapy with permanent seed implantation. Int J Clin Oncol. 2007;12(6):395–407. Epub 2007 Dec 21. Review. PubMed PMID: 18071858
3. Radiotherapy planning guidelines. Editorial supervision by the Japanese Society for Therapeutic Radiology and Oncology; 2012.
4. Nag S, Beyer D, Friedland J, Grimm P, Nath R. American Brachytherapy Society (ABS) recommendations for transperineal permanent brachytherapy of prostate cancer. Int J Radiat Oncol Biol Phys. 1999;44(4):789–99. Review. PubMed PMID: 10386635

5. Nag S, Bice W, DeWyngaert K, Prestidge B, Stock R, Yu Y. The American Brachytherapy Society recommendations for permanent prostate brachytherapy postimplant dosimetric analysis. Int J Radiat Oncol Biol Phys. 2000;46(1):221–30. Review. PubMed PMID: 10656396
6. ICRP. Radiation safety aspects of brachytherapy for prostate cancer using permanently implanted sources. A report of ICRP Publication 98. Ann ICRP. 2005;35(iii–ivi):3e50.
7. Manual for actions in early death cases occurring within one year after permanent implantation brachytherapy of prostate cancer. Editorial supervision by the Japanese Society for Therapeutic Radiology and Oncology/Japanese Urological Association/Japan Radiological Society/Japanese Society of Pathology/Japan Radioisotope Association; 2008.
8. Saito S, Ito K, Yorozu A, Aoki M, Koga H, Satoh T, Ohashi T, Shigematsu N, Maruo S, Kikuchi T, Kojima S, Dokiya T, Fukushima M, Yamanaka H. Nationwide Japanese Prostate Cancer Outcome Study of permanent iodine-125 seed implantation (J-POPS). Int J Clin Oncol. 2015;20(2):375–85. https://doi.org/10.1007/s10147-014-0704-4. Epub 2014 May 21. PubMed PMID: 24840041
9. Stock RG, Stone NN, Cesaretti JA, Rosenstein BS. Biologically effective dose values for prostate brachytherapy: effects on PSA failure and posttreatment biopsy results. Int J Radiat Oncol Biol Phys. 2006;64(2):527–33. Epub 2005 Oct 19. PubMed PMID: 16242258
10. Nag S, Ciezki JP, Cormack R, Doggett S, DeWyngaert K, Edmundson GK, Stock RG, Stone NN, Yu Y, Zelefsky MJ, Clinical Research Committee, American Brachytherapy Society. Intraoperative planning and evaluation of permanent prostate brachytherapy: report of the American Brachytherapy Society. Int J Radiat Oncol Biol Phys. 2001;51(5):1422–30. PubMed PMID: 11728703
11. Davis BJ, Horwitz EM, Lee WR, Crook JM, Stock RG, Merrick GS, Butler WM, Grimm PD, Stone NN, Potters L, Zietman AL, Zelefsky MJ, American Brachytherapy Society. American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy. Brachytherapy. 2012;11(1):6–19. https://doi.org/10.1016/j.brachy.2011.07.005. PubMed PMID: 22265434
12. Yoshida K, Ohashi T, Yorozu A, Toya K, Nishiyama T, Saito S, Hanada T, Shiraishi Y, Shigematsu N. Comparison of preplanning and intraoperative planning for I-125 prostate brachytherapy. Jpn J Clin Oncol. 2013;43(4):383–9. https://doi.org/10.1093/jjco/hys240. Epub 2013 Jan 11. PubMed PMID: 23315386
13. Katayama N, Yorozu A, Maruo S, Kojima S, Ohashi T, Tanaka N, Kikuchi T, Higashide S, Saito S, Dokiya T, Fukushima M, Yamanaka H. Predictive factors of rectal toxicity after permanent iodine-125 seed implantation: prospective cohort study in 2339 patients. Brachytherapy. 2016;15(6):736–45. https://doi.org/10.1016/j.brachy.2016.09.001. Epub 2016 Oct 6. PubMed PMID: 27720311
14. Ishiyama H, Satoh T, Kitano M, Kotani S, Uemae M, Baba S, Hayakawa K. Interactive-plan technique conquers the disadvantages of volume-reducing hormone therapy in 125I permanent implantation for localized prostate cancer. Int J Clin Oncol. 2009;14(1):53–5. https://doi.org/10.1007/s10147-008-0799-6. Epub 2009 Feb 20. PubMed PMID: 19225925
15. Nakano M, Yorozu A, Saito S, Sugawara A, Maruo S, Kojima S, Kikuchi T, Fukushima M, Dokiya T, Yamanaka H. Seed migration after transperineal interstitial prostate brachytherapy by using loose seeds: Japanese prostate cancer outcome study of permanent iodine-125 seed implantation (J-POPS) multi-institutional cohort study. Radiat Oncol. 2015;10:228. https://doi.org/10.1186/s13014-015-0532-3. PubMed PMID: 26577301; PubMed Central PMCID: PMC4650265
16. Nakano M, Uno H, Gotoh T, Kubota Y, Ishihara S, Deguchi T, Hayashi S, Matsuo M, Tanaka O, Hoshi H. Migration of prostate brachytherapy seeds to the vertebral venous plexus. Brachytherapy. 2006;5(2):127–30. PubMed PMID: 16644468
17. Sugawara A, Nakashima J, Kunieda E, Nagata H, Mizuno R, Seki S, Shiraishi Y, Kouta R, Oya M, Shigematsu N. Prostate brachytherapy seed migration to a left varicocele. Brachytherapy. 2012;11(6):502–6. https://doi.org/10.1016/j.brachy.2011.11.003. Epub 2011 Dec 20. PubMed PMID: 22192493

18. Ishiyama H, Satoh T, Kawakami S, Tsumura H, Komori S, Tabata K, Sekiguchi A, Takahashi R, Soda I, Takenaka K, Iwamura M, Hayakawa K. A prospective quasi-randomized comparison of intraoperatively built custom-linked seeds versus loose seeds for prostate brachytherapy. Int J Radiat Oncol Biol Phys. 2014;90(1):134–9. https://doi.org/10.1016/j.ijrobp.2014.05.009. Epub 2014 Jun 28. PubMed PMID: 24986744
19. Ishiyama H, Satoh T, Yorozu A, Saito S, Kataoka M, Hashine K, Nakamura R, Tanji S, Masui K, Okihara K, Ohashi T, Momma T, Aoki M, Miki K, Kato M, Morita M, Katayama N, Nasu Y, Kawanaka T, Fukumori T, Ito F, Shiroki R, Baba Y, Inadome A, Yoshioka Y, Takayama H, Hayakawa K. Multi-institutional retrospective analysis of learning curves on dosimetry and operation time before and after introduction of intraoperatively built custom-linked seeds in prostate brachytherapy. J Radiat Res. 2016;57(1):68–74. https://doi.org/10.1093/jrr/rrv065. Epub 2015 Oct 22. PubMed PMID: 26494116; PubMed Central PMCID: PMC4708919
20. Katayama N, Takemoto M, Takamoto A, Ihara H, Katsui K, Ebara S, Nasu Y, Kanazawa S. Comparison of implant quality between intraoperatively built custom-linked seeds and loose seeds in permanent prostate brachytherapy using sector analysis. J Radiat Res. 2016;57(4):393–9. https://doi.org/10.1093/jrr/rrw018. Epub 2016 Mar 13. PubMed PMID: 26976125; PubMed Central PMCID: PMC4973643
21. Ohashi T, Yorozu A, Toya K, Saito S, Momma T, Nagata H, Kosugi M, Shigematsu N, Kubo A. Comparison of intraoperative ultrasound with postimplant computed tomography—dosimetric values at Day 1 and Day 30 after prostate brachytherapy. Brachytherapy. 2007;6(4):246–53. Epub 2007 Oct 23. PubMed PMID: 17959425
22. Ohashi T, Momma T, Yamashita S, Nagatsuma K, Kanai K, Kitagawa K, Takahashi S, Hanada T, Yorozu A, Shigematsu N. Impact of MRI-based postimplant dosimetric assessment in prostate brachytherapy using contrast-enhanced T1-weighted images. Brachytherapy. 2012;11(6):468–75. https://doi.org/10.1016/j.brachy.2011.12.010. Epub 2012 Feb 11. PubMed PMID: 22330102
23. Katayama N, Takemoto M, Yoshio K, Katsui K, Uesugi T, Nasu Y, Matsushita T, Kaji M, Kumon H, Kanazawa S. T2*-weighted image/T2-weighted image fusion in postimplant dosimetry of prostate brachytherapy. J Radiat Res. 2011;52(5):680–4. Epub 2011 Aug 20. PubMed PMID: 21857148
24. Stone NN, Potters L, Davis BJ, Ciezki JP, Zelefsky MJ, Roach M, Fearn PA, Kattan MW, Stock RG. Customized dose prescription for permanent prostate brachytherapy: insights from a multicenter analysis of dosimetry outcomes. Int J Radiat Oncol Biol Phys. 2007;69(5):1472–7. Epub 2007 Aug 6. PubMed PMID:17689026
25. Morris WJ, Keyes M, Palma D, McKenzie M, Spadinger I, Agranovich A, Pickles T, Liu M, Kwan W, Wu J, Lapointe V, Berthelet E, Pai H, Harrison R, Kwa W, Bucci J, Racz V, Woods R. Evaluation of dosimetric parameters and disease response after 125 iodine transperineal brachytherapy for low- and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2009;73(5):1432–8. https://doi.org/10.1016/j.ijrobp.2008.07.042. Epub 2008 Nov 25. PubMed PMID: 19036530
26. Ohashi T, Yorozu A, Saito S, Momma T, Toya K, Nishiyama T, Yamashita S, Shiraishi Y, Shigematsu N. Outcomes following iodine-125 prostate brachytherapy with or without neoadjuvant androgen deprivation. Radiother Oncol. 2013;109(2):241–5. https://doi.org/10.1016/j.radonc.2013.09.022. Epub 2013 Oct 31. PubMed PMID: 24183866
27. Yorozu A, Kuroiwa N, Takahashi A, Toya K, Saito S, Nishiyama T, Yagi Y, Tanaka T, Shiraishi Y, Ohashi T. Permanent prostate brachytherapy with or without supplemental external beam radiotherapy as practiced in Japan: outcomes of 1300 patients. Brachytherapy. 2015;14(2):111–7. https://doi.org/10.1016/j.brachy.2014.06.008. Epub 2014 Aug 7. PubMed PMID: 25127123
28. Shiraishi Y, Yorozu A, Ohashi T, Toya K, Saito S, Nishiyama T, Yagi Y, Shigematsu N. A dose-response analysis of biochemical control outcomes after (125)I monotherapy for patients with favorable-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2014;90(5):1069–75. https://doi.org/10.1016/j.ijrobp.2014.08.340. PubMed PMID: 25539368

29. Tanaka N, Asakawa I, Katayama E, Hirayama A, Hasegawa M, Konishi N, Fujimoto K. The biochemical recurrence-free rate in patients who underwent prostate low-dose-rate brachytherapy, using two different definitions. Radiat Oncol. 2014;9:107. https://doi.org/10.1186/1748-717X-9-107. PubMed PMID: 24885896; PubMed Central PMCID: PMC4029825
30. Ishiyama H, Nakano M, Toya K, et al. Variability of treatment planning of seed implantation: a Japanese multicenter simulation study. Brachytherapy. 2017;pii:S1538–4721(17)30360–4. https://doi.org/10.1016/j.brachy.2017.05.007. [Epub ahead of print] PubMed PMID: 28623085
31. Okamoto K, Wada A, Kohno N. High biologically effective dose radiation therapy using brachytherapy in combination with external beam radiotherapy for high-risk prostate cancer. J Contemp Brachytherapy. 2017;9(1):1–6.
32. Ohashi T, Yorozu A, Saito S, Tanaka N, Katayama N, Kojima S, Maruo S, Kikuchi T, Dokiya T, Fukushima M, Yamanaka H. Urinary and rectal toxicity profiles after permanent iodine-125 implant brachytherapy in Japanese men: nationwide J-POPS multi-institutional prospective cohort study. Int J Radiat Oncol Biol Phys. 2015;93(1):141–9. https://doi.org/10.1016/j.ijrobp.2015.05.014. Epub 2015 May 15. PubMed PMID: 26279031
33. Tanaka N, Fujimoto K, Hirao Y, Asakawa I, Hasegawa M, Konishi N. Variations in international prostate symptom scores, uroflowmetric parameters, and prostate volume after (125)I permanent brachytherapy for localized prostate cancer. Urology. 2009;74(2):407–11. https://doi.org/10.1016/j.urology.2008.12.062. Epub 2009 Apr 18. PubMed PMID: 19376570
34. Tanaka N, Asakawa I, Hasegawa M, Fujimoto K. Urethral toxicity after LDR brachytherapy: experience in Japan. Brachytherapy. 2015;14(2):131–5. https://doi.org/10.1016/j.brachy.2014.09.009. Epub 2014 Nov 6. Review. PubMed PMID: 25455383
35. Oyama N, Aoki Y, Ito H, Miwa Y, Akino H, Sato Y, Shioura H, Kimura H, Yokoyama O. Alpha 1-adrenoceptor blocker may improve not only voiding but also storage lower urinary tract symptoms caused by (125) I brachytherapy for prostate cancer. ISRN Urol. 2014;2014:140654. https://doi.org/10.1155/2014/140654. eCollection 2014. PubMed PMID: 25006516; PubMed Central PMCID: PMC4004040
36. Tanaka N, Torimoto K, Asakawa I, Miyake M, Anai S, Hirayama A, Hasegawa M, Konishi N, Fujimoto K. Use of alpha-1 adrenoceptor antagonists in patients who underwent low-dose-rate brachytherapy for prostate cancer – a randomized controlled trial of silodosin versus naftopidil. Radiat Oncol. 2014;9:302. https://doi.org/10.1186/s13014-014-0302-7. PubMed PMID: 25544509; PubMed Central PMCID: PMC4300048
37. Cesaretti JA, Stone NN, Stock RG. Urinary symptom flare following I-125 prostate brachytherapy. Int J Radiat Oncol Biol Phys. 2003;56(4):1085–92. PubMed PMID: 12829146
38. Keyes M, Miller S, Moravan V, Pickles T, McKenzie M, Pai H, Liu M, Kwan W, Agranovich A, Spadinger I, Lapointe V, Halperin R, Morris WJ. Predictive factors for acute and late urinary toxicity after permanent prostate brachytherapy: long-term outcome in 712 consecutive patients. Int J Radiat Oncol Biol Phys. 2009;73(4):1023–32. https://doi.org/10.1016/j.ijrobp.2008.05.022. Epub 2008 Dec 26. PubMed PMID: 19111402
39. Sakayori M, Ohashi T, Momma T, Kaneda T, Nishimura S, Sutani S, Yamashita S, Shigematsu N. Quantitative analysis of genitourinary toxicity after iodine-125 brachytherapy for localized prostate cancer: followup of the International Prostate Symptom Score and Overactive Bladder Symptom Score. Brachytherapy. 2017;16(4):806–14. https://doi.org/10.1016/j.brachy.2017.04.241. Epub 2017 May 25. PubMed PMID: 28552494
40. Eriguchi T, Yorozu A, Kuroiwa N, Yagi Y, Nishiyama T, Saito S, Toya K, Hanada T, Shiraishi Y, Ohashi T, Shigematsu N. Predictive factors for urinary toxicity after iodine-125 prostate brachytherapy with or without supplemental external beam radiotherapy. Brachytherapy. 2016;15(3):288–95. https://doi.org/10.1016/j.brachy.2015.12.011. Epub 2016 Feb 28. PubMed PMID: 26924022
41. Miyake M, Tanaka N, Asakawa I, Hori S, Morizawa Y, Tatsumi Y, Nakai Y, Inoue T, Anai S, Torimoto K, Aoki K, Hasegawa M, Fujii T, Konishi N, Fujimoto K. Assessment of lower urinary symptom flare with overactive bladder symptom score and International Prostate Symptom Score in patients treated with iodine-125 implant brachytherapy: long-term follow-up experience at a single institute. BMC Urol. 2017;17(1):62. https://doi.org/10.1186/s12894-017-0251-1. PubMed PMID: 28806948; PubMed Central PMCID: PMC5556596

42. Nakamura R, Kikuchi K, Tanji S, Yabuuchi T, Uwano I, Yamaguchi S, Ariga H, Fujioka T. Narrow safety range of intraoperative rectal irradiation exposure volume for avoiding bleeding after seed implant brachytherapy. Radiat Oncol. 2012;7:15. https://doi.org/10.1186/1748-717X-7-15. PubMed PMID: 22293400; PubMed Central PMCID: PMC3293044
43. Shiraishi Y, Yorozu A, Ohashi T, Toya K, Seki S, Yoshida K, Kaneda T, Saito S, Nishiyama T, Hanada T, Shigematsu N. Dose constraint for minimizing grade 2 rectal bleeding following brachytherapy combined with external beam radiotherapy for localized prostate cancer: rectal dose-volume histogram analysis of 457 patients. Int J Radiat Oncol Biol Phys. 2011;81(3):e127–33. https://doi.org/10.1016/j.ijrobp.2011.01.012. Epub 2011 Mar 11. PubMed PMID: 21398047
44. Nishimura S, Yorozu A, Ohashi T, Sakayori M, Yagi Y, Nishiyama T, Saito S, Shiraishi Y, Yoshida K, Toya K, Shigematsu N. Five-year potency preservation after iodine-125 prostate brachytherapy. Int J Clin Oncol. 2014;19(5):940–5. https://doi.org/10.1007/s10147-013-0632-8. Epub 2013 Oct 31. PubMed PMID: 24170247
45. Okihara K, Yorozu A, Saito S, Tanaka N, Koga H, Higashide S, Kikuchi T, Nakano M. Assessment of sexual function in Japanese men with prostate cancer undergoing permanent brachytherapy without androgen deprivation therapy: analysis from the Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 Seed Implantation database. Int J Urol. 2017;24(7):518–24.
46. Tanaka N, Fujimoto K, Asakawa I, Hirayama A, Yoneda T, Yoshida K, Hirao Y, Hasegawa M, Konishi N. Variations in health-related quality of life in Japanese men who underwent iodine-125 permanent brachytherapy for localized prostate cancer. Brachytherapy. 2010;9(4):300–6. https://doi.org/10.1016/j.brachy.2009.07.013. Epub 2010 Aug 13. PubMed PMID: 20708440
47. Satoh T, Ishiyama H, Matsumoto K, Tsumura H, Kitano M, Hayakawa K, Ebara S, Nasu Y, Kumon H, Kanazawa S, Miki K, Egawa S, Aoki M, Toya K, Yorozu A, Nagata H, Saito S, Baba S. Prostate-specific antigen 'bounce' after permanent 125I-implant brachytherapy in Japanese men: a multi-institutional pooled analysis. BJU Int. 2009;103(8):1064–8. https://doi.org/10.1111/j.1464-410X.2008.08234.x. Epub 2008 Nov 25. PubMed PMID: 19040526
48. Tanaka N, Asakawa I, Fujimoto K, Anai S, Hirayama A, Hasegawa M, Konishi N, Hirao Y. Minimal percentage of dose received by 90% of the urethra (%UD90) is the most significant predictor of PSA bounce in patients who underwent low-dose-rate brachytherapy (LDR-brachytherapy) for prostate cancer. BMC Urol. 2012;12:28. https://doi.org/10.1186/1471-2490-12-28. PubMed PMID: 22974428; PubMed Central PMCID: PMC3487947
49. Namiki S, Satoh T, Baba S, Ishiyama H, Hayakawa K, Saito S, Arai Y. Quality of life after brachytherapy or radical prostatectomy for localized prostate cancer: a prospective longitudinal study. Urology. 2006;68(6):1230–6. Epub 2006 Dec 4. PubMed PMID: 17141839
50. Uesugi T, Saika T, Edamura K, Nose H, Kobuke M, Ebara S, Abarzua F, Katayama N, Yanai H, Nasu Y, Kumon H. Primary Gleason grade 4 impact on biochemical recurrence after permanent interstitial brachytherapy in Japanese patients with low- or intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2012;82(2):e219–23. https://doi.org/10.1016/j.ijrobp.2011.04.018. Epub 2011 Jun 2. PubMed PMID: 21640517
51. Ohashi T, Yorozu A, Saito S, Momma T, Nishiyama T, Yamashita S, Shiraishi Y, Shigematsu N. Combined brachytherapy and external beam radiotherapy without adjuvant androgen deprivation therapy for high-risk prostate cancer. Radiat Oncol. 2014;9:13. https://doi.org/10.1186/1748-717X-9-13. PubMed PMID: 24401540; PubMed Central PMCID: PMC3904455
52. Sekiguchi A, Ishiyama H, Satoh T, Tabata K, Komori S, Tsumura H, Kawakami S, Soda I, Iwamura M, Hayakawa K. 125Iodine monotherapy for Japanese men with low-and intermediate-risk prostate cancer: outcomes after 5 years of follow-up. J Radiat Res. 2014;55(2):328–33. https://doi.org/10.1093/jrr/rrt113. Epub 2013 Oct 8. PubMed PMID: 24105711; PubMed Central PMCID: PMC3951075

53. Tabata R, Kimura T, Kuruma H, Sasaki H, Kido M, Miki K, Takahashi H, Aoki M, Egawa S. Do androgen deprivation and the biologically equivalent dose matter in low-dose-rate brachytherapy for intermediate-risk prostate cancer? Cancer Med. 2016;5(9):2314–22. https://doi.org/10.1002/cam4.820. Epub 2016 Jul 25. PubMed PMID: 27456710; PubMed Central PMCID: PMC5055153
54. Shimbo M, Inoue K, Koike Y, Katano S, Kawashima K. Salvage I seed implantation for prostate cancer with postradiation local recurrence. Urol Int. 2013;90(3):294–300. https://doi.org/10.1159/000346322. Epub 2013 Mar 6. PubMed PMID:23467122
55. Hori S, Tanaka N, Asakawa I, Morizawa Y, Hirayama A, Hasegawa M, Konishi N, Fujimoto K. Salvage brachytherapy for seminal vesicle recurrence after initial brachytherapy for prostate cancer: a case report. BMC Res Notes. 2014;7:760. https://doi.org/10.1186/1756-0500-7-760. PubMed PMID: 25344831; PubMed Central PMCID: PMC4216847
56. Hosogoe S, Soma O, Matsumoto T, Imai A, Hatakeyama S, Yoneyama T, Hashimoto Y, Koie T, Ohyama C, Aoki M. Salvage brachytherapy for castration-resistant and external beam radiotherapy-resistant local recurrence 17 years after radical prostatectomy. Case Rep Urol. 2015;2015:839738. https://doi.org/10.1155/2015/839738. Epub 2015 Jun 11. PubMed PMID: 26171272; PubMed Central PMCID: PMC4480240
57. Sasaki H, Kido M, Miki K, Kuruma H, Takahashi H, Aoki M, Egawa S. Salvage partial brachytherapy for prostate cancer recurrence after primary brachytherapy. Int J Urol. 2014;21(6):572–7. https://doi.org/10.1111/iju.12373. Epub 2013 Dec 23. PubMed PMID: 24372730
58. Kunogi H, Wakumoto Y, Yamaguchi N, Horie S, Sasai K. Focal partial salvage low-dose-rate brachytherapy for local recurrent prostate cancer after permanent prostate brachytherapy with a review of the literature. J Contemp Brachytherapy. 2016;8(3):165–72. https://doi.org/10.5114/jcb.2016.60452. Epub 2016 Jun 13. PubMed PMID: 27504124; PubMed Central PMCID: PMC4965495
59. Miki K, Kiba T, Sasaki H, Kido M, Aoki M, Takahashi H, Miyakoda K, Dokiya T, Yamanaka H, Fukushima M, Egawa S. Transperineal prostate brachytherapy, usingI-125 seed with or without adjuvant androgen deprivation, in patients with intermediate-risk prostate cancer: study protocol for a phase III, multicenter, randomized, controlled trial. BMC Cancer. 2010;10:572. https://doi.org/10.1186/1471-2407-10-572. PubMed PMID: 20964826; PubMed Central PMCID:PMC2984426
60. Konaka H, Egawa S, Saito S, Yorozu A, Takahashi H, Miyakoda K, Fukushima M, Dokiya T, Yamanaka H, Stone NN, Namiki M. Tri-modality therapy with I-125 brachytherapy, external beam radiation therapy, and short- or long-term hormone therapy for high-risk localized prostate cancer (TRIP): study protocol for a phase III, multicenter, randomized, controlled trial. BMC Cancer. 2012;12:110. https://doi.org/10.1186/1471-2407-12-110. PubMed PMID: 22439742; PubMed Central PMCID: PMC3350387
61. Commission UNR. Consolidated guidance about materials licensees: program-specific guidance about medical use licenses. NUREG-1556. Washington, DC: US Nuclear Regulatory Commission; 2002. p. 9.
62. Commission UNR. Regulatory guide 8.39: release of patients administered radioactive materials. Washington, DC: US Nuclear Regulatory Commission; 1997.
63. Hanada T, Yorozu A, Shinya Y, Kuroiwa N, Ohashi T, Saito S, Shigematsu N. Prospective study of direct radiation exposure measurements for family members living with patients with prostate (125)I seed implantation: evidence of radiation safety. Brachytherapy. 2016;15(4):412–9. https://doi.org/10.1016/j.brachy.2016.04.007. Epub 2016 May 12. PubMed PMID: 27180131
64. Satoh T, Yamanaka H, Yamashita T, Aoki M, Egawa S, Saito S, Sakata S, Shibuya H, Sugiura N, Takahashi Y, Nishimura T, Hamada T, Miki T, Yorozu A, Dokiya T. Deaths within 12 months after (125)I implantation for brachytherapy of prostate cancer: an investigation of radiation safety issues in Japan (2003–2010). Brachytherapy. 2012;11(3):192–6. https://doi.org/10.1016/j.brachy.2011.06.009. Epub 2011 Sep 17. PubMed PMID: 21925958
65. Satoh T, Dokiya T, Yamanaka H, Saito S, Ishiyama H, Itami J, Shibuya H, Nakano T, Shigematsu N, Aoki M, Egawa S, Hashimoto M, Nishimura T, Yorozu A. Postmortem radiation safety and issues pertaining to permanent prostate seed implantation in Japan. Brachytherapy. 2015;14(2):136–41. https://doi.org/10.1016/j.brachy.2014.08.043. Epub 2014 Sep 6. Review. PubMed PMID: 25200350.

High-Dose-Rate Brachytherapy as Monotherapy for Prostate Cancer

13

Yasuo Yoshioka, Minako Sumi, and Masahiko Oguchi

Abstract

High-dose-rate (HDR) brachytherapy as monotherapy for prostate cancer has theoretical advantages in both aspects of radiation physics and biology compared to other radiotherapy modalities. The three-dimensional and four-dimensional dose distribution of HDR brachytherapy is superb, and HDR monotherapy maximizes the biological dose escalation. In the former part of this chapter, techniques in implant and treatment planning of HDR monotherapy are mentioned, followed by it's theoretical advantages. In the latter half, clinical evidence of HDR monotherapy is overviewed along with its history over 20 years. Since its dawning with four- to nine-fraction regimens, HDR monotherapy has been moving on to more and more hypofractionated regimens. The latest two- or single-fraction HDR monotherapy is vigorously discussed.

Keywords

High dose rate · Brachytherapy · Monotherapy · Prostate cancer · Hypofractionation

13.1 Introduction

Radiation therapy, including brachytherapy and external beam radiation therapy (EBRT), in addition to surgery, has been the mainstay of curative treatment for prostate cancer. Both low-dose-rate (LDR) permanent seed brachytherapy and high-dose-rate (HDR) temporary brachytherapy have become established as highly effective treatments for early and locally advanced prostate cancer. Historically,

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LDR brachytherapy with or without EBRT has been examined and assessed the most and became a standard treatment option. Next, HDR brachytherapy was introduced in the context of combination therapy with EBRT, as an alternative to LDR to boost EBRT. However, if a satisfactory dose distribution could be achieved with HDR brachytherapy as monotherapy, without EBRT, it would definitely be the most efficient method to achieve high conformity and dose escalation.

Several guidelines and recommendations have been published on prostate HDR brachytherapy by some authorized groups, including the Groupe Européen de Curiethérapie/European Society for Radiotherapy and Oncology (GEC-ESTRO) [1, 2], the American Brachytherapy Society (ABS) [3], the American Society of Clinical Oncology/Cancer Care Ontario [4], the American College of Radiology (ACR) [5], and the National Comprehensive Cancer Network (NCCN) [6]. In most of them, a combination therapy of HDR and EBRT is considered as a standard treatment option, whereas HDR monotherapy has not been well described reflecting the fact that the evidence of HDR monotherapy has not been enough accumulated yet. On the other hand, there have been published some review articles where the potential of HDR monotherapy is highly evaluated [7–12]. In this chapter, theoretical advantage of HDR monotherapy as a radical treatment for prostate cancer will be discussed in terms of both radiation physics and biology, and then the reported clinical results will be thoroughly reviewed. Although salvage or focal HDR monotherapy may also be an important topic, they will not be mentioned.

13.2 Technique and Theory

13.2.1 Technique: Applicator Implant and Treatment Planning

1. *Applicator needle implant*
   A sample of implant technique has been previously described in detail by Osaka University Hospital in Japan [10]. Under epidural anesthesia, the patient is placed in a dorsal lithotomy position, with the perineal region sterilized. A balloon catheter is inserted into the bladder, with air-mixed gel placed within the prostatic urethra to enable visualization of the urethra on ultrasonography (US). Under real-time transrectal-US (TRUS) guidance, metallic applicator needles (Trocar Point Needles and Needle Stoppers; Elekta, Stockholm, Sweden) are placed through the perineal skin, using an in-house template. The template is made of transparent acryl with 167 needle holes spaced at 5-mm intervals. The needles are placed along the line that encompasses the prostate at the largest cross-section on US, except for the rectal side where the needles are placed 2–3 mm inside the prostate contour. For T3 tumors, needles can be placed outside the prostate capsule and/or into the seminal vesicles. Inner needles are inserted at 1-cm intervals, to adequately cover the base and apex of the prostate, taking care to avoid the urethra. The total number of needles inserted is usually around 15. The tips of the needles are placed 2 cm within the bladder lumen for the reason described in the following section. Placing at least two

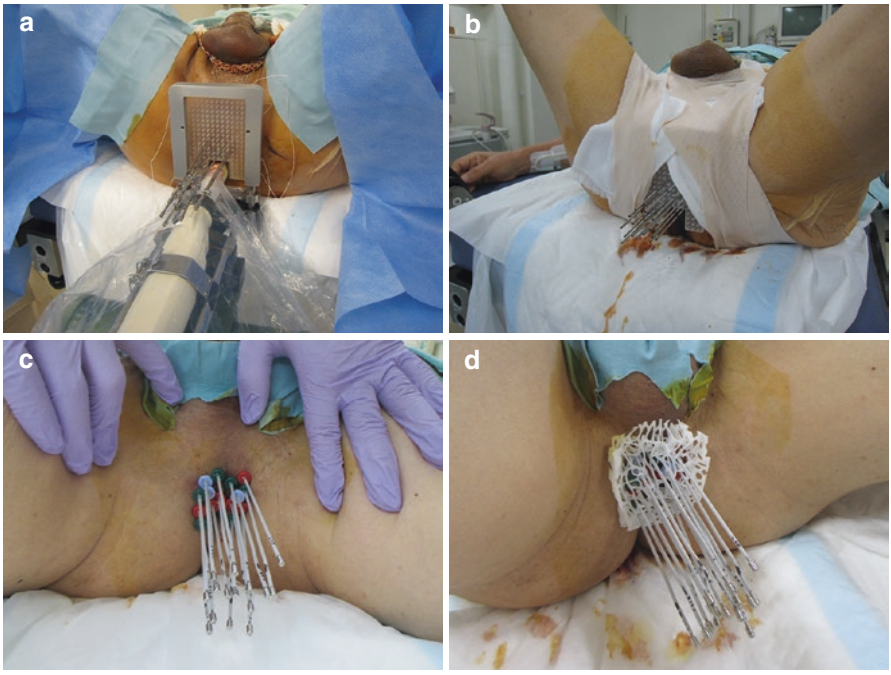

Fig. 13.1 (**a**) Metallic applicator needle implant under real-time transrectal ultrasonography guidance. The patient can be awake with the aid of epidural anesthesia, or under general anesthesia, in lithotomy position. Template holes had been superimposed on the ultrasonography monitor. (**b**) Fixation of the template with elastic tape. Before taping, the template had been sutured to the perineal skin. Needle stoppers are sandwiched by the template and its cover plate, preventing needle displacement. (**c**) Plastic applicator needle implant without using a template. Under real-time transrectal ultrasonography guidance, needles were implanted by freehand. Next, a button was attached to each needle and was adhered by instant glue. (**d**) Using a small piece of thermoplastic shell, the buttons and needles were fixed to the perineal skin. Because no metallic material was used, MRI-based treatment planning would be possible

metallic fiducial markers inside the prostate gland, as far apart as possible, with one at the base and another at the apex, would be useful for recognizing the relative shift between the prostate and the needles, as well as deformation of the prostate itself due to edema. Differently from the abovementioned method using the metallic needles (Fig. 13.1a, b), a method using plastic applicator needles (e.g., ProGuide Sharp Needles; Elekta) is also recommended (Fig. 13.1c, d).

2. *Treatment planning*
   After the implantation of the needles, computed tomography (CT) data are acquired with the patient in the supine position (not in lithotomy). The CT slice thickness is 1.25 mm in helical mode. One hour before CT data acquisition and each irradiation fraction, the urinary balloon catheter is clamped in place to keep the urine within the bladder lumen, so that the cranial side of the bladder wall and the bowel are kept away from the irradiation volume.

CT-based treatment planning is performed with the aid of Oncentra Brachy (Elekta). The clinical target volume (CTV) includes the whole prostate gland with a 5-mm margin except for the posterior (rectal) margin, which varies from 2 to 5 mm depending on the distance to the rectal wall. If extracapsular and/or seminal vesicle invasion are observed or strongly suspected, that area is included in the CTV and applicators are placed there. The planning target volume (PTV) is equal to the CTV. However, in the old era, they added 1-cm margin to the CTV in the cranial direction only, and the PTV included the bladder base. The top 2 cm of the applicators were placed within the bladder lumen, so that the PTV included a 1-cm margin in the cranial direction around the CTV. This margin was established, not only to avoid the cold area at the base of the prostate but also to compensate for possible needle displacement in the caudal direction. Recently this margin is being abandoned, and they are shifting to make a replan at every fraction.

The dose distribution is created by geometric optimization (volume method) and manual modification (Fig. 13.2a, b). The following dose constraints are applied: the dose to the whole urethra should be <125% of the prescription dose, preferably <110%, and the dose to the whole rectal mucosa should be <100% of the prescription dose, preferably <75%. The PTV coverage requirements are D90 > 100% (mandatory) and V100 > 97% (preferable).

3. *Patient management*
   If multiple fractions are given during one implant session, the patient remains in bed for several hours to several days, normally undergoing irradiation twice daily with an interval of ≥6 h. Continuous epidural anesthesia is useful to control pain. Anticoagulated patients are told to stop their drugs 1–2 weeks before the implant. The patients should be given purgatives before the implant and a glycerin enema in the morning of implant and are also given low-residue meals to suppress defecation during the treatment course. Prophylactic antibiotics are administered. Pneumatic compression devices are attached to the patients' lower legs to prevent deep vein thrombosis during the treatment course. To minimize bleeding (both from the perineum and intravesically), a coagulating agent is administered at the time of the implant and at the time of needle removal. Immediately after pulling the needles out, the physician should manually compress the prostate using both hands, one via the perineum and the other via the rectum (as in a digital examination), to stop the bleeding. In addition, pulling the balloon catheter, which has been replaced with a larger three-way catheter for bladder irrigation, with the balloon inflated to its maximum, helps to stop bleeding from the bladder neck. For intravesical bleeding, bladder irrigation with cold saline is effective, and the continuous bladder irrigation technique is used to prevent clots from occluding the balloon catheter when intravesical bleeding is protracted.
4. *Neoadjuvant and/or adjuvant androgen deprivation therapy*
   The benefits of adding neoadjuvant and/or adjuvant androgen deprivation therapy (ADT) to HDR monotherapy are controversial. Additional benefit of com-

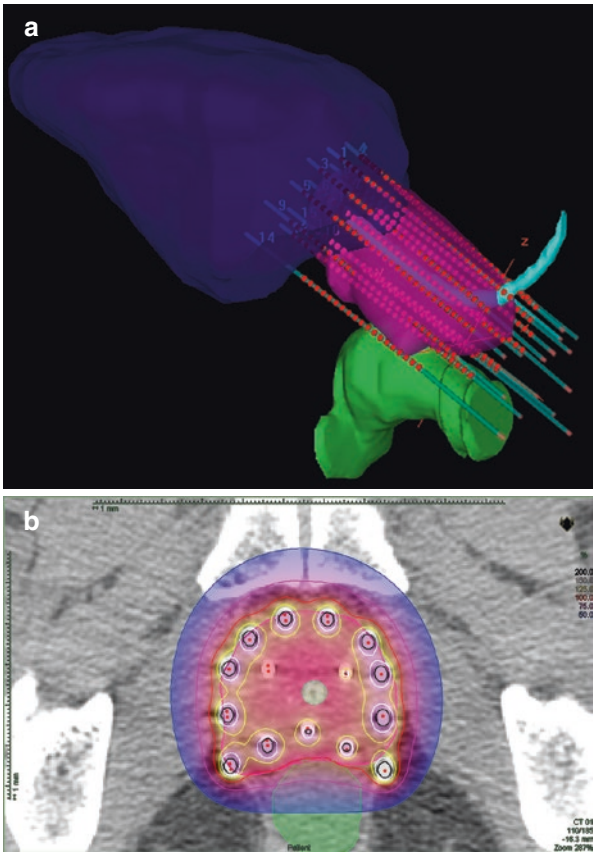

Fig. 13.2 (**a**) Three-dimensional reconstruction of the prostate and proximal seminal vesicles (purple), rectum (green), bladder (blue), urethra (cyan), and applicator needles and source dwell positions (red). Dwell positions were automatically selected by designating the area up to 7 mm outside the prostate or seminal vesicles. Note that some needles and dwell positions were entirely outside the prostate gland and/or partly in the seminal vesicles or in the bladder lumen. (**b**) A dose distribution plot of transverse plane. Note that the urethral dose was <125% of the prescription dose and the rectal dose <100%. Most parts of the rectum received <75% of the prescription dose and half of the rectum <50%

bining ADT over irradiation alone would be assumed smaller in the case of HDR brachytherapy than for EBRT (e.g., classical 70-Gy EBRT), because the biologically effective dose (BED) of HDR brachytherapy is far higher than that of EBRT. However, some interaction between ADT and radiation may still occur, and the volume reduction effect may be associated with less toxicity. Unfavorable intermediate-risk patients (with two or three intermediate features) and high-risk patients may receive 6 months of neoadjuvant ADT. For high-risk patients, further ADT may be also added in an adjuvant setting with a duration of 1.5 or 2.5 years.

13.2.2 Advantage and Pitfall of HDR Monotherapy in Terms of Radiation Physics

1. As a general feature of brachytherapy, including both LDR and HDR, radiation dose can be concentrated into the tumor, which is mainly due to the inverse square law. Brachytherapy enables high conformity, while sparing the surrounding normal tissue by its rapid dose falloff. Some researchers made a simulation study that showed dosimetric superiority of LDR and HDR brachytherapy over intensity-modulated radiation therapy, proton therapy, or carbon ion therapy [13].
2. Throughout the procedure of HDR brachytherapy, the public, patient's family, or medical staff are never exposed to radiation. Patients can stay in a regular ward since there is no need for a shielded room. Patients only need to be in an HDR unit room for irradiation for approximately 30 min per fraction.
3. HDR treatment planning is based on the CT images obtained after needle insertion or on the TRUS images obtained at the time of needle insertion. The dwell positions of the stepping source are determined in terms of real anatomy after the needle insertion. The dwell time for each dwell position is then calculated with an optimization algorithm.
4. Unlike for EBRT, inter-/intra-fraction organ motion is not a problem with HDR brachytherapy. In the case of EBRT, several factors including daily setup errors; retention of feces, gas, or urine; respiratory motion; or peristaltic motion result in discrepancies between the coordinates of the tumor and the radiation beam. With brachytherapy, these two coordinates are always concordant because the tumor and the radioactive sources move in unison, so that PTV is normally identical to CTV. The overall treatment time for HDR monotherapy is typically in 1 or 2 days, which is significantly shorter than for EBRT.
5. Unlike for LDR brachytherapy, HDR brachytherapy needles can be placed at the extracapsular lesion and even into the seminal vesicles and/or into the bladder lumen. The cable-connected stepping source simply moves back and forth within the closed space without any risk of source migration or dropping out. Therefore, the indication for HDR monotherapy can potentially even be extended to T3a/b or some T4 tumors. The dwell time optimization makes a significant urethral dose reduction possible for HDR compared to that for LDR [14]. Short irradiation time of HDR avoids the dosimetric uncertainties of LDR related to postimplant volume changes due to needle trauma and subsequent edema or deformation during the overall treatment period of several months.
6. One possible pitfall of HDR brachytherapy is the problem of applicator needle displacement during treatment, which has been pointed out by some groups [15–21]. However, this problem does not arise if there is one fraction per implant or if they replan at every fraction. Another possible drawback of HDR is the requirement of hospitalization and patients having to stay in bed during the treatment period.
7. HDR prostate monotherapy is still evolving and being developed, with ongoing research to determine optimal dose-fractionations and dose-volume constraints

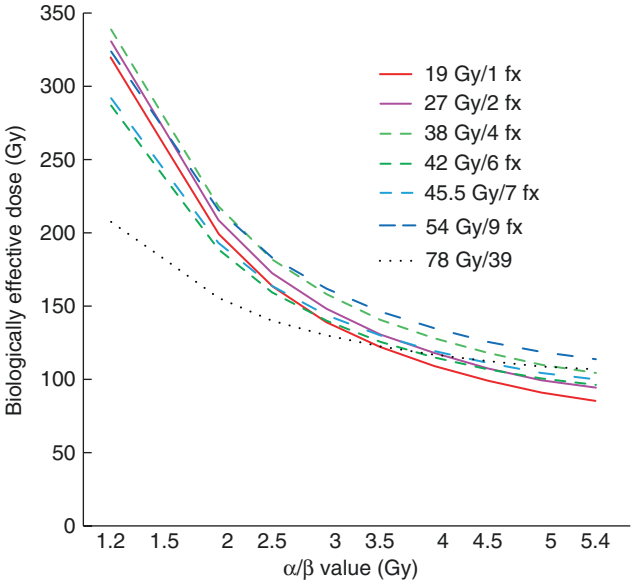

Fig. 13.3 Biologically effective doses from various regimens of high-dose-rate brachytherapy as monotherapy that have been reported in the literature (solid lines for one- or two-fraction regimen; dashed lines for four- to nine-fraction regimens), at different α/β ratios, are juxtaposed to those from a typical regimen of conventionally fractionated external beam radiation therapy (dotted line)

[22]. For example, a new technique enabling more accurate implantation into seminal vesicles has been developed [23]. In view of its high degree of freedom in the process of treatment planning, there may still be some room for improvement in the dwell time optimization algorithm [24, 25]. Recent trends of HDR monotherapy are moving toward a smaller number of fractions, which will be described in detail at the latter part of this chapter. Such an extremely hypofractionated regimen would maximize the therapeutic ratio and at the same time avoid the HDR brachytherapy drawback of hospitalization and needle displacement during the treatment period. In the era of one- to three-fraction HDR monotherapy, it should become mandatory to make a treatment planning at every fraction, which could be considered as a completed form of adaptive radiation therapy.

13.2.3 Theoretical Advantage and Potential Pitfall of HDR Monotherapy in Terms of Radiation Biology

Brenner and Hall in 1999 [26], as well as others later on [27–30], reported a very low α/β ratio for prostate cancer, mostly in the range of 1.2–3.1 Gy. These findings that the α/β ratio for prostate cancer is less than that for the surrounding late-responding normal tissue have made hypofractionation attractive, and HDR monotherapy can maximize this advantage of hypofractionation. Figure 13.3 shows

biologically effective doses (BED) from various regimens of HDR monotherapy that have been reported in the literature. Assuming $\alpha/\beta = 1.5$ Gy for prostate cancer, and using the classical linear quadratic (LQ) formula, the BED for prostate cancer would be estimated as 238–279 Gy, which would correspond to 102–119 Gy of biologically equivalent dose in 2 Gy per fraction (EQD_{2Gy}). As for late toxicity, EQD_{2Gy} would range from 84 to 97 Gy, assuming $\alpha/\beta = 3.0$ Gy. This means that, theoretically, hypofractionation with a large fraction size can enhance BED for prostate cancer without increasing BED for late-responding tissue.

However, when we remind that we are using an extremely high dose per fraction as around 10 Gy or even nearly 20 Gy, we should pay careful attention to such discussions on BED or EQD_{2Gy}. Potential pitfalls seem to include the following: (1) Does LQ formula work out well in the area of 10–20 Gy per fraction? (2) Is α/β ratio of prostate cancer really 1.5 Gy uniformly? Miyakawa and Shibamoto et al. insisted that LQ formula may not work well in the area of >8 Gy per fraction, based on their experiment on cell survival of the EMT6 mouse mammary sarcoma line, determined by a standard colony assay [31]. To the contrary, Brenner et al. maintained that LQ model is reasonably well validated, experimentally and theoretically, up to about 10 Gy/fraction and would be reasonable for use up to about 18 Gy per fraction [32]. Tumor heterogeneity with regard to α/β ratio would become another potential pitfall. Even if most of the prostate cancer cells had 1.5 Gy of α/β ratio, what would happen when that prostate cancer tissue partly had a component of 5.0 Gy? Looking again (Fig. 13.3), 19 Gy in a single fraction would correspond to only 65 Gy of EQD_{2Gy}, assuming $\alpha/\beta = 5.0$ Gy, which would be significantly lower than 78 Gy in 39 fractions used in typical EBRT.

Unknown mechanism may arise in such a high-dose-per-fraction area that would unexpectedly injure prostate cancer cells and/or healthy normal tissue cells. For example, one may imagine a microenvironmental scenario such that mesenchymal tissue supporting microvessels would be injured reversibly or irreversibly by such a high dose per fraction, the mechanism of which would not be taken into consideration by the theory of repair from sublethal damage. In addition, a single-fraction HDR monotherapy would refuse the classically well-known effect in fractionated radiation therapy: reassortment and reoxygenation. Which, cancer cells or normal cells, would benefit or be injured relatively more by such unknown mechanisms? Anyway, the clinical results especially for a single-fraction HDR monotherapy should be observed with the greatest caution, which will be discussed again in several sections later in this chapter.

13.3 Clinical Evidence

13.3.1 Nine- to Seven-Fraction HDR Monotherapy: Japanese Evidence

HDR brachytherapy used as monotherapy for prostate cancer was initiated in Japan in 1995, which was reported in 2000 by Yoshioka et al. [33]. They delivered eight

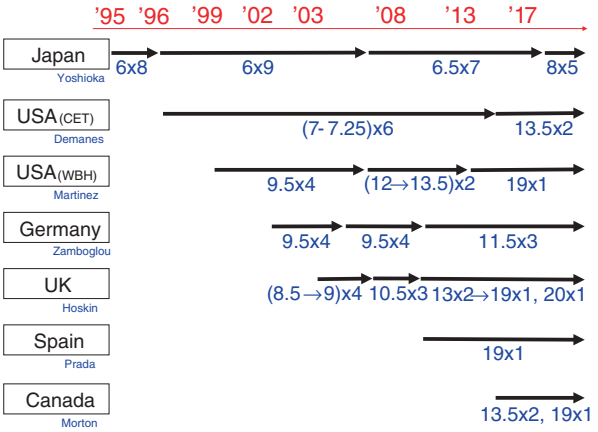

Fig. 13.4 Transition of dose fractionation in high-dose-rate brachytherapy as monotherapy for prostate cancer (numbers: ■Gy x ▲fractions)

or nine fractions of 6 Gy each, in total 48 or 54 Gy over 5 days [34–36]. After 10 years, they changed their dose fractionation into 45.5 Gy in seven fractions over 4 days, with 6.5 Gy per each fraction [37] (Fig. 13.4). With a median 8-year follow-up and a total of 20 years of experience, they reported biochemical control rates of 91% for intermediate-risk and 77% for high-risk patients at 8 years. Late grade 3 GU and GI toxicity rates were 1 and 2% at 8 years [38]. Similarly, Yoshida et al. reported their clinical results of HDR monotherapy using 49 Gy/7 Gy/7 fractions or 54 Gy/6 Gy/9 fractions. All 48 patients were high risk and received ADT. The 5-year biochemical control rate was 87%, and late grade 3 GU and GI toxicity rates were 4 and 2% [39].

In 2017, collected data of Japan nationwide, multicenter, retrospective study on HDR monotherapy was published by Yoshioka et al. [40]. From 1995 through 2013, 524 patients, including 14% low-risk, 40% intermediate-risk, and 47% high-risk patients, were treated with HDR brachytherapy as monotherapy at five institutions in Japan. Patients >85% were treated with 7–9 fraction regimens. Respectively, 34%, 58%, and 91% of low-, intermediate-, and high-risk patients received ADT also. Median follow-up was 5.9 years. The 5-year biochemical control rates were 95%, 94%, and 89% for low-, intermediate-, and high-risk patients. Late grade 3 GU and GI toxicity rates were 1 and 0.2% at 5 years. Compared to American series, one distinct characteristic of Japanese series is that Japanese indication for HDR monotherapy included high-risk patients and subsequently the use of ADT was more frequent than in the American series as will be described in the next section.

13.3.2 Six- to Four-Fraction HDR Monotherapy: American Evidence

Demanes et al. at California Endocuriethérapy Cancer Center (CET) in the USA started HDR monotherapy in 1996 with 42–43.5 Gy in six fractions, including two implants with three fractions each [41]. With a median follow-up period of 6.5 years, they reported long-term results for 448 patients including 288 low-risk and 160 intermediate-risk patients. The actuarial 6- and 10-year PSA progression-free survival rate was 99 and 98%. Late grade 3–4 GU toxicity rate was 5%, with GI 0% [42].

Martinez et al. at William Beaumont Hospital (WBH) in the USA launched HDR monotherapy with 38 Gy in four fractions in 1999 [43, 44]. This four-fraction regimen, which can be accomplished within 2 days, was introduced into Europe, including Germany [45] and Switzerland [46].

Rogers et al. reported their clinical results of HDR monotherapy for 284 intermediate-risk patients with a median follow-up of 2.7 years. Their treatment consisted of two implant sessions, each with three fractions of 6.5 Gy during a one-night hospitalization for a total of 39 Gy in six fractions for a mean of 19 days. The 5-year biochemical disease-free survival was 94%, with 0.7% late grade 3 GU toxicity without any late Grade 3 GI toxicity [47]. In general, American researchers seem to indicate HDR monotherapy for low- and favorable intermediate-risk patients, by contrast with Japanese or European researchers (Table 13.1).

13.3.3 Three- or Two-Fraction HDR Monotherapy: Awaiting Mature Results

Three-fraction HDR monotherapy has ever been reported from three countries including Australia, the UK, and Germany. Barkati et al. in Australia conducted a dose escalation study using three fractions of 10 Gy, 10.5 Gy, 11 Gy, and 11.5 Gy. They successfully reached to the highest dose level, showing acceptable acute and late toxicities [48].

Zamboglou et al. published the largest series of HDR monotherapy with >700 patients from a single institution in Germany. The transition of dose fractionations used by them looks interesting; first, they treated with one implant in four fractions of 9.5 Gy. Second, they used two implants, separated by 2 weeks, each with two fractions of 9.5 Gy. Finally, they adopted three implants, separated by 3 weeks, each with a single fraction of 11.5 Gy. Although their cohort included 25% of intermediate- and 20% of high-risk patients, they reported as high as 94% biochemical control rate at 5 years for the entire cohort [49]. Strouthos et al. recently updated the results for the three-fraction-in-three-implant cohort with 450 patients, showing a 5-year biochemical control rate of 95% with a prolonged median follow-up of 4.7 years, with late grade 3 GU toxicity as 0.8% without any late grade 3 GI toxicity [50]. Similarly, Kukiełka et al. in Poland used three separate implants with single fraction per implant but with 15 Gy each and 45 Gy in total [51].

Table 13.1 Literature on clinical results of high-dose-rate brachytherapy as monotherapy for prostate cancer

Author (reference)	Total dose (Gy)/fraction[a]	No. of patients	Risk group	Median follow-up (year)	Androgen deprivation therapy (%)	Biochemical control rate (%) (at years)	Late toxicity ≥ grade 2 (%)[b]		Late toxicity grade 3 (%)[b]	
							GU	GI	GU	GI
Yoshioka [38]	48/8, 54/9, 45.5/7	79	Intermediate	7.7	44	93 (5y), 91 (8y)	11	5	1	1
		111	High		94	81 (5y), 77 (8y)				
Demanes [42]	42–43.5/6 (2 implants)	288	Low	6.5	9	99 (6y), 98 (10y)	NA	NA	5[c]	0
		160	Intermediate							
Martinez [58, 63]	38/4	319	L233, I86	5.5	19	97 (5y)	47	4	6	0
	24/2	79	L48, I31	3.5	5	87 (5y)	33	5	0	0
	27/2	96	L56, I40	2.9	3	90 (5y)	49	5	8	0
	19/1	58	L38, I20	2.9	0	93 (3y)	10	3	0	2
Rogers [47]	39/6 (2 implants)	284	Intermediate	2.7	16	94 (5y)	2	0	1	0
Zamboglou [49]	38/4, 38/4 (2 implants), 34.5/3 (3 implants)	395	Low	4.4	6	95 (5y)	27	3	4[d]	2
		177	Intermediate		24	93 (5y)				
		146	High		60	93 (5y)				
Barkati [48]	30/3	19	Low to intermediate	3.3	9	88 (3y), 85 (5y)	59	5	21	0
	31.5/3	19								
	33/3	19								
	34.5/3	22								
Yoshida [39]	38/4, 49/7, 54/9	48	High	6.3	100	87 (5y)	15	4	4	2
Ghadjar [46]	38/4	28	Low	3.0	14	100 (3y)	36	6	11	0
		8	Intermediate							

(continued)

Table 13.1 (continued)

Author (reference)	Total dose (Gy)/fraction[a]	No. of patients	Risk group	Median follow-up (year)	Androgen deprivation therapy (%)	Biochemical control rate (%) (at years)	Late toxicity ≥ grade 2 (%)[b]		Late toxicity grade 3 (%)[b]	
							GU	GI	GU	GI
Hoskin [53, 56]	34/4	30	L5, I14, H11	5.0	57	99 (3y) for I, 91 (3y) for H	33	13	3	0
	36/4	25	L1, I9, H15	4.5	76		40	4	16	0
	31.5/3	106	I49, H57	9.0	87	90 (5y), 81 (7y)	33	6	11	1
	26/2	138	I69, H69	5.3	76	93 (4y), 90 (5y)	11	2	2	0
	19/1	23	I28, H21	4.1	74	94 (4y)	15	2	2	0
	20/1	26								
Kukiełka [51]	45/3 (3 implants)	47	Low	4.8	87	97 (5y)	34	1	1	0
		27	Intermediate							
		3	High							
Prada [60]	19/1	44	Low	6.0	33	66 (6y)	0	0	0	0
		16	Intermediate							
Morton [61]	27/2 (2 implants)	83	L16, I67	1.7	0	NA	34	1	0	0
	19/1	87	L23, I64				48	3	1	0

Abbreviations: *GU* genitourinary, *GI* gastrointestinal

[a]1 implant unless noted

[b]Mostly by a crude rate, including some scored per event not per patient

[c]Including one patient with grade 4, who developed fistula after multiple TUR procedures

[d]Including two grade 4

Hoskin et al. in the UK started HDR monotherapy with four-fraction regimen giving 34 or 36 Gy in total. Soon they changed their regimen into 31.5 Gy in three fractions and then into 26 Gy in two fractions [52–54]. Finally, they are investigating a single-fraction regimen that will be mentioned in the next section [55, 56]. Their indication for HDR monotherapy was almost restricted only to intermediate- or high-risk patients, which is a similar concept to that of Yoshioka et al. in Japan and also is characterized by a high rate of ADT use.

Martinez and Krauss et al. compared three regimens, including the aforementioned 38 Gy in four fractions, 24 Gy in two fractions, and 27 Gy in two fractions. They found the acute and late toxicity profiles associated with these three HDR monotherapy schedules were similar and were well tolerated. Combined with the fact that the clinical outcomes were similar, they concluded that all three regimens may be acceptable options for the management of low- to intermediate-risk prostate cancer [57, 58].

13.3.4 Single-Fraction HDR Monotherapy: Dream or Truth?

Single-fraction HDR monotherapy would be an ideal form of HDR brachytherapy or, rather, an ultimate form of all radiotherapy. From a viewpoint of HDR brachytherapist, the problem of applicator displacement would be solved in case of single-fraction HDR. In addition, patient need not be hospitalized. From a viewpoint of radiation oncologist, only "one shot" of radiotherapy would be a highly attractive and challenging option. Patient convenience would be maximized, while burden of medical cost and machine and human resources would be minimized. Whether a single-fraction HDR monotherapy can be a viable treatment method or not is the hottest issue in our radiotherapy society.

Prada et al. in Spain reported first on single-fraction HDR monotherapy in 2012 [59]. Their preliminary results of 40 patients treated with 19 Gy HDR since 2008 were 100% for low-risk and 88% for intermediate-risk patients with 32-month actuarial biochemical control. However, in their second report, the actuarial biochemical control was reported as 66% at 6 years, which was not satisfactory [60]. Considering also their very low rate of toxicity that no grade 2 or more was observed, they implied a possibility that 19 Gy was not an enough dose for single-fraction HDR. In this aspect, Morton et al. in Canada conducted an interesting study, where they retrospectively calculated the dose having been received by the recurrent intraprostatic nodule in patients who had undergone single fraction 19 Gy HDR monotherapy [61, 62]. They found that most of the recurrent intraprostatic nodules had received doses >19 Gy (prescription dose), which may also imply the possibility that 19 Gy was not an optimal prescription dose. Some researchers may interpret the results presented from Spain and Canada as an evidence that LQ model may not work well in the area of such an extremely high dose per fraction, because 19 Gy would be an enough high dose of 260 Gy in BED or of 111 Gy in EQD_{2Gy}, if LQ model had worked well assuming $\alpha/\beta = 1.5$ Gy.

To the contrary, Hoskin et al. and Krauss et al. presented promising results of 19 Gy (or 20 Gy) single-fraction HDR monotherapy. Hoskin et al. reported 4-year biochemical relapse-free survival as 94% for 19 Gy or 20 Gy single-fraction HDR brachytherapy, which was similar to their own results obtained from two-fraction regimen (13 Gy × 2, 93%) or three-fraction regimen (10.5 Gy × 3, 91%). The 4-year estimates of grade 3 toxicity of single fraction were 2% for GU and 0% for GI, which were also comparable to those of two- or three-fraction regimen [55, 56]. Krauss et al. reported 3-year biochemical control rate of 93% without any grade 3 GU toxicity but with 2% GI toxicity [63].

Major and Polgár et al. in Hungary are conducting an interesting randomized trial comparing LDR and HDR brachytherapy as monotherapy for prostate cancer. In their initial report on dosimetric comparison, HDR had an advantage in terms of homogeneity, conformity, and doses to the urethra and rectum [64]. Mature clinical results are awaited.

Conclusion

HDR brachytherapy as monotherapy for prostate cancer has theoretical advantages in both aspects of radiation physics and biology compared to other radiotherapy modalities. Japanese groups made first clinical evidence with 9–7 fraction HDR monotherapy. American groups built robust evidence for 6–4 fraction regimens. Three- or two-fraction HDR monotherapy has been investigated vigorously at many centers including Europe, and their mature results are being awaited. Single-fraction HDR monotherapy is in the midst of clinical trials and is the most attractive issue in radiotherapy research society. HDR brachytherapy as monotherapy for prostate cancer has made a great progress with its history of >20 years and will still be evolving.

References

1. Kovács G, Pötter R, Loch T, et al. GEC/ESTRO-EAU recommendations on temporary brachytherapy using stepping sources for localised prostate cancer. Radiother Oncol. 2005;74:137–48.
2. Hoskin PJ, Colombo A, Henry A, et al. GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localised prostate cancer: an update. Radiother Oncol. 2013;107:325–32.
3. Yamada Y, Rogers L, Demanes DJ, et al. American brachytherapy society. American brachytherapy society consensus guidelines for high-dose-rate prostate brachytherapy. Brachytherapy. 2012;11:20–32.
4. Chin J, Rumble RB, Kollmeier M, et al. Brachytherapy for patients with prostate cancer: American Society of Clinical Oncology/Cancer Care Ontario joint guideline update. J Clin Oncol. 2017;35:1737–43.
5. Hsu IC, Yamada Y, Assimos DG, et al. ACR appropriateness criteria high-dose-rate brachytherapy for prostate cancer. Brachytherapy. 2014;13:27–31.
6. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Prostate Cancer. Version 2.2017. http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed 4 Oct 2017.
7. Yoshioka Y, Yoshida K, Yamazaki H, et al. The emerging role of high-dose-rate (HDR) brachytherapy as monotherapy for prostate cancer. J Radiat Res. 2013;54:781–8.

8. Skowronek J. Low-dose-rate or high-dose-rate brachytherapy in treatment of prostate cancer – between options. J Contemp Brachytherapy. 2013;5:33–41.
9. Zaorsky NG, Doyle LA, Hurwitz MD, et al. Do theoretical potential and advanced technology justify the use of high-dose rate brachytherapy as monotherapy for prostate cancer? Expert Rev Anticancer Ther. 2014;14:39–50.
10. Yoshioka Y, Suzuki O, Otani Y, et al. High-dose-rate brachytherapy as monotherapy for prostate cancer: technique, rationale and perspective. J Contemp Brachytherapy. 2014;6:91–8.
11. Demanes DJ, Ghilezan MI. High-dose-rate brachytherapy as monotherapy for prostate cancer. Brachytherapy. 2014;13:529–41.
12. Zaorsky NG, Davis BJ, Nguyen PL, et al. The evolution of brachytherapy for prostate cancer. Nat Rev Urol. 2017;14:415–39.
13. Georg D, Hopfgartner J, Gòra J, et al. Dosimetric considerations to determine the optimal technique for localized prostate cancer among external photon, proton, or carbon-ion therapy and high-dose-rate or low-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys. 2014;88:715–22.
14. Grills IS, Martinez AA, Hollander M, et al. High dose rate brachytherapy as prostate cancer monotherapy reduces toxicity compared to low dose rate palladium seeds. J Urol. 2004;171:1098–104.
15. Damore SJ, Syed AM, Puthawala AA, et al. Needle displacement during HDR brachytherapy in the treatment of prostate cancer. Int J Radiat Oncol Biol Phys. 2000;46:1205–11.
16. Hoskin PJ, Bownes PJ, Ostler P, et al. High dose rate after loading brachytherapy for prostate cancer: catheter and gland movement between fractions. Radiother Oncol. 2003;68:285–8.
17. Mullokandov E, Gejerman G. Analysis of serial CT scans to assess template and catheter movement in prostate HDR brachytherapy. Int J Radiat Oncol Biol Phys. 2004;58:1063–71.
18. Simnor T, Li S, Lowe G, et al. Justification for inter-fraction correction of catheter movement in fractionated high dose-rate brachytherapy treatment of prostate cancer. Radiother Oncol. 2009;93:253–8.
19. Yoshida K, Yamazaki H, Nose T, et al. Needle applicator displacement during high-dose-rate interstitial brachytherapy for prostate cancer. Brachytherapy. 2010;9:36–41.
20. Foster W, Cunha JA, Hsu IC, et al. Dosimetric impact of interfraction catheter movement in high-dose rate prostate brachytherapy. Int J Radiat Oncol Biol Phys. 2011;80:85–90.
21. Kolkman-Deurloo IK, Roos MA, Aluwini S. HDR monotherapy for prostate cancer: a simulation study to determine the effect of catheter displacement on target coverage and normal tissue irradiation. Radiother Oncol. 2011;98:192–7.
22. Konishi K, Yoshioka Y, Isohashi F, et al. Correlation between dosimetric parameters and late rectal and urinary toxicities in patients treated with high-dose-rate brachytherapy used as monotherapy for prostate cancer. Int J Radiat Oncol Biol Phys. 2009;75:1003–7.
23. Yoshida K, Kuroda S, Yoshida M, et al. New implant technique for separation of the seminal vesicle and rectal mucosa for high-dose-rate prostate brachytherapy. Brachytherapy. 2007;6:180–6.
24. Yoshioka Y, Nishimura T, Kamata M, et al. Evaluation of anatomy-based dwell position and inverse optimization in high-dose-rate brachytherapy of prostate cancer: a dosimetric comparison to a conventional cylindrical dwell position, geometric optimization, and dose-point optimization. Radiother Oncol. 2005;75:311–7.
25. Sumida I, Shiomi H, Yoshioka Y, et al. Optimization of dose distribution for HDR brachytherapy of the prostate using attraction-repulsion model. Int J Radiat Oncol Biol Phys. 2006;64:643–9.
26. Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. Int J Radiat Oncol Biol Phys. 1999;43:1095–101.
27. Fowler J, Chappell R, Ritter M. Is alpha/beta for prostate tumors really low? Int J Radiat Oncol Biol Phys. 2001;50:1021–31.
28. Brenner DJ, Martinez AA, Edmundson GK, et al. Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue. Int J Radiat Oncol Biol Phys. 2002;52:6–13.

29. Wang JZ, Guerrero M, Li XA. How low is the alpha/beta ratio for prostate cancer? Int J Radiat Oncol Biol Phys. 2003;55:194–203.
30. Miralbell R, Roberts SA, Zubizarreta E, et al. 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:e17–24.
31. Miyakawa A, Shibamoto Y, Otsuka S, et al. Applicability of the linear-quadratic model to single and fractionated radiotherapy schedules: an experimental study. J Radiat Res. 2014;55:451–4.
32. Brenner DJ. The linear-quadratic model is an appropriate methodology for determining isoeffective doses at large doses per fraction. Semin Radiat Oncol. 2008;18:234–9.
33. Yoshioka Y, Nose T, Yoshida K, et al. High-dose-rate interstitial brachytherapy as a monotherapy for localized prostate cancer: treatment description and preliminary results of a phase I/II clinical trial. Int J Radiat Oncol Biol Phys. 2000;48:675–81.
34. Yoshioka Y, Nose T, Yoshida K, et al. High-dose-rate brachytherapy as monotherapy for localized prostate cancer: a retrospective analysis with special focus on tolerance and chronic toxicity. Int J Radiat Oncol Biol Phys. 2003;56:213–20.
35. Yoshioka Y, Konishi K, Oh RJ, et al. High-dose-rate brachytherapy without external beam irradiation for locally advanced prostate cancer. Radiother Oncol. 2006;80:62–8.
36. Yoshioka Y, Konishi K, Sumida I, et al. Monotherapeutic high-dose-rate brachytherapy for prostate cancer: five-year results of an extreme hypofractionation regimen with 54 Gy in nine fractions. Int J Radiat Oncol Biol Phys. 2011;80:469–75.
37. Yoshioka Y, Konishi K, Suzuki O, et al. Monotherapeutic high-dose-rate brachytherapy for prostate cancer: a dose reduction trial. Radiother Oncol. 2014;110:114–9.
38. Yoshioka Y, Suzuki O, Isohashi F, et al. High-dose-rate brachytherapy as monotherapy for intermediate- and high-risk prostate cancer: clinical results for a median 8-year follow-up. Int J Radiat Oncol Biol Phys. 2016;94:675–82.
39. Yoshida K, Yamazaki H, Takenaka T, et al. High-dose-rate interstitial brachytherapy in combination with androgen deprivation therapy for prostate cancer: are high-risk patients good candidates? Strahlenther Onkol. 2014;195:1015–20.
40. Yoshioka Y, Kotsuma T, Komiya A, et al. Nationwide, multicenter, retrospective study on high-dose-rate brachytherapy as monotherapy for prostate cancer. Int J Radiat Oncol Biol Phys. 2017;97:952–61.
41. Demanes DJ, Martinez AA, Ghilezan M, et al. High-dose-rate monotherapy: safe and effective brachytherapy for patients with localized prostate cancer. Int J Radiat Oncol Biol Phys. 2011;81:1286–92.
42. Hauswald H, Kamrava MR, Fallon JM, et al. High-dose-rate monotherapy for localized prostate cancer: 10-year results. Int J Radiat Oncol Biol Phys. 2016;94:667–74.
43. Martinez A, Pataki I, Edmundson G, et al. Phase II prospective study of the use of conformal high-dose-rate brachytherapy as monotherapy for the treatment of favorable stage prostate cancer: a feasibility report. Int J Radiat Oncol Biol Phys. 2001;49:61–9.
44. Martinez AA, Demanes J, Vargas C, et al. High dose rate prostate brachytherapy: an excellent accelerated hypofractionated treatment for favourable prostate cancer. Am J Clin Oncol. 2010;33:481–8.
45. Martin T, Baltas D. Kureck R, et al. 3D conformal HDR brachytherapy as monotherapy for localized prostate cancer. A pilot study. Strahlenther Oncol. 2004;180:225–32.
46. Ghadjar P, Keller T, Pentsch CA, et al. Toxicity and early treatment outcomes in low and intermediate-risk prostate cancer managed by high-dose rate brachytherapy as monotherapy. Brachytherapy. 2009;8:45–51.
47. Rogers CL, Alder SC, Rogers RL, et al. High dose brachytherapy as monotherapy for intermediate risk prostate cancer. J Urol. 2012;187:109–16.
48. Barkati M, Williams SG, Foroudi F, et al. High-dose-rate brachytherapy as a monotherapy for favorable-risk prostate cancer: a phase II trial. Int J Radiat Oncol Biol Phys. 2012;82:1889–96.
49. Zamboglou N, Tselis N, Baltas D, et al. High-dose-rate interstitial brachytherapy as monotherapy for clinically localized prostate cancer: treatment evolution and mature results. Int J Radiat Oncol Biol Phys. 2013;85:672–8.

50. Strouthos I, Tselis N, Chatzikonstantinou G, et al. High dose rate brachytherapy as monotherapy for localised prostate cancer. Radiother Oncol. 2018;126:270–7.
51. Kukiełka AM, Dąbrowski T, Walasek T, et al. High-dose-rate brachytherapy as a monotherapy for prostate cancer--single-institution results of the extreme fractionation regimen. Brachytherapy. 2015;14:359–65.
52. Corner C, Rajas AM, Bryant L, et al. A phase II study of high dose rate afterloading brachytherapy as monotherapy for the treatment of localized prostate cancer. Int J Radiat Oncol Biol Phys. 2008;72:441–6.
53. Hoskin P, Rojas A, Lowe G, et al. High-dose-rate brachytherapy alone for localized prostate cancer in patients at moderate or high risk of biochemical recurrence. Int J Radiat Oncol Biol Phys. 2012;82:1376–84.
54. Hoskin P, Rojas A, Ostler P, et al. High-dose-rate brachytherapy with two or three fractions as monotherapy in the treatment of locally advanced prostate cancer. Radiother Oncol. 2014;112:63–7.
55. Hoskin P, Rojas A, Ostler P, et al. High-dose-rate brachytherapy alone given as two or one fraction to patients for locally advanced prostate cancer: acute toxicity. Radiother Oncol. 2014;110:268–71.
56. 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.
57. Ghilezan M, Martinez A, Gustason G, et al. High-dose-rate brachytherapy as monotherapy delivered in two fractions within one day for favorable/intermediate-risk prostate cancer: preliminary toxicity data. Int J Radiat Oncol Biol Phys. 2012;83:927–32.
58. Jawad MS, Dilworth JT, Gustafson GS, et al. Outcomes associated with 3 treatment schedules of high-dose-rate brachytherapy monotherapy for favorable-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2016;94:657–66.
59. Prada PJ, Jimenez I, González-Suárez H, et al. High-dose-rate interstitial brachytherapy as monotherapy in one fraction and transperineal hyaluronic acid injection into the perirectal fat for the treatment of favorable stage prostate cancer: treatment description and preliminary results. Brachytherapy. 2012;11:105–10.
60. 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;119:411–6.
61. Morton G, Chung HT, McGuffin M, et al. Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: early toxicity and quality-of life results from a randomized phase II clinical trial of one fraction of 19 Gy or two fractions of 13.5 Gy. Radiother Oncol. 2017;122:87–92.
62. Mendez LC, Ravi A, Chung H, et al. Pattern of relapse and dose received by the recurrent intraprostatic nodule in low- to intermediate-risk prostate cancer treated with single fraction 19 Gy high-dose-rate brachytherapy. Brachytherapy. 2018;17:291–7.
63. Krauss DJ, Ye H, Martinez AA, et al. Favorable preliminary outcomes for men with low- and intermediate-risk prostate cancer treated with 19-Gy single-fraction high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys. 2017;97:98–106.
64. Major T, Polgár C, Jorgo K, et al. Dosimetric comparison between treatment plans of patients treated with low-dose-rate vs. high-dose-rate interstitial prostate brachytherapy as monotherapy: initial findings of a randomized clinical trial. Brachytherapy. 2017;16:608–15.

Single-Fraction HDR Boost

14

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Abstract

In this chapter, the authors are going to describe the reason why we propose to administer the boost with a single dose of HDR brachytherapy: first, it is an excellent way to escalate the dose, and second it is a very accurate and sure method.

We are going to comment about different authors that are using single-dose boost or several fraction boost and the advantages and withdrawals of both. The main advantage is that we only need one surgical procedure for needle insertion, and thus movement between fractions can be avoided. And it can be done in real-time administering the brachytherapy in the operating theatre.

We are going to discuss about dose equivalence to normofractionation using alpha-beta model. And last, we are going to describe our technique in detail and our institution's result.

Keywords

Prostate neoplasm · High-risk prostate cancer · HDR boost · Single-fraction boost · Combined treatment · Prostate brachytherapy

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14.1 Introduction

HDR brachytherapy is probably one of the best methods of administering the boost in patients with intermediate- or high-risk prostate cancer. Numerous clinical studies [1–5] have shown that dose-escalation radiotherapy improves both local and biochemical disease control in intermediate- and high-risk prostate cancer. Also, it has been proven that local control improves by escalating doses to 78 Gy or more, but dose escalation increases late genitourinary (GU) and gastrointestinal (GI) toxicity, particularly in the rectum [6–8]. Various approaches have been proposed to achieve dose escalation. Some researchers use external beam radiotherapy (EBRT) alone (either IMRT or 3D-RT), while others add a boost, typically delivered by high-dose-rate brachytherapy (HDRB) [9, 10]. The use of a boost has been reported to improve outcomes and reduce toxicity in high-risk prostate cancer patients compared to external beam radiotherapy alone [11, 12]. Prostate brachytherapy is an excellent way to escalate the dose, because the needles are inserted inside the prostate through the perineum, and thanks to the rapid falloff of the dose, the organs at risk, the rectum and bladder, receive very low doses. It is also a very accurate and sure method. Especially in higher risk cohorts, interstitial high-dose-rate brachytherapy in combination with external beam radiotherapy is recognized as an established therapy and has been proven to be more efficient than EBRT alone in one randomized trial, level 1 evidence [9]. The indications for brachytherapy boost in dose-escalation schedules with external beam are wide ranging with all patients having localized disease eligible for this technique. Exclusion criteria are few encompassing patients medically unfit for the procedure and those with significant urinary outflow symptoms [13].

There are some important practical and dosimetric advantages for employing HDR prostate brachytherapy. The use of image-guided catheter or needle placement enables accurate implantation which can be extended to include extracapsular disease and seminal vesicles. It is possible to individualize the source positions over the full length of the prostate based on a defined planning target volume and organs at risk. Dose distribution optimization by inverse planning enables highly conformal dose delivery. The fixation of the prostate by the implant and rapid radiation delivery minimize the problems of target and OAR movement. The use of high doses per fraction has a biological dose advantage for tumours with a low alpha-beta ratio of which prostate is a common example. For a given prescribed dose and target coverage, HDR brachytherapy equivalent uniform doses are significantly higher than the EUDs achieved by external beam radiotherapy. This effect is caused by the inhomogeneous dose distribution with very high doses inside the target volume. Temporary brachytherapy (BT) using a stepping source does not need any source preparation time, and there is good radiation protection for personnel. Finally the use of a single source for all patients using a multipurpose facility makes brachytherapy highly cost-effective [13].

14.2 Single-Dose vs Several-Fraction Boost

Once we have justified the use of a brachytherapy boost to escalate the dose, we are going to explain the differences between single-dose boost and several-fraction boost. Different authors have employed several combinations of external RT and single or several-fraction boost. Several fractions can be administered with one implant [14]. Other authors prefer to administer only one fraction per implant, usually in two implants [15]. There is no consensus regarding the timing of each modality; in some centres brachytherapy is given before external beam and in others between EBRT fractions, while elsewhere it is given after completion of external beam. There are a wide range of EBRT target volume concepts and treatment schedules reported in the literature, and it is not possible to recommend one specific prescription. Maybe the most common treatment schedule in intermediate- and high-risk prostate cancer patients is 45 Gy of EBRT plus two fractions of HDR brachytherapy, although treatment schemes can vary considerably due to the lack of a generally accepted standard. Most authors have used a multifractionated boost approach. However, the single-fraction boost technique used at our institution has become increasingly common, as studies by Yamada et al. [16], Morton et al. [17] and Agoston et al. [10] confirm. In fact, Agoston and colleagues used a nearly identical approach to ours—60 Gy of EBRT plus a single 10 Gy HDRB boost—to treat 280 intermediate- and high-risk patients. Their results were excellent (5-year BRFS for the first 100 consecutive pts. of 85.5%).

At our centre, the treatment schedule is 60 Gy EBRT plus a single-fraction boost of 9 Gy HDRB [7, 8]. The single-boost approach is still relatively uncommon, but interest appears to be increasing [10, 16, 17]. At our institution, we have used this approach successfully since 2002 for all high-risk (and selected intermediate-risk) prostate cancer patients in which EBRT plus HDRB is preferred to EBRT alone to reduce intestinal irradiation and to maintain organ risk dose constraints.

14.3 Advantages of EBRT Plus Single-Fraction HDR Boost

Now we are going to explain the advantages of EBRT plus single-fraction HDR: HDR single boost has many advantages over treatment schedules requiring multifractionated boosts. The single-implant technique avoids interfraction movements of non-active needle [18]. The risk of errors due to needle displacement that can occur in treatments involving multiple fractions is avoided. This displacement can be very important. In Reynes study, median catheter displacement was 8.7 ± 3.3 mm (range, 2.7 ± 1.1 mm–14.7 ± 1.7 mm) [19]. Needle displacement can generate geometric variability, which can then require a new CT scan to verify needle depth and may also require a new treatment plan. Moreover, spinal anaesthesia—which is required to insert the transperineal needle—only needs to be administered once, thus reducing the consequences related to the recurring trauma [20] of multiple

implants. A single implant also shortens hospitalization time, reduces the need for analgesia and minimizes the associated risk of deep venous thrombosis. Consequently, this technique results in better patient comfort and convenience. Another advantage of a single implant is the biological benefit offered by an "ultra-hypofractionated" single dose of radiation. Prostate cancer cells are believed to be highly sensitive to the dose per fraction. It is estimated that, unlike most cancer cells, prostate cancer cells have a low α/β ratio (between 1.2 and 3 Gy) [21], and this implies that such cells should be more responsive to high-dose radiation. Thus, a hypofractionated irradiation schedule, theoretically, offers an improved radiobiological advantage in terms of selective tumour-cell killing without a concomitant increase in the development of late side effects [22]. Interestingly, our treatment schedule results in lower overall doses (EQD2 of 87 Gy and 203 Gy BED) than the schemes proposed by other authors, but even with these lower doses, our results are similar to those reported by other authors who use higher doses. This lower dose may confer a benefit in terms of toxicity and is another advantage of our single-fraction technique.

Dose definition and reporting also depend on the target: some authors report the dose administered just to the peripheral zone, the area where the majority of cancers arise; Galalae, for instance, has recently actualized Kiel's results at 15 years using a protocol of 50 Gy external RT to the pelvis plus two fractions of 15 Gy to the peripheral zone in one implant [12]. In our institution, we report the dose administered to the whole prostate.

Another interesting point to discuss is the high doses that can be administered with brachytherapy. One of the theoretical advantages of HDRB over EBRT for dose escalation is the ability to increase the BED dose, which should improve tumour control while sparing important organs at risk such as the rectum and bladder. We can transform the doses administered with brachytherapy in equivalent 2 Gy/day to compare with the dose we can administer with external radiotherapy, using the equivalence in alpha-beta terms [23]. In our fractionation schedule, the EQD2 to the tumour is 87 Gy with a BED value of 203 Gy according to linear-quadratic model. If we assume an α/β ratio of 3.0 Gy, the EQD2 would be 81.6 Gy, with a BED of 136 Gy. Other authors have also reported their results using different schemes, stratifying by its biological equivalent dose (BED) [14].

14.4 Technique of HDR Prostate Brachytherapy Boost at ICO

We are going to describe our technique [7, 8]: after spinal anaesthesia, the patient is placed in lithotomy position. A bladder catheter is placed, and the bladder is filled with diluted radiological contrast. The ultrasound (US) probe is inserted in the rectum, and we obtain a good US image both in axial and longitudinal. A needle-guidance template is then attached to the US probe close to the perineum. Rigid steel or flexible plastic catheters can be used for the implant procedure, although we usually employ plastic needles. The position of the patient and the template position are critical before implantation is commenced. The urethra should be identified and positioned along the

central row of the template (usually "row D"); the inferior row of applicator positions must reflect the lowest part of the gland to be implanted, and if seminal vesicles are to be included in the PTV, it is essential these are also considered in the set-up [13]. Needles are inserted under transrectal ultrasound guidance. Three metallic clips are inserted to mark the base and the apex of the prostate. We do this because the prostate can be very well defined with the ultrasound, but when we do the CT scan, the cranial and caudal limits of the prostate are not so easily identified. Needle depth is determined by direct visualization on ultrasound and fluoroscopy.

The needle distribution is decided inside the operating theatre depending on the prostate volume and the position of the urethra. The number of needles we use depends on the prostate volume and shape, between 14 and 18. Special care must be taken not to insert the needles close to the urethra nor the rectum; they may not be able to contribute maximally to the dose distribution due to the OAR constraint. Peripheral coverage is most important, so it is vital to have a ring of catheters around the edge of the peripheral zones, with a distance of about 3 mm from the prostate CTV border. It is also important to scroll up and down the ultrasound images during implantation to ensure there is not only good cover at the centre of the gland but also at the base and apex where the volume changes [13]. We usually do a peripheral implant and add some central needles to cover completely the whole prostate, which is our clinical target volume (CTV). In brachytherapy typically we add no margin because there are no positioning errors, so CTV = PTV (planning target volume). Once the needles are inserted, we can sew them to the perineum and perform a CT scan for dosimetry.

The CT scan is performed for volume delineation of the prostate and risk organs following recovery from anaesthetic and transfer to the imaging department. CT acquisition should be at no more than 2–3 mm. The Oncentra programme (Nucletron B.V., Veenendaal, Netherlands) is used for dosimetry. The total prescribed HDRB dose to the PTV is 9 Gy. The prescription constraints are as follows: V100 >= 98%, V150 <=50% and D90 > 105% but <115. For the rectum and urethra (high-risk organs), the constraints are as follows: rectum D2 cc <=75%, Dmax <100%; urethra D2% <=120% (in EQD_2 rectum approximately 73 Gy and urethra <90Gy) [8]. Other volumes that are important for quality of life-related outcomes and can be delineated are the penile bulb, the bladder neck and, if using MRI, the neurovascular bundle (Fig. 1).

Once the planning is finished, the machine treatment data are then transferred to the afterloader's computer. The patient should be treated as soon as possible after planning and dose calculation. Treatment will be delivered in one of two scenarios: either in the operating room with the patient still in the lithotomy position under anaesthetic or sedation and the transrectal ultrasound in situ or in a brachytherapy suite distant from the operating room after removal of the transrectal ultrasound and recovery from the anaesthetic. In the first setting, it is indispensable that the physicist is inside the operating theatre to do the planning, and that is time-consuming; in the second setting, careful quality assurance is required to identify movement of catheters and changes in OARs in relation to the images used for planning. Before radiation exposure, verification of the implant position is essential. Minimum

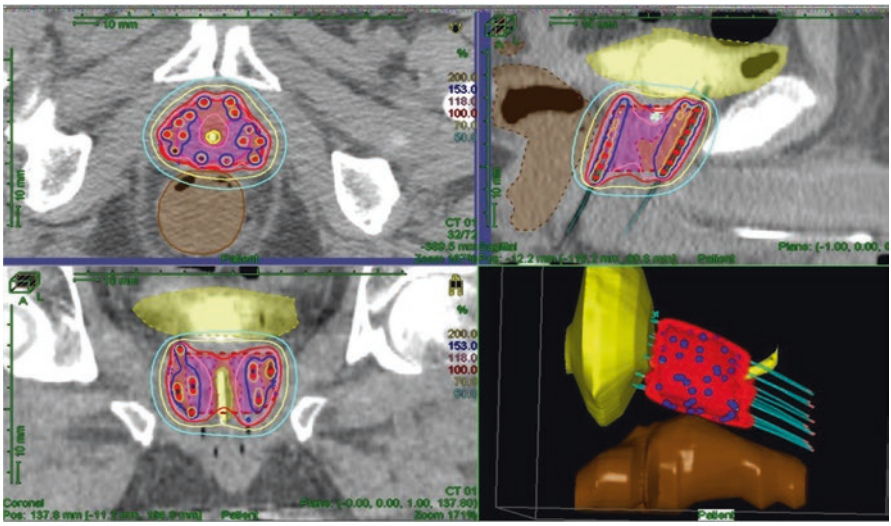

Fig. 1 Example of a single-fraction HDR boost

requirements are for the position of the perineal template to be reviewed and confirmed by direct measurement to identify any displacement from the original position on the skin. As we only administer a single-fraction boost dose, the catheter displacement is minimal. A 9 Gy boost takes usually about 15 min, depending on the activity of the HDR source.

14.5 Experience with HDR Prostate Brachytherapy Boost at ICO

We have previously reported our results in 377 patients diagnosed with intermediate- or high-risk prostate cancer with a 9 Gy HDR single fraction after 60 Gy external beam radiotherapy [7, 8]. In our institution, we tend to administer brachytherapy as a boost mostly in the high-risk group, and we recommend to these population 3 years of complete androgen blockage. All patients were included in the overall statistical analyses (OS, CSS). Median follow-up was 50 months. However, patients with <26 months of follow-up were excluded from the BRFS analysis in accordance with the recommendations of the Phoenix definition for biochemical relapse.

Median follow-up in the patients with at least 26 months of follow-up (271 pts) was 60 months. OS and CSS for the entire cohort at 5 years were, respectively, 88% (95% confidence interval [CI], 84–92) and 98% (95% CI, 97–99). Only five deaths directly attributable to prostate cancer were observed at the end of follow-up period. The 5-year BRFS rate for the 271 pts with ≥26 months of follow-up was 91%. With this combination, we obtain a 5-year BRFS of 91% with very low late toxicity, only 4.6% grade 2 and 1.6% grade 3 gastrointestinal toxicity and 12.2% grade 2 and just 0.8% grade 3 chronic genitourinary toxicity.

References

1. Martinez AA, Gustafson G, Gonzalez J, et al. Dose escalation using conformal high-dose-rate brachytherapy improves outcome in unfavorable prostate cancer. Int J Radiat Oncol Biol Phys. 2002;53(2):316–27.
2. Vargas CE, Martinez AA, al BTP e. High-dose irradiation for prostate cancer via a high-dose-rate brachytherapy boost: results of a phase I to II study. Int J Radiat Oncol Biol Phys. 2006;66(2):416–23.
3. Al-Mamgani A, van Putten WLJ, Heemsbergen WD, et al. Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2008;72:980–8.
4. Dearnaley DP, Sydes MR, Graham JD, et al. Escalated-dose versus standard dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. Lancet Oncol. 2007;8:475–87.
5. Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M.D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys. 2008;70:67–74.
6. Peeters STH, Heemsbergen WD, van Putten WLJ, et al. Acute and late complications after radiotherapy for prostate cancer: results of a multicenter randomized trial comparing 68Gy to 78 Gy. Int J Radiat Oncol Biol Phys. 2005;61:1019–34.
7. Pistis F, Guedea F, Pera J, et al. External beam radiotherapy plus high-dose-rate brachytherapy for treatment of locally advanced prostate cancer: the initial experience of the Catalan Institute of Oncology. Brachytherapy. 2010;9(1):15–22.
8. Boladeras A, Santorsa L, Gutierrez C, et al. External beam radiotherapy plus single-fraction high dose rate brachytherapy in the treatment of locally advanced prostate cancer. Radiother Oncol. 2014;112(2):227–32.
9. Hoskin PJ, Rojas AM, Bownes PJ, et al. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. Radiother Oncol. 2012;103:217–22.
10. Agoston P, Major T, Fröhlich G, et al. Moderate dose escalation with single-fraction high-dose-rate brachytherapy boost for clinically localized intermediate- and high-risk prostate cancer: 5-year outcome of the first 100 consecutively treated patients. Brachytherapy. 2011;10:376–84.
11. Galalae RM, Martinez A, Nuernberg N, et al. Hypofractionated conformal HDR brachytherapy in hormone naïve men with localized prostate cancer. Is escalation to very high biologically equivalent dose beneficial in all prognostic risk groups? Strahlenther Onkol. 2006;182:135–41.
12. Galalae RM, Zakikhany NH, Geiger F, et al. The 15-year outcomes of high-dose-rate brachytherapy for radical dose escalation in patients with prostate cancer-a benchmark for high-tech external beam radiotherapy alone? Brachytherapy. 2014;13:117–22.
13. Hoskin PJ, Colombo A, Henry A, et al. GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localised prostate cancer: an update. Radiother Oncol. 2013;107(3):325–32. https://doi.org/10.1016/j.radonc.2013.05.002.
14. Vigneault E, Mbodji K, Magnan S, et al. High-dose-rate brachytherapy boost for prostate cancer treatment: different combinations of hypofractionated regimens and clinical outcomes. Radiother Oncol. 2017;124(1):49–55. https://doi.org/10.1016/j.radonc.2017.06.012.
15. Martinez AA, Gonzalez J, Ye H, et al. Dose escalation improves cancer-related events at 10 years for intermediate- and high-risk prostate cancer patients treated with hypofractionated high-dose-rate boost and external beam radiotherapy. Int J Radiat Oncol Biol Phys. 2011;79:363–70.
16. Yamada Y, Bhatia S, Zaider M, et al. Favorable clinical outcomes of three dimensional computer-optimized high-dose-rate prostate brachytherapy in the management of localized prostate cancer. Brachytherapy. 2006;5:157–64.
17. Morton G, Loblaw A, Cheung P, et al. Is single fraction 15 Gy the preferred high dose-rate brachytherapy boost dose for prostate cancer? Radiother Oncol. 2011;100:463–7.

18. Hoskin PJ, Bownes PJ, Ostler P, et al. High dose rate afterloading brachytherapy for prostate cancer: catheter and gland movement between fractions. Radiother Oncol. 2003;68:285–8.
19. Reynés-Llompart G, Pino F, Modolell I, Gullón C, et al. Impact of prostate catheter displacement in inverse planning--simulated annealing and geometric optimization. Brachytherapy. 2016;15(1):112–7. https://doi.org/10.1016/j.brachy.2015.10.003.
20. Aitkenhead AR. Injuries associated with anaesthesia. A global perspective. Br J Anaesth. 2005;95:95–109.
21. Fatyga M, Williamson JF, Dogan N, et al. A comparison of HDR brachytherapy and IMRT techniques for dose escalation in prostate cancer: a radiobiological modeling study. Med Phys. 2009;36:3995–4006.
22. Proust-Lima C, Taylor JMG, Sécher S, et al. Confirmation of a low a/b ratio for prostate cancer treated by external beam radiation therapy alone using a posttreatment repeated-measures model for PSA dynamics. Int J Radiat Oncol Biol Phys. 2011;79:195–201.
23. Nag S, Gupta N. A simple method of obtaining equivalent doses for use in HDR brachytherapy. Int J Radiat Oncol Biol Phys. 2000;46:507–13.

Part IV

Breast

Brachytherapy APBI: Japanese Experience and Asian Trend

15

Takayuki Nose

Abstract

Interstitial multi-catheter brachytherapy APBI (IMB-APBI) has been established as a treatment option for early breast cancer in Europe and North America, where simple lumpectomy can be indicated for most patients. In Asia, IMB-APBI is gradually gaining popularity but still in a much slower pace. The breast size in Asia is commonly smaller, and the surgical approach is accordingly different from Western countries. Among them, Japanese breast-conserving surgery, cylindrical resection, is especially different in that it leaves no cavity in the breast. The CTV after Asian surgery, therefore, needs special consideration. Consensus on surgical approach and CTV for small breast is still open for discussion. In this chapter we focus on the surgical techniques and evidences from Asian countries.

Keywords

Interstitial multi-catheter brachytherapy · APBI · Cylindrical resection · Small breast · Breast conservation

15.1 Introduction

Accelerated partial-breast irradiation (APBI) has first evolved in Europe since the 1980s and then spread out to North America since the 1990s. Most of their early experiences were limited to interstitial multi-catheter brachytherapy APBI (IMB-APBI).

In Asian countries, the acceptance of APBI was slower than in Western countries. In late 1990s through the early 2000s, two hospitals in Japan started initial

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experiences for IMB-APBI. As of 2017, only six groups from Asian countries, Japan, four; South Korea, one; and Singapore, one, have reported IMB-APBI results. Experiences of non-IMB-type APBI using single- or multi-lumen brachytherapy (MammoSite®, Savi®, Contura®, clearPath®) have been more limited or even scarce in Asia. In this chapter, we focus on IMB-APBI techniques and evidences.

15.2 Breast-Conserving Surgery for Small Breast

The breast size in Asia is generally smaller than that in Europe and North America. Applicable breast-conserving surgery is technically different from that used in Western countries. In large-breasted countries, lumpectomy is the standard surgical option. A surgical defect after lumpectomy, i.e., a lumpectomy cavity, is surrounded by the remaining mammary gland in all directions (Fig. 15.1).

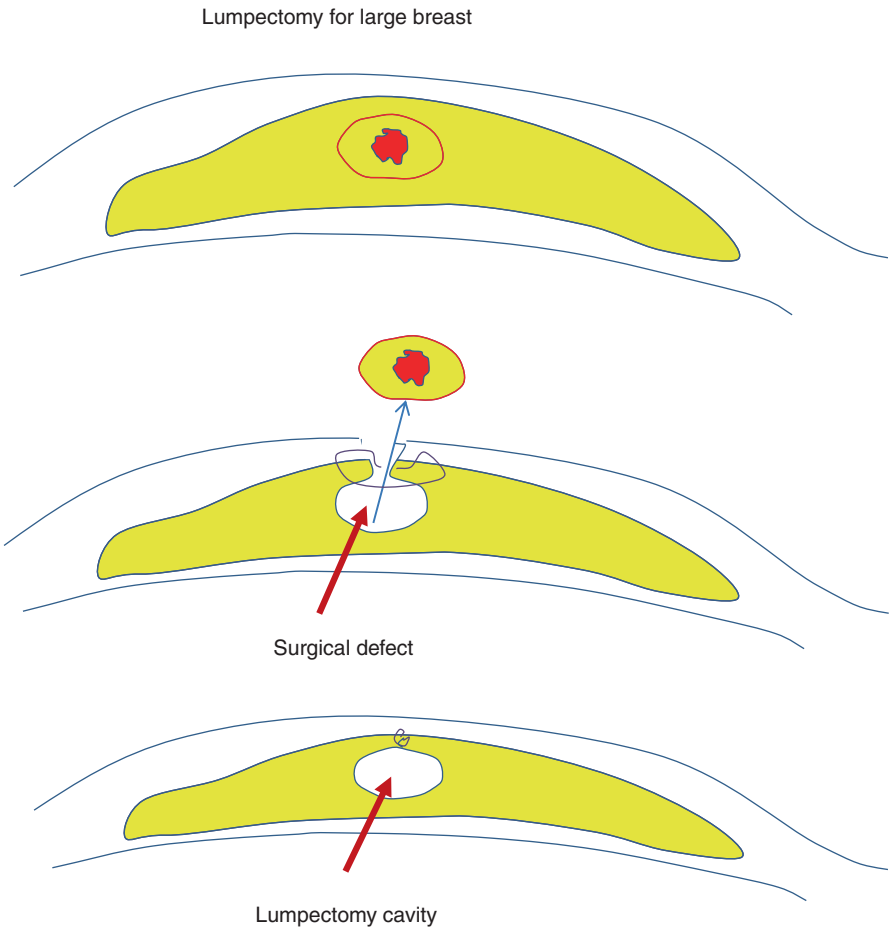

Fig. 15.1 Lumpectomy for large breast

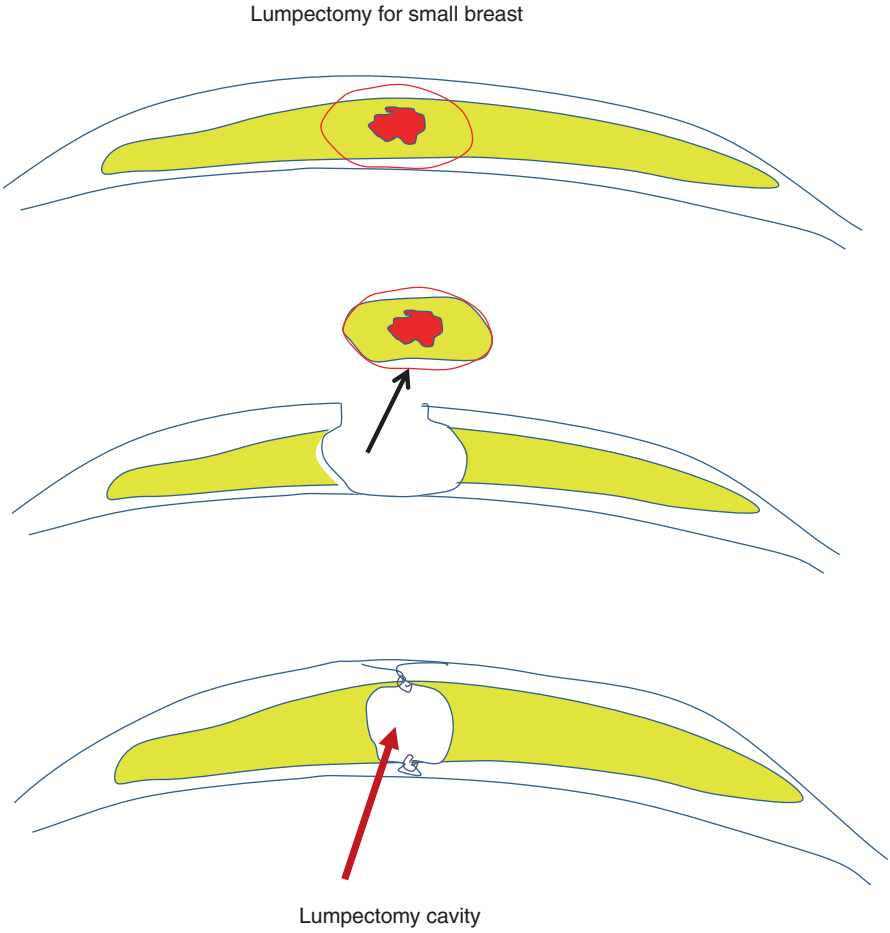

Fig. 15.2 Lumpectomy for small breast

For a small breast, a lumpectomy cavity is often surrounded by a mammary gland only in lateral directions. Typically, anterior and posterior margins for the lumpectomy cavity are free of mammary gland: only subcutaneous fat tissue and pectoral muscle are bordering on the anterior margin and on the posterior margin, respectively (Fig. 15.2). The lumpectomy resection volume depends on tumor volume, irrespective of the breast size or the mammary gland thickness (Fig. 15.3).

15.3 Breast-Conserving Surgery in Japan: Cylindrical Resection

In Japan, breast-conserving surgery started to replace radical mastectomy gradually in the late 1980s. In those days, there still was a nationwide allergy to "nuclear things" or "radiation exposure," affected by the two atomic bomb tragedies which

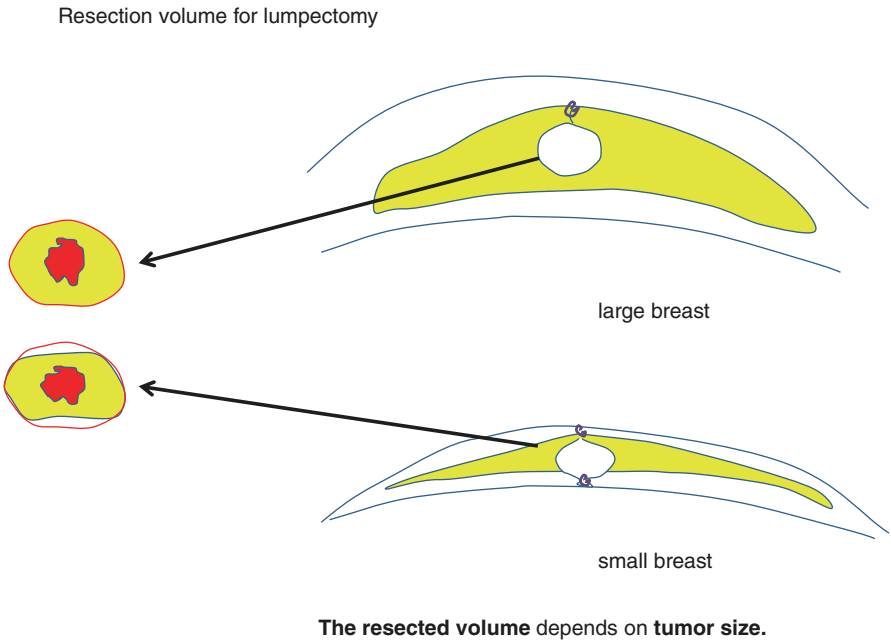

Fig. 15.3 Resection volume for lumpectomy

occurred in 1945. National hesitation in using radiation to humans was still prevalent even 40 years after the tragedies. The breast-conserving pioneers in Japan, unsurprisingly, pursued breast conservation without radiation, by securing negative margin >5 mm. For this purpose, "cylindrical resection approach" was developed. This approach removed the index tumor en bloc wrapped in the tissue from beneath the skin all down to the chest wall muscles with an arbitrary lateral margin (Fig. 15.4). The cut end is vertical to the chest wall all around the surgical defect, while the cut end for lumpectomy is round shaped in anteroposterior direction (Figs. 15.1, 15.2, 15.4). To avoid severe deformity by the large cylindrical defect, the surgical margins were always sutured together to leave no cavity in the breast (Fig. 15.4). Interestingly, as shown in Fig. 15.5, the resection volume depends not on tumor volume but on mammary gland thickness. The larger the breast, the larger the resection volume. From oncologic viewpoint, this approach was particularly suitable for a small breast, easy to secure negative margins in anterior and posterior directions and easy to assess lateral surgical margin status based on a comprehensible, vertical histopathological specimen. When a positive margin was reported at an intraoperative rapid histopathological exam, an additional crescent-shaped

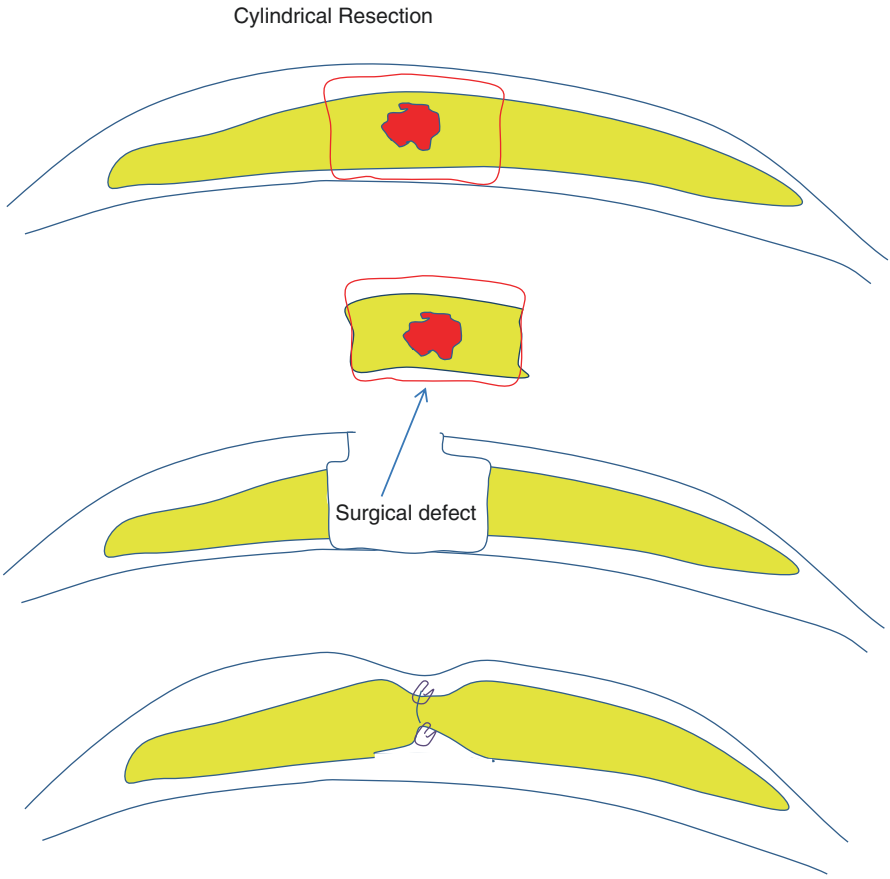

Fig. 15.4 Cylindrical resection

volume from beneath the skin through the chest wall muscle was removed in relevant direction to secure negative margin. From cosmetic viewpoint, this approach damaged cosmesis markedly due to the larger resection volume than lumpectomy.

As time elapsed, radiotherapy has been gradually accepted in Japan as a safe and vital method for cancer treatment along with the technical progress of radiotherapy. The essential role of radiotherapy after breast-conserving surgery has gained popularity. At this time, "cylindrical resection" had already been authorized as the standard breast-conserving surgery instead of lumpectomy. Cylindrical resection and postoperative radiotherapy were, even ironically, combined in Japan despite the inherent aim of this surgery to omit radiotherapy.

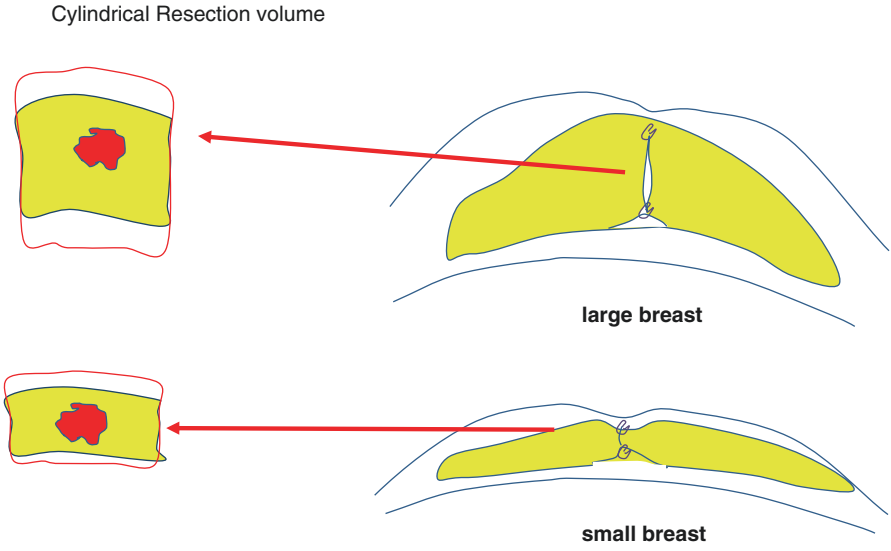

Fig. 15.5 Cylindrical resection volume

15.4 CTV for APBI

CTV for APBI is defined as the mammary gland volume surrounding the surgical bed with a specified margin distance.

15.4.1 CTV After Lumpectomy

CTV after lumpectomy for a large breast is depicted in Fig. 15.6. When the remaining mammary gland is thick enough, CTV for APBI is simply an expansion of the lumpectomy cavity.

For a small breast, lumpectomy cavity is typically not surrounded by the mammary gland on anterior and posterior margins. CTV for APBI is limited only laterally to the cavity for a small breast (Fig. 15.7). Irrespective of the breast size, CTV depends on the tumor size and also on the resultant lumpectomy cavity volume.

15.4.2 CTV After Cylindrical Resection

Judging from a post-cylindrical resection CT, the original tumor location in the anteroposterior direction is difficult to find especially for a large breast (Fig. 15.5). The full thickness of the mammary gland is inevitably targeted for APBI (Fig. 15.8). Irrespective of the breast size, CTV depends not on tumor size but only on gland thickness. The sutured mammary gland makes the lateral target identification

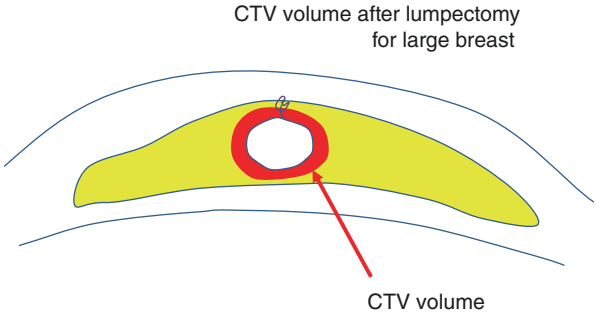

Fig. 15.6 CTV volume after lumpectomy for large breast

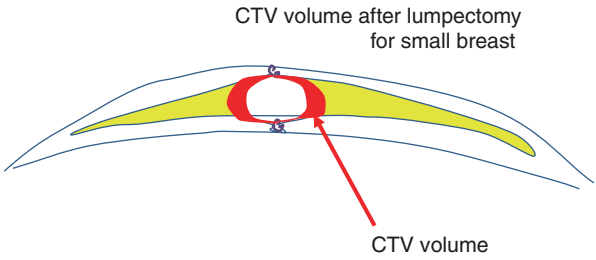

Fig. 15.7 CTV volume after lumpectomy for small breast

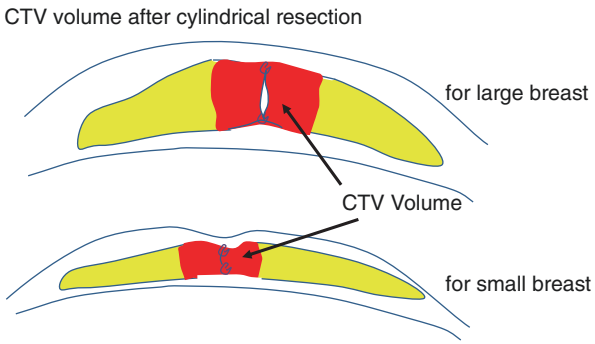

Fig. 15.8 CTV volume after cylindrical resection

The CTV volume depends on ***gland thickness.***

uncertain as well. To compensate for the lateral and anteroposterior uncertainty, CTV after cylindrical resection tends to be even larger than the CTV after lumpectomy.

15.5 Japanese Experience

15.5.1 Cylindrical Resection Experience

15.5.1.1 Osaka Medical Center

From 1998 to 2003, the first Asian IMB-APBI study was initiated at Osaka Medical Center. They recruited 20 patients including high risk of pT2 (n = 6), pN1 (n = 3), and positive or close (<5 mm) surgical margin (n = 3). During the same general

anesthesia for breast-conserving surgery (cylindrical resection) and axillary dissection, 11 applicators (range, 6–18) were implanted perioperatively around the sutured margin. Two-dimensional planning was used. Median V100 and V150 were 107 cm^3 (range, 65–368 cm^3) and 24 cm^3 (range, 12–95 cm^3), respectively. The median DNR value was 0.23 (range, 0.19–0.31). They delivered high-dose rate (HDR) of 36–42 Gy/6–7 fr over 3–4 days. Irradiation was started before the final histological confirmation. Finally 15% of the patients had positive/close margin (<5 mm) for intraductal component at the permanent histological report. At 52 months, one inflammatory recurrence (5%) was observed for a patient with negative hormone receptor and negative surgical margin. One patient presented prolonged, as long as 27 months, fat necrosis complicated with infection. For cosmetic outcome, excellent and good results were observed only for 75% of the patients evaluated by Harvard 4-point scale [1].

15.5.1.2 Osaka National Hospital

From 2002 through 2006, Yoshida et al. treated 45 patients of Tis–T2 breast cancer using IMB-APBI at Osaka National Hospital. They included high-risk patients with T2 (n = 12), pN1 (n = 11), pN2 (n = 2), and positive or close (<5 mm) surgical margin (n = 15). Applicators were implanted either perioperatively (n = 26) or postoperatively (n = 19). Two-dimensional planning was used. Median V100 and V150 were 141 cm^3 (range, 39–315 cm^3) and 38 cm^3 (range, 12–83 cm^3), respectively. The median DNR was 0.29 (range, 0.2–0.41). HDR 36 Gy/6 fr (n = 43) or 42 Gy/7 fr (n = 2) was delivered over 3–4 days. At a median follow-up of 31 months (4–54 months), 4% of local recurrence and 4% of distant metastasis were observed. Seven wound complications, four with and three without infection, and two rib fractures were observed. The significant risk factors for wound complications were nonadministration of prophylactic antibiotics during IMB-APBI ($p < 0.01$), perioperative implant ($p < 0.05$), and large V100 ($p < 0.01$) and V150 ($p < 0.05$). Cosmetic outcome was not available from this group [2, 3].

15.5.1.3 Multi-institutional Prospective Feasibility Study (UMIN000001677)

Based on the above two studies, a prospective multi-institutional feasibility study was performed to verify reproducibility of IMB-APBI among six hospitals in Japan from 2009 to 2016. Forty-six low-risk patients (tumor <= 3 cm, pN0, surgical margin negative for exposure, ER or PR positive) participated in the study. Cylindrical resection and postoperative implant after confirming the permanent histopathology were the mainstays of the protocol treatment. Planning was performed using 3D images. HDR 36 Gy/6 fr over 3–4 days was delivered. The median cylindrical resection volume was 81 cm^3 (range, 28–260 cm^3). Median V100 and V150 were 117 cm^3 (range, 40–282 cm^3) and 36 cm^3 (range, 12–96 cm^3), respectively. The median DNR value was 0.30 (range, 0.22–0.51).

The primary endpoint of planning reproducibility among six hospitals was prospectively and statistically confirmed in terms of the clip dose (>= 36 Gy/6 fr), dose nonhomogeneity ratio (<0.35), and V100 (principally 40–150 cm^3). This result

warrants the execution of phase II or III multi-institutional clinical trials using IMB-APBI. Five-year clinical results were also reported: no local, regional, nor metastatic breast cancer recurrences were observed; early and late sequelae were within the previous IMB-APBI results; excellent or good cosmesis was observed in only for 74% of the patients. Yoden et al. found larger resection volume in small bra cup sizes (A/B) resulted in fibrosis >=G2, which strongly correlated with unfavorable cosmetic outcome at 30 months follow-up [4–6].

15.5.2 Lumpectomy Experience

One of the most active APBI centers in the world is Tokyo-West Tokushukai Hospital. Since 2008 through 2017, 432 patients have undergone IMB-APBI. Their indication was principally limited to low-risk patients (clinical tumor size <=3 cm, negative sentinel lymph node exam, surgical margin negative for exposure). However, irradiation started before the final histopathological confirmation, about 10% of the patients were with positive or close surgical margin (<5 mm). Different from other Japanese groups, lumpectomy was employed by this group. The lumpectomy volume was 32 cm^3 (range, 6–133 cm^3). Intraoperative implantation of applicators was used, and HDR 32 Gy/8 fr was delivered. Median V100 and V150 were 22 cm^3 (range, 1–106 cm^3) and 8 cm^3 (range, 1–59 cm^3), respectively. The median DNR value was 0.36 (range, 0.20–0.56).

At a median follow-up of 50 months (range, 3–109 months), local recurrence rate was 2% (TR, four patients; E, four patients). Fat necrosis was observed in 1.4% of the patients, hemorrhage after catheter removal in 1.2%, and wound break by infection in 4.4%. After they employed hidden scar approach for skin incision, no wound trouble was observed thereafter. As for cosmesis, excellent and good evaluation was recorded in 88% of the patients by using BCCT.core software with minimal follow-up of 5 years and consent agreement to breast photos [7–10].

15.6 South Korean Experience

Between 2002 and 2006, 48 prospectively selected patients with early-stage breast cancer received APBI using IMB-APBI following breast-conserving surgery. Their median age was 52 years (range, 36–78). They included T2 (31%), pN1 (8%), hormonal receptor negative (23%), and close margins (<0.2 cm) (13%). Applicators (median 5, range 4–6), arranged in a single plane (35%) for small and flat excision cavity or double plane (65%) for larger cavity, were perioperatively implanted. Planning was two dimensionally performed using four titanium clips. The PTV surface is 1–2 cm from the clips. The mean V100 and V150 were 45 cm^3 (range, 12–101 cm^3) and 23 cm^3 (range, 5–46 cm^3), respectively. The mean DNR was 0.5 (range, 0.43–0.56). After confirmation of final pathology, 6–9 days after implant, HDR dose of 30 Gy or 34 Gy in ten fractions given twice daily within 5 days was delivered to the tumor bed plus a 1–2 cm margin. Ninety-two percent of the patients

received adjuvant systemic treatments. The median follow-up was 53 months (range, 36–95 months). The 5-year actuarial local recurrence rate was 4.6%. Local recurrences occurred only in patients with close margins (<0.2 cm). No regional or distant relapse occurred. Grade 1 late skin and G 2 late subcutaneous toxicity were seen in 11 (22.9%) and 26 (54.2%) patients, respectively. The volumes receiving 100% and 150% of the prescribed dose were significantly higher in the patients with late subcutaneous toxicity ($p = 0.02$ and 0.03, respectively). Cosmesis was excellent or good in 90% (Ex, 71%; Gd, 19%; Fr, 10%; Pr 0%) [11].

15.7 Singaporean Experience

Between 2008 and 2014, Tang et al. performed IMB-APBI for 121 patients (Chinese, 71%; other Asian, 15%). Their indication was limited to low-risk patients (tumor <3 cm, pN0, negative surgical margin), and 72% were ER positive. All patients underwent lumpectomy and axillary evaluation by sentinel node biopsy or axillary clearance. After histopathological confirmation of the indication within 8 weeks post-lumpectomy, mean 18 applicators (range, 8–25) were implanted with the help of templates and CT guidance using contrast in the cavity and surgical clips. HDR 34 Gy/10 fr was delivered to the volume expanded from the cavity by 15–20 mm. Median V100 and V150 were 162 cm^3 (range, 34–330 cm^3) and 39 cm^3 (range, 15–70 cm^3), respectively. The mean DNR was 0.24 (range, 0.16–0.43 cm^3). At the median follow-up of 30 months (range, 4–67 months), no local recurrence was observed for the 95 patients examined by follow-up mammograms. One patient relapsed with bone metastases. Fibrosis and fat necrosis (<= G2) were observed in three and two patients, respectively. Cosmetic outcome was not available from this group.

They also displayed important volume data. Median breast volume and mean lumpectomy cavity volume were 850 cm^3 (range, 216–2108 cm^3) and 24 cm^3 (range, 3–62 cm^3). Results for the IMB-APBI for these comparatively small breast-sized Asian population seem encouraging to promote international Asian IMB-APBI study [12–14].

15.8 Summary

Table 15.1 summarizes treatment parameters and clinical results from six Asian groups.

For lumpectomy series, Tokyo-West and Singaporean groups displayed similar resection volumes as 32 cm^3 and 24 cm^3, respectively, and they were less than half the cylindrical resection volume of 81 cm^3 for the Japanese multi-institutional group. V100 values for Tokyo-West and South Korean groups were 22 cm^3 and 45 cm^3, respectively. They were also less than half the V100 values for cylindrical resection groups of 107 cm^3, 141 cm^3, 117 cm^3. The Singaporean V100 of 162 cm^3 was, however and surprisingly, larger than all other groups from both lumpectomy series and cylindrical resection series.

Table 15.1 Treatment parameters and clinical results from six Asian groups

	Lumpectomy			Cylindrical resection		
Study group	Tokyo-West	South Korea	Singapore	Osaka Medical Center	Osaka National Hospital	Japanese multi-institutional
Resection volume	32 cm^3	NR	24 cm^3 (cavity volume)	NR	NR	81 cm^3
V100	22 cm^3	45 cm^3	162 cm^3	107 cm^3	141 cm^3	117 cm^3
Total treatment volume[a]	54 cm^3	NR	186 cm^3	NR	NR	198 cm^3
IBTR[b]	2% at 4 year	4.6% at 5 year	0% at 2.5 year	5% at 4 year	4% at 2.5 year	0% at 5 year
Dose schedule	32 Gy/8fr	30–34 Gy/10fr	34 Gy/10fr	36–42 Gy/6–7 fr	36–42 Gy/6–7 fr	36 Gy/6 fr
Cosmesis (ex/Gd)	88%	90%	NR	75%	NR	74%

[a]The sum of resection volume and V100
[b]*IBTR* ipsilateral breast tumor recurrence

For cylindrical resection series, the cosmetic outcomes for Ex/Gd were 75% and 74% for Osaka Medical Center and for the Japanese multi-institutional group, seemingly reproducible among them, and much worse than the lumpectomy series that displayed 88% and 90% for cosmetic outcomes.

Total treatment volumes, as the sum of resection volume and V100, were available for Tokyo-West, Singaporean, and Japanese multi-institutional groups as 54, 186, and 198 cm^3, respectively. Annual IBTR rates for these three groups were all lower than 0.5%, satisfactory level as the contemporary breast conserving therapy series. Among these three groups, cosmetic outcomes for Ex/Gd ratios were available only for Tokyo-West and Japanese multi-institutional groups as 88% and 74%, respectively. For these two Japanese groups, the large difference of the total treatment volumes (54 cm^3, 198 cm^3) might have contributed to the difference of cosmetic outcomes. Somewhere between these two total treatment volumes, there should be an ideal range of volumes that might best balance the oncologic and cosmetic outcomes.

References

1. Nose T, Komoike Y, Yoshida K, et al. A pilot study of wider use of accelerated partial breast irradiation: intraoperative margin-directed re-excision combined with sole high-dose-rate interstitial brachytherapy. Breast Cancer. 2006;13:289–99.
2. Yoshida K, Nose T, Masuda N, et al. Preliminary result of accelerated partial breast irradiation after breast-conserving surgery. Breast Cancer. 2009;16:105–12.
3. Tanaka E, Yamazaki H, Yoshida K, et al. Objective and longitudinal assessment of dermatitis after postoperative accelerated partial breast irradiation using high-dose-rate interstitial brachytherapy in patients with breast cancer treated with breast conserving therapy: reduction of moisture deterioration by APBI. Int J Radiat Oncol Biol Phys. 2011;81:1098–104.

4. Otani Y, Nose T, Dokiya T, et al. A Japanese prospective multi-institutional feasibility study on accelerated partial breast irradiation using interstitial brachytherapy: treatment planning and quality assurance. Radiat Oncol. 2015;10:126. https://doi.org/10.1186/s13014-015-0430-8.
5. Yoden E, Nose T, Otani Y, et al. Uncertainty of cosmetic evaluation after accelerated partial breast irradiation: interim analysis of a Japanese prospective multi-institutional feasibility study. Jpn J Radiol. 2017;35:381–8.
6. Nose T, Otani Y, Asahi S, et al. A Japanese prospective multi-institutional feasibility study on accelerated partial breast irradiation using interstitial brachytherapy: clinical results with a median follow-up of 26 months. Breast Cancer. 2016;23:861–8.
7. Sato K, Mizuno Y, Fuchikami H, et al. Comparison of radiation dose to the left anterior descending artery by whole and partial breast irradiation in breast cancer patients. J Contemp Brachytherapy. 2015;7:23–8.
8. Sato K, Mizuno Y, Fuchikami H, et al. Impact of young age on local control after partial breast irradiation in Japanese patients with early stage breast cancer. Breast Cancer. 2017;24:79–85.
9. Sato K, Fuchikami H, Kato M, et al. Efficacy of single-stage breast-conserving treatment using multicatheter partial breast brachytherapy evaluated by GEC-ESTRO phase 3 trial. J Contemp Brachytherapy. 2017;9:424–30.
10. Sato K, Fuchikami H, Takeda N, et al. Proceedings for the 19th Japan brachytherapy group annual meeting. 2017;44:S3–2 (in Japanese)
11. Yeo SG, Kim J, Kwak GH, et al. Research Accelerated partial breast irradiation using multicatheter brachytherapy for select early-stage breast cancer: local control and toxicity. Radiat Oncol. 2010;5:56.
12. Tang JI, Tan PW, Koh VY, et al. Multi-catheter interstitial accelerated partial breast irradiation – tips and tricks for a good insertion. J Contemp Brachytherapy. 2014;6:85–90.
13. Koh VY, Buhari SA, Tan PW, et al. Comparing a volume based template approach and ultrasound guided freehand approach in multicatheter interstitial accelerated partial breast irradiation. J Contemp Brachytherapy. 2014;6:173–7.
14. Koh VY, Tan PW, Buhari SA, et al. Accelerated partial breast irradiation in an Asian population: dosimetric findings and preliminary results of a multicatheter interstitial program. OncoTargets and Therapy. 2016;9:5561–6.

Breast: Hungarian Experience and European Trend

16

Csaba Polgár

Abstract

Before the era of breast-conserving therapy, BT implants were used to treat large inoperable breast tumors. Later interstitial BT has been used to deliver an additional dose to the tumor bed after BCS and WBI. Based on the obvious dosimetric advantages of interstitial breast implants (over external beam techniques) supported by the encouraging results of modern boost series utilizing stepping-source afterloading technology, multicatheter HDR/PDR BT remains a standard treatment option for boosting the tumor bed after BCS and WBI.

APBI is an attractive treatment approach with considerable advantages over conventional WBI opening new prospects for interstitial breast BT. Contemporary APBI trials using interstitial BT with strict patient selection criteria resulted in an annual LR rate <1%.

Development of new standards for 3D CT image-based BT treatment planning together with the implementation of inverse dose planning will further improve the conformity of dose distribution delivered by multicatheter implants maximizing the ballistic advantage of interstitial breast BT.

Keywords

Breast-conserving therapy · Radiotherapy · Brachytherapy · Accelerated partial breast irradiation · Tumor bed boost

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16.1 Introduction

Before the era of breast-conserving therapy, interstitial brachytherapy (BT) implants (with or without external beam irradiation) were used to treat large inoperable tumors [1]. Later interstitial BT with rigid needles or multiple flexible catheters have been used to deliver an additional (boost) dose to the tumor bed after breast-conserving surgery (BCS) and whole-breast irradiation (WBI) [2–4]. In the last two decades, the new concept of accelerated partial breast irradiation (APBI) opened a new perspective for breast BT [3, 5]. APBI is an attractive treatment approach that shortens the 3- to 7-week course of conventional postoperative radiotherapy (RT) to 4–5 days. The acceleration of RT eliminates the disadvantages of the extended treatment period, especially for elderly patients, working women, and those who live at a significant distance from the RT facility. The rationale for APBI is that the majority of local recurrences (LRs) occur in close proximity to the tumor bed [2, 3]. Less than 20% of LRs appear "elsewhere" in the breast, and the absolute number of such failures is very low (e.g., far less than 1% per year and similar to the rate of new contralateral tumors) [6]. In addition, some elsewhere failures are likely to be new primary breast cancer that arose after initial therapy and hence would not have been prevented by WBI. Thus, in the last two decades, APBI using interstitial implants has been intensively evaluated in phase I–II and III clinical trials as a possible alternative to conventional WBI [3].

In this chapter, we give an overview on Hungarian and European experience with interstitial breast BT used as a boost or sole postoperative irradiation after BCS.

16.2 Indications for Interstitial Breast Brachytherapy

16.2.1 Indications for Tumor Bed Boost

The standard technique of RT after BCS is to treat the whole breast by teletherapy via tangential fields up to a total dose of 40–50 Gy in 15–25 fractions. The main rationale to give an additional dose to the tumor bed after WBI was based on the clinical observation that 67–100% of ipsilateral breast recurrences originated from the vicinity of the original index lesion [2]. Based on the analysis of dose-response curves, van Limbergen et al. [4] reported that above 50 Gy, an increase of 15 Gy would reduce the LR rate by a factor of 2. To date, three randomized trials have confirmed that a boost dose of 10–16 Gy after 50 Gy WBI significantly decreased the LR rate [2, 7–10]. Patient age less than 50 years, close, microscopically positive or unknown surgical margins, and the presence of extensive intraductal component (EIC) are generally accepted as absolute indications for boost irradiation [2, 4, 5]. Other factors (e.g., lymphovascular invasion (LVI), high grade, and large tumor size >3 cm) can be also considered for the indication of a tumor bed boost.

Traditionally low-dose-rate (LDR) BT, electrons, or photons have been used to deliver the boost dose to the tumor bed [1, 7, 10–12]. Later high-dose-rate (HDR) BT has been also accepted as a safe alternative boost modality [13–20]. Interstitial

BT is preferable in cases of deep-seated tumor bed in large-volume breasts. Obviously, BT offers the practical advantage of more conformal treatment of small volumes to higher doses and lower doses to the skin [2, 4]. Therefore, in addition to external beam boost modalities, interstitial BT is a standard treatment option to deliver an additional dose to the tumor bed after BCS and WBI.

16.2.2 Indications for APBI

Patient selection in early European APBI clinical trials was flawed [21–24]. In later studies patient selection criteria were refined excluding patients with high risk for multicentricity from APBI protocols [25–30]. Based on the limited scientific evidence available in 2009, the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) Breast Cancer Working Group has generated and published the European recommendations on patient selection for APBI [31]. These recommendations provide conservative and useful clinical guidance regarding the safe use of APBI outside the context of clinical trials. In addition to the GEC-ESTRO "good candidate" group, the GEC-ESTRO recommendations defined an intermediate group of patients ("possible candidate" group) for whom APBI considered acceptable only in the context of prospective clinical trials. The third group of women ("high-risk" group) should not be treated with APBI, as there is enough evidence against the use of APBI for such patients.

16.3 Techniques and Treatment Planning

Different techniques exist, but the implantation of the breast is always performed using stainless steel trocars which are then exchanged with flexible plastic catheters. Then, the catheters are fixed to the skin with locking buttons and are trimmed at a consistent length. There are some centers where the boost dose is delivered with a single fraction. In this case the rigid needles are used not only for insertion but also for the irradiation. In intraoperative setting visual inspection of the lumpectomy cavity helps to place the needles, but when the implantation is performed a few weeks after BCS, some sort of image guidance before or during the insertions is necessary for placing the adequate number of catheters in right geometry in relation to the extent of the tumor bed. Different types of imaging modalities can be used, including US, mammography, and CT. The use of a template around the involved breast is of great help to implant the needles parallelly according to a regular (usually triangular) geometry. The template with the holes has to be visualized on an image together with the cavity geometry in order to select the appropriate holes to be used for needle insertions. In Hungary for breast implantation, CT guidance is used to preplan the implant geometry as well as for treatment planning. A preimplant CT imaging is performed, and the cavity is outlined in axial slices, and the target volume is created according to the contouring protocol (Fig. 16.1). Then, using 3D rendering the patient is rotated in the "needle's eye view," and the target

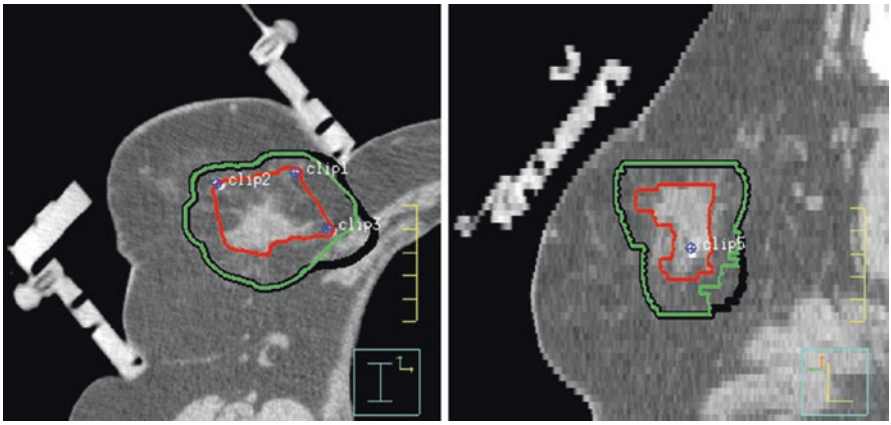

Fig. 16.1 PTV definition on preimplant CT images for multicatheter APBI. Tumor bed, red line; expanded tumor bed, black line; final PTV, green line. The final PTV is defined excluding the pectoral muscle and a 5 mm rim of tissue below the skin

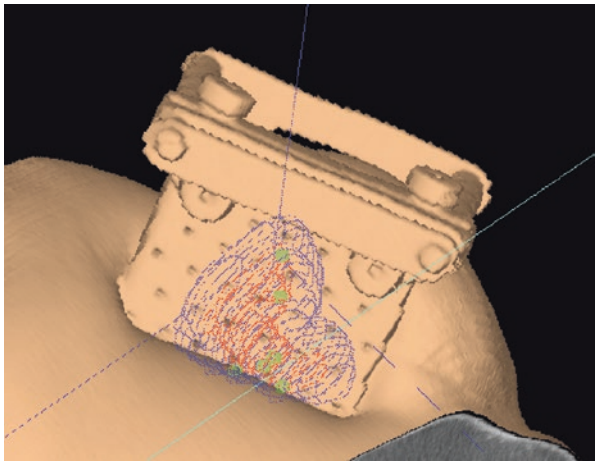

Fig. 16.2 Needle's eye view of the template on the breast. The projections of the excision cavity (red wireframes) with the surgical clips (green dots) and the target volume (blue wireframes) help to identify the holes to be used for inserting needles

volume is projected on the rendered template with the holes (Fig. 16.2). By visual inspection the holes covering the target volumes are identified, and their coordinates are recorded. Then, using the predefined coordinates, the needles are inserted into the breast which are later replaced with plastic catheters. Another (postimplant) CT image set is acquired for planning, and the tumor bed, target volume, and organs at risk are outlined (Fig. 16.3). According to the target definition rules used in the GEC-ESTRO APBI trial, the planning target volume (PTV) is defined as the expansion of the contoured tumor bed (including surgical clips) in each direction with an individual margin of 20 mm minus the actual width of the pathological surgical margin [32]. The expansion of the PTV is limited to 5 mm below the skin and at the pectoral fascia. Finally the catheters are reconstructed and dose planning is performed (Fig. 16.4).

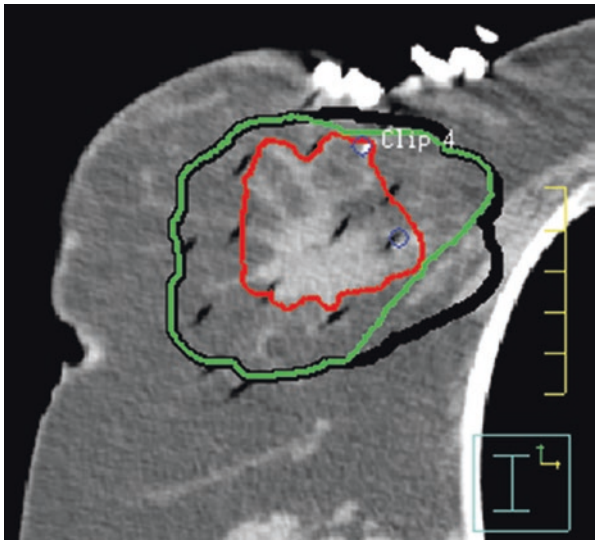

Fig. 16.3 PTV definition on postimplant CT image for multicatheter APBI. Tumor bed, red line; expanded tumor bed, black line; final PTV, green line. The final PTV is defined excluding the pectoral muscle and a 5 mm rim of tissue below the skin

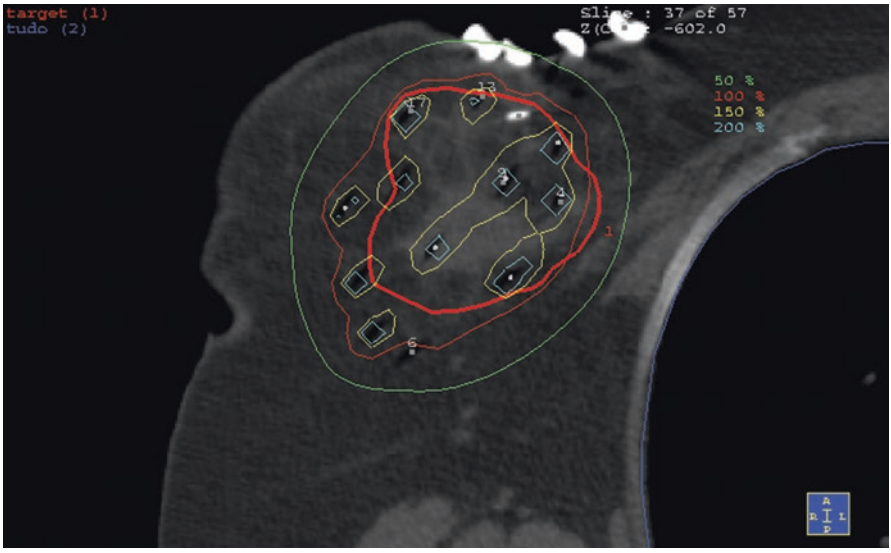

Fig. 16.4 Dose distribution on postimplant CT image. PTV, thick red line; 100% reference isodose, thin red line; 50% isodose, green line; 150% isodose, yellow line; 200% isodose, blue line

A good implant in interstitial BT is characterized by adequate dose coverage, high-dose homogeneity inside, and steep dose falloff outside the target volume. The treatment planning and plan evaluation have to be based on the real 3D volume of the PTV and organs at risk [33]. For the evaluation of dose homogeneity within a breast implant, the dose nonuniformity ratio (DNR = V150/V100) is used [3, 33, 34]. In breast implants, the DNR is expected to be in the range of 0.2–0.35. For a

CT-based plan, after delineation of the target volume and critical organs, target- and organ-related dose volume histograms (DVH) can be calculated, and additional parameters can be defined for plan evaluation [33, 34]. The coverage index (CI) is the fraction of the PTV receiving a dose equal to or greater than the prescribed dose (PD). According to European (GEC-ESTRO) standards, CI should be at least 0.9, which means that at least 90% of the PTV should be covered by the PD. Maximum skin dose should not exceed 70% of the PD to avoid early and late skin side effects.

16.4 Hungarian and European Results

16.4.1 Results of Interstitial Implants as a Boost After WBI

Only a few reports compared the outcome in patients treated with interstitial BT or external beam boost (Table 16.1) [1, 7–9, 12, 17]. In the classical trial of the Institut Curie, women with 3–7 cm breast cancer treated by irradiation alone were randomized to LDR BT versus cobalt-60 teletherapy boost after WBI [1]. The 8-year LR rate was significantly lower with BT compared to external beam boost (24% vs 39%; $p = 0.02$). However, in the postoperative setting, a similar local

Table 16.1 Results of European comparative studies with different boost techniques after whole-breast irradiation with a median FUP ≥ 5 years

Institution/ study	Technique	Patient no.	Boost dose (Gy)	Median FUP (years)	5-year LR % (n)	*p*-value	Exc./ good cosmesis %	*p*-value
Institut Curie, Paris [1]	LDR Cobalt-60	126 129	20–25 11–36	8.1 8.1	24 (8−y)[b] 39 (8−y)[b]	0.02	71 75	0.6
EORTC [7]	LDR ELE Photons	225 1640 753	15 16 16	17.2 17.2 17.2	6.2[a] 9.9[a] 7.8[a]	0.094	NR NR NR	NA
Hôpital Tenon, Paris [12]	LDR ELE	169 161	15–25 5–20	6.7 6.9	8.1 (10−y) 13.5 (10−y)	0.32	61 83	0.001
Budapest [8, 9]	HDR ELE	66 237	8–14.25 16	5 5	8.5 5.6	0.43	90 86	0.29
University Rostock [17]	HDR ELE + photons	75 181	8–12 6–14	7.8 7.8	5.9 (10−y) 12.5 (10−y)	0.023	NR NR	NA

FUP follow-up period, *LR* local recurrence, *LDR* low-dose-rate, *HDR* high-dose-rate, *ELE* electrons, *EORTC* European Organisation for Research and Treatment of Cancer, *NR* not reported, *NA* not applicable

[a]Crude rate

[b]Patients treated with radiotherapy alone

Table 16.2 Results of European HDR brachytherapy boost series with a median FUP ≥ 5 years

Institution	Patient no.	RT scheme (dose [Gy]x fraction no.)	Median FUP (years)	5-years LR %	Annual LR %	Exc./good cosmesis %
Linz [15]	212	10 × 1	5.2	4.6	0.92	78
Barcelona [16]	294	2–2.5 × 8–11	5.8	9 (9-years)	1.00	96
Wien [20]	274	7–12 × 1	8.7	3.9 (10-years)	0.39	38
Valencia [14]	125	4.4 × 3	7	4.2	0.84	77
Brno [18]	215	8–12 × 1	5.8	1.5	0.30	73
Rostock [17]	75	8–12 × 1	7.8	5.9 (10-years)	0.59	NR
Budapest [19]	100	4–4.75 × 3; 6.4 × 2; 8–10.35 × 1	7.8	7 (8-years)	0.87	57
Madrid [35]	210	7 × 1	7.1	5.3 (10-years)	0.53	85
Valencia [13]	167	7 × 1	7.7	4.9 (10-years)	0.49	97
All patients	1672		5.2–8.7	1.5–9	0.30–1.00	38–97

HDR high-dose-rate, *RT* radiotherapy, *FUP* follow-up period, *LR* local recurrence, *NR* not reported

control and cosmetic results have been reported for women boosted either with interstitial implants or electrons/photons [8, 9, 12]. In the EORTC boost trial, the 20-year cumulative incidence of LR was 9.9% for the 1640 patients who received an electron boost, 7.8% in the 753 patients who received a photon boost, and only 6.2% in the 225 patients who had an interstitial LDR BT boost [7]. The difference was not significant ($p = 0.094$); however the trial was not powered to detect the possible difference in local control between different boost modalities. Knauerhase et al. [17] reported that a median dose of 10 Gy HDR BT boost yielded significantly lower 10-year actuarial LR rate compared to external beam boost (5.9% vs 12.5%; $p = 0.023$).

The long-term results of several other European clinical studies proved that HDR BT used either as a single fraction of 7–12 Gy or as a fractionated boost was safe and yielded excellent local control (Table 16.2) [13–16, 18–20, 35].

16.4.2 Results of Interstitial Implants as Sole APBI

16.4.2.1 Early APBI Brachytherapy Trials

Two European centers pioneered the use of different APBI regimens for unselected patients in the 1980s and early 1990s [21–24]. However, results in all of these early studies were poor, with high LR rates (Table 16.3). The high rates of local failure seen in these early APBI studies reflect inadequate patient selection criteria and/or suboptimal treatment technique and lack of appropriate quality assurance (QA) procedures.

Table 16.3 Results of early European interstitial brachytherapy APBI trials with a median FUP ≥5 years

Institution	Dose rate	RT scheme (dose [Gy]x fraction no.)	Median FUP (years)	Crude LR % (*n*)	Annual LR %	Excellent/good cosmesis %
Guy's Hospital I [22, 23]	LDR	55 × 1	6	37 (10 of 27)	6.2	83
Guy's Hospital II [21]	MDR	11 × 4	6.3	18 (9 of 49)	2.9	81
Uzsoki Hospital [24]	MDR	50 × 1	12	24 (17 of 70)	2	50
All patients			6–12	25 (36 of 146)	2–6.2	50–83

APBI accelerated partial breast irradiation, *RT* radiotherapy, *FUP* follow-up period, *LR* local recurrence, *MDR* medium-dose rate, *LDR* low-dose-rate

Uzsoki Hospital's Cobalt-Needle APBI Study

One of the first prospective APBI studies using interstitial implants was conducted in Hungary at the Uzsoki Hospital between 1987 and 1992 [24]. Due to the lack of ^{192}Ir wires in Hungary, special cobalt-60 sources were designed and manufactured to allow manual afterloading of interstitial BT catheters. During this period, 70 patients were treated with these needles following BCS, without use of WBI. Any patient with a pathologic T1 or T2 tumor that was clinically unifocal was eligible. Two to eight (median: 5) catheters with a fixed 4 cm active length were implanted into the tumor bed in a single plane. A dose of 50 Gy was prescribed at 5 mm from the surface of the sources, given in a single session of 10–22 h with 2.3–5.0 Gy per hour. The volume included within the reference isodose surface was quite small (median: 36 cm^3). Twelve-year results of this series showed that the crude LR rate was 24%, with 59% of patients having grade 3 or 4 complications. Unfortunately, at that era most patients did not have preoperative mammographic evaluation, and the vast majority of pathology reports did not contain such important informations as microscopical margin status and the presence of multifocality. Hence, most of the patients treated in this study would not at all be considered eligible for breast-conserving therapy today. Therefore, it is likely that the high rate of LR in this study was due to having persistent (not recurrent!) tumor due to inadequate patient selection criteria and radiological and pathological evaluation, as well as a very small, inadequate implant volume [36]. The high rate of toxicity may have resulted from giving a high total dose (86–134 Gy LDR equivalent dose) of unfractionated medium-dose-rate (MDR) BT. Despite its obvious limitations, the pioneering experience of the Uzsoki Hospital subsequently served as a basis for the development of more successful APBI series at the Hungarian National Institute of Oncology, Budapest, carried out later [19, 26, 27].

Guy's Hospital Studies

Fentiman et al. [21–23] also explored the feasibility and limitations of partial breast BT in two consecutive pilot trials performed at the Guy's Hospital, London, UK. In the first study, conducted in 1987–1988, 27 patients were treated with LDR implants using

rigid needles [22, 23]. The target volume included a 2 cm margin around the tumor bed. The dose prescription was based on the Paris dosimetry system with a dose of 55 Gy given over 5–6 days using manually afterloaded ^{192}Ir wires. With a median follow-up of 6 years, 10 of 27 patients (37%) experienced recurrence in the treated breast [23].

A second Guy's Hospital study enrolled 50 patients between 1990 and 1992 [21]. Patient selection criteria and surgical and implant techniques were similar to the first Guy's Hospital series. A MDR remote-controlled afterloading system employing caesium-137 was used to give a total dose of 45 Gy in 4 fractions over 4 days. At a median follow-up of 6.3 years, 8 of 49 patients (18%) developed a breast relapse.

It is to be noted that the surgical technique and patient selection criteria used in these studies were far from optimal. No attempt was made to achieve a wide excision either grossly or microscopically. As a consequence, the surgical margins were involved in 56% of patients in the first study and in 43% of patients in the second one. Furthermore, in the first study, 41% of patients had tumors containing EIC, and in both studies 44% had positive axillary lymph nodes.

16.4.2.2 Contemporary APBI Brachytherapy Trials

Based on the controversial results of earlier studies, several European groups created APBI trial protocols incorporating more strict patient selection criteria and better implant quality. As a result, the outcomes of these studies have been much improved (Table 16.4) [25–30, 37–40].

Table 16.4 Results of European contemporary interstitial brachytherapy APBI trials with a median FUP of ≥5 years

Institution/study	Dose rate	RT scheme (dose [Gy]x fraction no.)	Median FUP (years)	Crude LR % (*n*)	Annual LR %	Excellent/good cosmesis %
Örebro Medical Centre [25]	PDR	50/0.83[a]	7.2	6.0 (3 of 50)	0.83	56
Hungarian phase II [28, 39]	HDR	4.33 × 7; 5.2 × 7	13.8	11.1 (5 of 45)	0.80	80
German-Austrian phase II [29]	PDR/HDR	50/0.6[a]/4 × 8	5.25	2.9 (8 of 274)	0.55	90
Hungarian phase III [26]	HDR	5.2 × 7	10.2	5.7 (5 of 88)	0.56	85
University Nice-Sophia [38]	HDR	3.4 × 10; 4 × 8	5.1	1.4 (1 of 70)	0.27	96
GEC-ESTRO phase III [30, 40]	PDR/HDR	50/0.6–0.8[a]/4 × 8; 4.3 × 7	6.6	1.4 (9 of 633)	0.21	93
University of Perugia [37]	HDR	4 × 8	8	3.3 (8 of 240)	0.41	96
All patients			5.1–13.8	2.8 (39 of 1400)	0.21–0.83	56–96

APBI accelerated partial breast irradiation, *FUP* follow-up period, *LR* local recurrence, *HDR* high-dose-rate, *PDR* pulsed-dose-rate

[a]Total dose/pulse dose

Hungarian Studies

Between 1996 and 1998, 45 selected patients with early-stage invasive breast cancer were treated with APBI using interstitial HDR implants at the Hungarian National Institute of Oncology, Budapest [27, 28, 39]. Patients were eligible for sole BT if they met all of the following conditions: unifocal tumor, tumor size ≤20 mm (pT1), microscopically clear surgical margins, pathologically negative axillary nodes or only axillary micrometastases (pN1mi), histological grade 1 or 2, and technical suitability for breast implantation. Exclusion criteria were pure DCIS or LCIS (pTis), invasive lobular carcinoma, or the presence of EIC. The planning target volume (PTV) was defined as the excision cavity plus a margin of 1–2 cm. A total dose of 30.3 Gy (n = 8) or 36.4 Gy (n = 37) in 7 fractions over 4 days was delivered to the PTV. The 7-year results (and later the 12- and 15-year update) of this study were reported, including comparison with results of a control group treated during the same time period with conventional WBI [27, 28, 39]. The control group comprised 80 consecutive patients who met the eligibility criteria for APBI but who were treated with 50 Gy WBI with (n = 36) or without (n = 44) 10–16 Gy tumor bed boost. The 12-year actuarial rate of LR was not significantly different between patients treated with APBI (9.3%) and WBI (11.1%). There were no significant differences in either the 12-year probability of disease-free survival (75% and 74%, respectively) or cancer-specific survival (91% and 89%, respectively).

Based on the encouraging results of the first Hungarian study, a randomized study was conducted between 1998 and 2004 at the same institution in Budapest [26]. Initial eligibility criteria were similar to those for the previous study. In addition, the trial allowed patients with breast technically unsuitable for performing interstitial implantation to enroll and be treated with an external beam (EB) approach. By May 2004, 258 eligible patients had been randomized to receive either 50 Gy WBI (n = 130) or partial breast irradiation (PBI, n = 128). The latter consisted of either 36.4 Gy (given over 4 days using 7 fractions of 5.2 Gy) with HDR multicatheter BT (n = 88) or limited-field electron irradiation (n = 40) giving a dose of 50 Gy in 25 fractions. There has been no significant difference in the 10-year actuarial rate of LR (APBI, 5.9%, vs WBI, 5.1%) and disease-free (85% vs 84%), cancer-specific (94% vs 92%), or overall survival (80% vs 82%) between the two treatment arms [26].

Örebro Series

The first APBI study using PDR BT was begun in December 1993 at the Örebro Medical Centre in Sweden [25]. Inclusion criteria included being age 40 years or older with a unifocal breast cancer measuring 5 cm or less without an EIC which was excised with clear inked margins and up to three positive axillary lymph nodes. Freehand plastic tube implants were used to cover the PTV defined as the excision cavity plus 3 cm margins. Fifty patients were treated to a total dose of 50 Gy using pulses of 0.83 Gy delivered over 5 days. At a median follow-up time of 86 months, the 7-year actuarial LR rate was 4%.

German-Austrian Multicentric APBI Trial

In the year 2000, two German and two Austrian institutions decided to start the first European multi-institutional phase II trial to investigate the efficacy and safety of HDR/PDR multicatheter APBI [29]. The four participating centers recruited 274 patients between 2000 and 2005. Patients were eligible for APBI, if they had a tumor diameter ≤3 cm, complete resection with clear margins ≥2 mm, pathologically negative axillary lymph nodes, or singular nodal micrometastasis (pN1mi), hormone receptor-positive tumors, and patient age ≥35 years. Patients were excluded from the protocol if they showed a multicentric invasive growth pattern, poorly differentiated tumors, residual microcalcifications, EIC, or lymph vessel invasion. Among the 274 patients, 175 (64%) received PDR and 99 (36%) HDR BT. Prescribed dose in the PDR BT group was 49.8 Gy in 83 pulses of 0.6 Gy each hour. Prescribed dose for HDR BT was 32 Gy in 8 fractions of 4 Gy, twice daily. The PTV was confined to the tumor bed plus a safety margin of 2–3 cm in each direction. At a median follow-up of 63 months, eight patients (2.9%) had developed ipsilateral breast recurrence, yielding a 5- and 8-year actuarial LR rate of 2.3% and 5.0%, respectively.

University of Perugia Series

Recently, Italian investigators from the University of Perugia reported the long-term results of a phase II prospective study with APBI using multicatheter HDR BT [37]. Inclusion criteria were age ≥40 years, infiltrating carcinoma without lobular histology, DCIS, tumor size ≤2.5 cm, surgical margins ≥2 mm, and negative axillary lymph nodes. Patients having invasive lobular carcinoma, EIC, or lymphovascular invasion were excluded. 240 patients received 32 Gy in 8 fractions of 4 Gy over 4 days. At a median follow-up of 96 months, eight patients (3.3%) developed recurrence in the treated breast. The 5- and 10-year cumulative incidences of LR were 1.8% and 6.6%, respectively.

The GEC-ESTRO Multicentric Randomized APBI Trial

Based on the success of the Hungarian and German-Austrian APBI studies, a multicentric phase III APBI protocol has been developed by the Breast Cancer Working Group of the GEC-ESTRO [30, 40]. Between April 2004 and July 2009, 1184 patients were enrolled at 16 centers from 7 European countries. Patients in the control group were treated with 50 Gy WBI plus 10 Gy electron boost, whereas in the APBI arm, patients were treated with HDR or PDR multicatheter BT. The primary end point of the study was LR as a first event within 5 years. The scientific hypothesis to be assessed and statistically tested was “nonrelevant non-inferiority” of the experimental treatment. Eligibility criteria included unifocal DCIS or invasive carcinoma of the breast, tumor size ≤3 cm, microscopic negative margins of at least 2 mm, no EIC, no lymphovascular invasion, no more than one micrometastasis in axillary lymph nodes (pN1mi), and patient age ≥40 years. The PTV was defined as the excision cavity plus 2 cm margin minus the minimum clear pathological margin. Postimplant CT scans were mandatory for the documentation of target coverage and

dose homogeneity. Median follow-up was 6.6 years. The 5-year cumulative incidence of LR was 1.44% with APBI and 0.92% with WBI ($p = 0.42$) [30]. The difference between treatments was below the relevance margin of 3%. Therefore, APBI using multicatheter BT was proved to be non-inferior to WBI. Late side effects and cosmetic results have been reported recently [40]. Five-year toxicity profiles and cosmetic results were similar in patients treated in the two arms of the study, with significantly fewer grade 2–3 late skin side effects (6.9% versus 10.7%; $p = 0.020$) after APBI with interstitial BT. These findings provided further clinical evidence for the routine use of interstitial multicatheter brachytherapy-based APBI in the treatment of patients with selected breast cancer after BCS.

16.5 Summary and Future Perspectives of Interstitial Breast Brachytherapy

Before the era of breast-conserving therapy, BT implants were used to treat large inoperable breast tumors. Later interstitial BT has been used to deliver an additional dose to the tumor bed after BCS and WBI. Based on the obvious dosimetric advantages of interstitial breast implants (over external beam techniques) supported by the encouraging results of modern boost series utilizing stepping-source afterloading technology, multicatheter HDR/PDR BT remains a standard treatment option for boosting the tumor bed after BCS and WBI.

APBI is an attractive treatment approach with considerable advantages over conventional WBI opening new prospects for interstitial breast BT. Contemporary APBI trials using interstitial BT with strict patient selection criteria resulted in an annual LR rate <1%.

Development of new standards for 3D CT image-based BT treatment planning together with the implementation of inverse dose planning will further improve the conformity of dose distribution delivered by multicatheter implants maximizing the ballistic advantage of interstitial breast BT.

References

1. Forquet A, Campana F, Mosseri V, et al. Iridium-192 versus cobalt-60 boost in 3-7 cm breast cancer treated by irradiation alone: final results of a randomized trial. Radiother Oncol. 1995;34:114–20.
2. Polgar C, Fodor J, Major T, et al. The role of boost irradiation in the conservative treatment of stage I-II breast cancer. Pathol Oncol Res. 2001;7:241–50.
3. Polgár C, Major T. Breast brachytherapy: interstitial breast brachytherapy. In: Montemaggi P, Trombetta L, Brady LW, editors. Brachytherapy: an international perspective. Cham (Switzerland): Springer International Publishing; 2016. p. 145–67.
4. van Limbergen E. Indications and technical aspects of brachytherapy in breast conserving treatment of breast cancer. Cancer Radiother. 2007;7:107–20.
5. Polgar C, Major T. Current status and perspectives of brachytherapy for breast cancer. Int J Clin Oncol. 2009;14:7–24.

6. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347(16):1227–32.
7. Bartelink H, Maingon P, Weltens C, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 2015;16:47–56.
8. Polgar C, Fodor J, Orosz Z, et al. Electron and high dose rate brachytherapy boost in the conservative treatment of stage I-II breast cancer. First results of the randomized Budapest boost trial Strahlenther Onkol. 2002;178:615–23.
9. Polgar C, Fodor J, Orosz Z, et al. Electron and brachytherapy boost in the conservative treatment of stage I-II breast cancer: 5-year results of the randomized Budapest boost trial. Radiother Oncol. 2002;64(Suppl. 1):S15.
10. Romestaing P, Lehingue Y, Carrie C, et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. J Clin Oncol. 1997;15:963–8.
11. Moreno F, Guedea F, Lopez J, et al. External beam irradiation plus ^{192}Ir implant after breast-preserving surgery in women with early breast cancer. Int J Radiat Oncol Biol Phys. 2000;48:757–65.
12. Touboul E, Belkacemi Y, Lefranc JP, et al. Early breast cancer: influence of type of boost (electron vs iridium-192 implant) on local control and cosmesis after conservative surgery and radiation therapy. Radiother Oncol. 1995;34:105–13.
13. Guinot JL, Baixauli-Perez C, Soler P, et al. High-dose-rate brachytherapy boost effect on local tumor control in young women with breast cancer. Int J Radiat Oncol Biol Phys. 2015;91:165–71.
14. Guinot JL, Roldan S, Maronas M, et al. Breast-conservative surgery with close or positive margins: can the breast be preserved with high-dose-rate brachytherapy boost? Int J Radiat Oncol Biol Phys. 2007;68:1381–7.
15. Hammer J, Seewald DH, Track C, et al. Breast cancer: primary treatment with external-beam radiation therapy and high-dose-rate iridium implantation. Radiology. 1994;193:573–7.
16. Henriquez I, Guix B, Tello JI, et al. Long term results of high-dose-rate (HDR) brachytherapy boost in preserving-breast cancer patients: the experience of radiation oncology medical institute (IMOR) of Barcelona. Radiother Oncol. 2001;60(Suppl. 1):S11.
17. Knauerhase H, Strietzel M, Gerber B, et al. Tumor location, interval between surgery and radiotherapy, and bosst technique influence local control after breast-conserving surgery and radiation: retrospective analysis of monoinstitutional long-term results. Int J Radiat Oncol Biol Phys. 2008;72:1048–55.
18. Neumanova R, Petera J, Frgala T, et al. Long-term outcome with interstitial brachytherapy boost in the treatment of women with early-stage breast cancer. Neoplasma. 2008;54:413–23.
19. Polgar C, Jánváry L, Major T, et al. The role of high-dose-rate brachytherapy boost in breast-conserving therapy: long-term results of the Hungarian National Institute of oncology. Rep Pract Oncol Radiother. 2010;15:1–7.
20. Resch A, Pötter R, van Limbergen E, et al. Long-term results (10 years) of intensive breast conserving therapy including a high-dose and large-volume interstitial brachytherapy boost (LDR/HDR) for T1/T2 breast cancer. Radiother Oncol. 2002;63:47–58.
21. Fentiman IS, Deshmane V, Tong D, et al. Caesium^{137} implant as sole radiation therapy for operable breast cancer: a phase II trial. Radiother Oncol. 2004;71:281–5.
22. Fentiman IS, Poole C, Tong PJ, et al. Iridium implant treatment without external radiotherapy for operable breast ancer: a pilot study. Eur J Cancer. 1991;27:447–50.
23. Fentiman IS, Poole C, Tong D, et al. Inadequacy of iridium implant as a sole radiation treatment for operable breast cancer. Eur J Cancer. 1996;32A:608–11.
24. Póti Z, Nemeskéri C, Fekésházi A, et al. Partial breast irradiation with interstitial ^{60}Co brachytherapy results in frequent grade 3 or 4 toxicity. Evidence based on a 12-year follow-up of 70 patients. Int J Radiat Oncol Biol Phys. 2004;58:1022–33.

25. Johansson B, Karlsson L, Liljegren G, et al. Pulsed dose rate brachytherapy as the sole adjuvant radiotherapy after breast-conserving surgery of T1-T2 breast cancer: first long time results from a clinical study. Radiother Oncol. 2009;90:30–5.
26. Polgar C, Fodor J, Major T, et al. Breast-conserving therapy with partial or whole breast irradiation: ten-year results of the Budapest randomized trial. Radiother Oncol. 2013;108:197–202.
27. Polgar C, Major T, Fodor J, et al. HDR brachytherapy alone versus whole breast radiotherapy with or without tumor bed boost after breast conserving surgery: seven-year results of a comparative study. Int J Radiat Oncol Biol Phys. 2004;60:1173–81.
28. Polgar C, Major T, Fodor J, et al. Accelerated partial breast irradiation using high-dose-rate interstitial brachytherapy: 12-year update of a prospective clinical study. Radiother Oncol. 2010;94:274–9.
29. Strnad V, Hildebrandt G, Pötter R, et al. Accelerated partial breast irradiation: 5-year results of the German-Austrian multicenter phase II trial using interstitial multicatheter brachytherapy alone after breast-conserving surgery. Int J Radiat Oncol Biol Phys. 2011;80:17–24.
30. Strnad V, Ott OJ, Hildebrandt G, et al. Accelerated partial breast irradiation (APBI) using sole interstitial multicatheter brachytherapy versus whole breast irradiation with boost after breast conserving surgery for low risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised phase 3 non-inferiority trial. Lancet. 2016;387:229–38.
31. Polgar C, van Limbergen E, Pötter R, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Européen de Curiethérapie – European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast Cancer working group based on clinical evidence (2009). Radiother Oncol. 2010;94:264–73.
32. Major T, Gutiérrez C, Guix B, et al. Recommendations from GEC ESTRO breast Cancer working group (II): target definition and target delineation for accelerated or boost partial breast irradiation using multicatheter interstitial brachytherapy after breast conserving open cavity surgery. Radiother Oncol. 2016;118:199–204.
33. Major T, Polgar C. Treatment planning for multicatheter interstitial brachytherapy of breast cancer - from Paris system to anatomy-based inverse planning. J Contemp Brachytherapy. 2017;9:89–98.
34. Major T, Polgar C, Lövey K, et al. Dosimetric characteristics of accelerated partial breast irradiation with CT image-based multicatheter interstitial brachytherapy: a single institution's experience. Brachytherapy. 2011;10:421–6.
35. Rodríguez Pérez A, Samper Ots PM, López Carrizosa MC, et al. Early-stage breast cancer conservative treatment: high-dose-rate brachytherapy boost in a single fraction of 700 cGy to the tumour bed. Clin Transl Oncol. 2012;14:362–8.
36. Polgar C, Major T, Strnad V, et al. What can we conclude from the results of an out-of-date breast brachytherapy study? In regard to Póti Z, Nemeskéri C, Fekeshazy a, et al. (Int J Radiat Oncol biol Phys 2004;58:1022-1033). Int J Radiat Oncol Biol Phys. 2004;60:342–3.
37. Aristei C, Maranzano E, Lancelotta V, et al. Partial breast irradiation with interstitial multicatheter high-dose-rate brachytherapy. Long-term results of a phase II prospective study. Radiother Oncol. 2017;124:208–13.
38. Genebes C, Chand ME, Gal J, et al. Accelerated partial breast irradiation in the elderly: 5-year results of high-dose rate multi-catheter brachytherapy. Radiat Oncol. 2014;9:115.
39. Polgar C, Major T, Fodor J, et al. Accelerated partial breast irradiation with multicatheter brachytherapy: 15-year results of a phase II clinical trial. Acta Medica Marisiensis. 2011;57:717–20.
40. Polgar C, Ott OJ, Hildebrandt G, et al. Late side-effects and cosmetic results of accelerated partial breast irradiation using interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, phase 3 trial. Lancet Oncol. 2017;18:259–68.

Part V

Head and Neck

Low-Dose-Rate Brachytherapy for Oral Cancer

17

Ryoichi Yoshimura

Abstract

Patients with T1–2 stage oral cancer or a positive surgical margin without lymph node or distant metastases are eligible for low-dose-rate interstitial brachytherapy (LDR-BT), and iridium-192 hairpins and single pins for tongue cancer and Au-198 grains for oral cancer are presently the most commonly used sources of radioactivity. Their sources are implanted according to the Paterson and Parker method or the Paris method, and a computer dose calculation using X-ray films is obtained after implantation. The prescription dose to PTV is 60–70 Gy over 5–7 days with iridium-192 hairpins and single pins and 80–90 Gy permanently with Au-198 grains. The 5-year survival rate for patients with oral cancer and treated by LDR-BT can be over 70%.

Keywords

Oral cancer · Tongue cancer · Low-dose-rate interstitial brachytherapy Iridium-192 · Au-198 · Paterson and Parker method · Paris method

17.1 Introduction

Low-dose-rate interstitial brachytherapy (LDR-BT) was introduced in the early 1900s. Regarding oral cancer, many treatment results have been reported from both Japan and around the world, and these results were comparable to surgery [1–3] and showed that a high quality of life (QOL) could be maintained [4]. However, because of the potential for medical staff to be exposed to radiation, the need for shielded

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rooms, and the insufficient supply of radioactive sources, the numbers of LDR-BT treatment facilities and oral cancer patients receiving LDR-BT are decreasing.

Reportedly, more than 360,000 patients were diagnosed as having oral cancer worldwide in 2012 [5]. LDR-BT should be continued as long as there are oral cancer patients who do not wish to undergo resection.

17.2 Treatment Policy

17.2.1 Eligibility

Patients with T1–2 stage oral cancer or a positive surgical margin without lymph node or distant metastases are eligible for LDR-BT.

A physical advantage of LDR-BT is its ability to irradiate the target with a high dose while reducing the dose to neighboring normal tissues, whereas a biological advantage of LDR-BT is its ability to allow effective reoxygenation and redistribution during irradiation. Therefore, LDR-BT can be performed in cases experiencing recurrences after surgery or who have a prior history of external-beam radiotherapy (EBRT) to the head and neck region, with a low incidence of complications [6, 7]. However, when the thickness of the cancer is greater than 10 mm, the risk of recurrence is three times higher than that in cases with a cancer thickness of less than 5 mm [8].

17.2.2 LDR Sources

Iridium-192 hairpins and single pins and Au-198 grains are presently the most commonly used sources of radioactivity (Fig. 17.1). Iridium-192 hairpins and single pins are used for tongue cancer and are implanted temporarily. During the treatment, the patient must remain within a shielded room, and a nasal feeding tube and analgesics are necessary. Au-198 grains are implanted permanently in patients with oral cancer excluding tongue cancer or in patients with tongue cancer and an advanced age, severe comorbidities, or a poor performance status. Patients with implanted Au-198 grains can eat and speak immediately after the implantation but, in Japan, must remain within a shielded room until the residual radioactivity in the body decays to 700 MBq.

17.3 Treatment Technique

17.3.1 Treatment Plan

The gross tumor volume (GTV) is evaluated by visual inspection, tumor palpation, and sometimes MRI. The clinical target volume (CTV) is the GTV plus a 5-mm margin for expected cancer invasion. The planning target volume (PTV) is equal to the CTV.

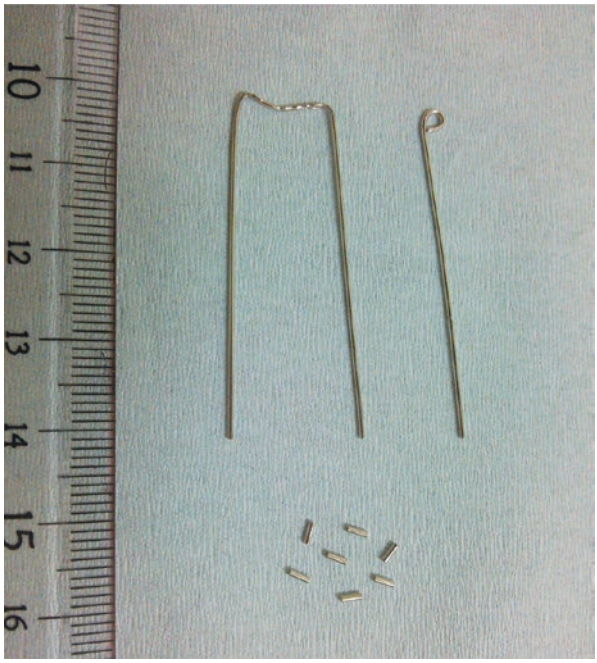

Fig. 17.1 Ir-198 hairpin, single pin, and Au-198 grains

17.3.2 Source Arrangement and Dose Prescription

Ir-192 hairpins and single pins are usually arranged in a single plane according to the Paterson and Parker method or the Paris method. When they are implanted according to the Paterson and Parker method, the distance between pins should be 8 mm so as to avoid areas with a low irradiation dose, and the prescribed dose is 60–70 Gy over 5–7 days within a plane of 5 mm from the sources. When the pins are implanted according to the Paris method, an Ir-192 hairpin is calculated as two linear sources with a length of 46.5 mm, and a single pin is calculated as a linear source with a length of 47.6 mm. The prescribed dose is 60–70 Gy over 5–7 days as a minimum target dose.

Au-198 grains are usually arranged in a single plane according to the Paterson and Parker method, and they are implanted at a depth of 5 mm from the mucosal surface with a distance of 10 mm between grains. The prescribed dose is 80–90 Gy permanently within a plane of 5 mm from the sources.

17.3.3 Implantation

The patient is asked to sit on the treatment seat, and markers showing the implantation site are inked onto the mucosa. The patient is given a local anesthetic, and in cases where Ir-192 hairpins or single pins are being used, guide needles are implanted according to the marks, and their arrangement is checked using X-ray

imaging. The Ir-192 hairpins and single pins are then implanted through the guide needles, and the guide needles are removed. The Ir-192 hairpins and single pins are secured in place on the tongue using stitches, and a spacer is placed so as to ensure an appropriate distance between the radioactive source and the mandibular bone.

For cases treated with Au-198 grains, the grains are inserted using special insertion needles under local anesthesia. A spacer is used for patients with tongue cancer.

17.3.4 Dose Evaluation

After implantation, a computer dose calculation using X-ray films obtained from an anterior-posterior view and a lateral view is performed. In cases using Ir-192 hairpins and single pins, the period of implantation is calculated and set so that the irradiation dose within the PTV reaches the prescription dose, but the high-dose area (usually 200% of the prescription dose) does not spread beyond the area surrounding the pins (Fig. 17.2). For cases treated with Au-198 grains, the number of implanted grains is confirmed, and the dose distribution is calculated using X-ray films (Fig. 17.3).

17.4 Follow-Up

Patients who have undergone LDR-BT should receive follow-up examinations from both a radiation oncologist and an oral surgeon. The patient should be seen every 2 weeks as long as mucositis is present and then every month thereafter until 1 year after implantation, every 2 or 3 months until 2 years after implantation, and every 3–6 months until 5 years after implantation. Most recurrences and/or lymph node metastases are found within 2 years after brachytherapy [9].

17.5 Treatment Results

The 5-year survival rate of T1N0 tongue cancer patients after LDR-BT is reported to be around 83%, while that of T2 N0 tongue cancer patients is 70%–80% [1–3]. The incidence of cervical lymph node metastasis is reported to be 25%–30% for T1 N0 patients and 27%–50% for T2N0 patients [1–3].

The recurrence rates of T1-2N0M0 cancer of the buccal mucosa, floor of the mouth, and the palate and gingiva are reported to be 13% [10], 20% [11], and 26% [12], respectively.

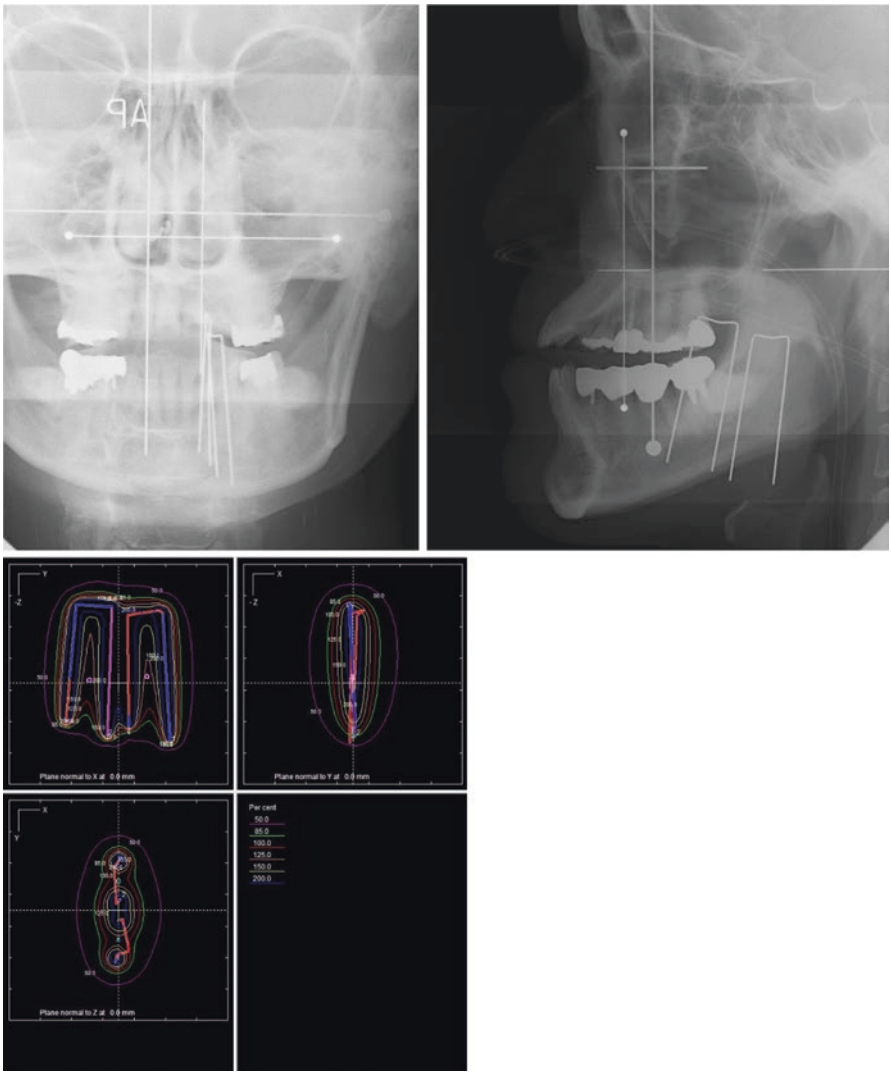

Fig. 17.2 Anterior-posterior view and lateral view after implantation of Ir-192 hairpins for tongue cancer and dose distribution

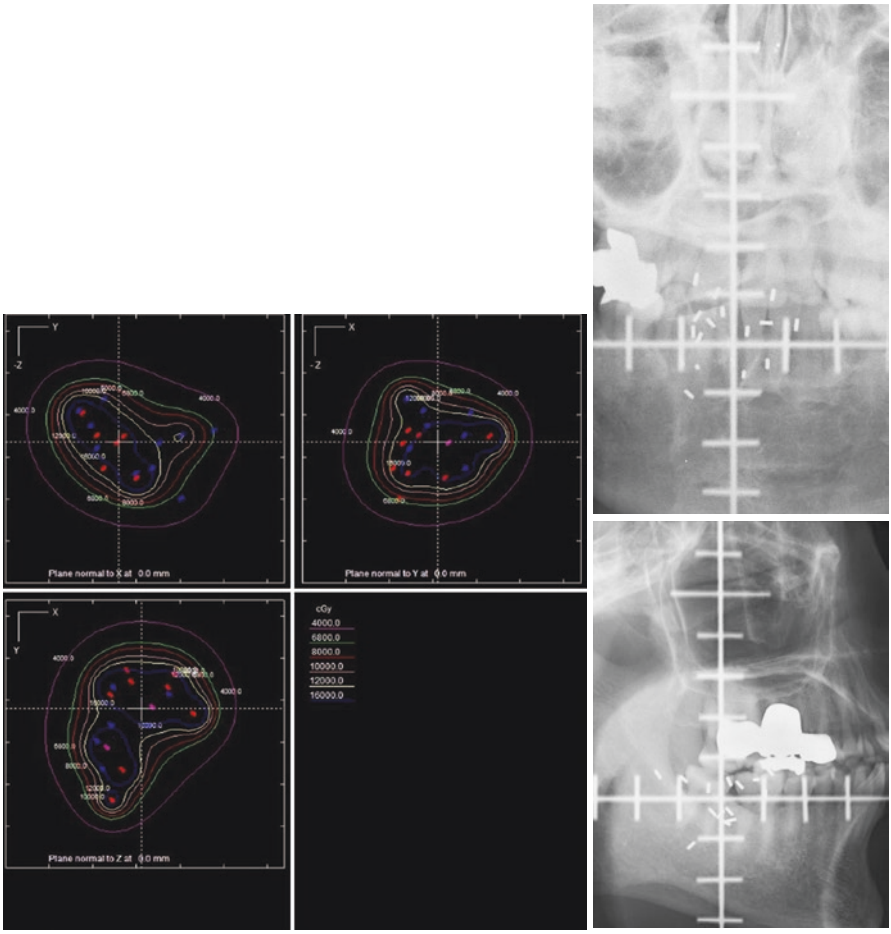

Fig. 17.3 Anterior-posterior view and lateral view after implantation of Au-198 grains for tongue cancer and dose distribution

17.6 Complications

Mucositis within and around the treatment area occurs on the oral mucosa in all patients but disappears within 2–3 months. Oral ulcers or mandibular bone necrosis reportedly occur in 6%–10% of tongue cancer patients [1, 2], but the occurrence of oral ulcers can be prevented by abstaining from smoking, drinking alcohol, and eating foods that cause irritation. The incidence of mandibular bone necrosis can be reduced by using a spacer [13].

17.7 Future Outlook

Recently, high-resolution MRI and PET images, etc. have become available. LDR-BT has become somewhat old-fashioned, as it is performed based on visual inspection and tumor palpation. The fusion of old techniques and new imaging modalities should improve local control. Moreover, combined therapy with chemotherapy and/or limited surgery might improve the survival rate while maintaining a high QOL.

References

1. Shibuya H, Hoshina M, Takeda M, et al. Brachytherapy for stage I & II oral tongue cancer: an analysis of past cases focusing on control and complications. Int J Radiat Oncol Biol Phys. 1993;26:51–8.
2. Fujita M, Hirokawa Y, Kashiwado K, et al. Interstitial brachytherapy for stage I and II squamous cell carcinoma of the oral tongue: factors influencing local control and soft tissue complications. Int J Radiat Oncol Biol Phys. 1999;44:767–75.
3. Inoue T, Inoue T, Yoshida K, et al. Phase III trial of high- vs. low-dose-rate interstitial radiotherapy for early mobile tongue cancer. Int J Radiat Oncol Biol Phys. 2001;51:171–5.
4. Yoshimura R, Shibuya H, Miura M, et al. Quality of life of oral cancer patients after low-dose-rate interstitial brachytherapy. Int J Radiat Oncol Biol Phys. 2009;73:772–8.
5. Ghantous Y, Abu EI. Global incidence and risk factors of oral cancer. Harefuah. 2017;156:645–9.
6. Ayukawa F, Shibuya H, Yoshimura R, et al. Curative brachytherapy for recurrent/residual tongue cancer. Strahlenther Onkol. 2006;3:133–7.
7. Yoshimura R, Shibuya H, Hayashi K, et al. Repeat brachytherapy for patients with residual or recurrent tumors of oral cavity. Int J Radiat Oncol Biol Phys. 2012;83:1198–204.
8. Oota S, Shibuya H, Yoshimura R, et al. Brachytherapy of stage II mobile tongue carcinoma. Prediction of local control and QOL. Radiat Oncol. 2006;21:1–8.
9. Shibuya H, Yoshimura R, Oota S, et al. Brachytherapy has been providing us a chance to conserve the form and function of the mobile tongue. Jap J Clin Radiol. 2002;47:741–9.
10. Shibuya H, Takeda M, Matsumoto S, et al. Brachytherapy for non-metastatic squamous cell carcinoma of the buccal mucosa. Acta Oncol. 1993;32:327–30.
11. Matsumoto S, Takeda M, Shibuya H, et al. T1 and T2 squamous cell carcinoma of the floor of the mouth: results of brachytherapy mainly using au-198 grains. Int J Radiat Oncol Biol Phys. 1996;34:833–41.
12. Takeda M, Shibuya H, Inoue T. The efficacy of gold-198 grains mold therapy for mucosal carcinomas of the oral cavity. Acta Oncol. 1996;35:463–7.
13. Miura M, Takeda M, Sasaki T, et al. Factors affecting mandibular complications in low dose rate brachytherapy for oral tongue carcinoma with special reference to spacer. Int J Radiat Oncol Biol Phys. 1998;41:763–70.

High-Dose-Rate Brachytherapy for Oral Cancer

18

Naoya Kakimoto

Abstract

The application of high-dose-rate (HDR) interstitial brachytherapy (ISBT) has expanded to many areas such as the treatment of cervical cancer, endometrial cancer, vaginal cancer, prostate cancer, and breast cancer. Likewise, HDR-ISBT is also regularly used to treat oral cavity cancers, as it offers high local control rates and low toxicity. Advantages of HDR-ISBT to treat oral cancers include (1) accurate dose calculations which are made possible by complete fixation of the flexible treatment catheters, (2) parallel source arrangement through a linked double-button technique or custom-made vinyl template technique, (3) homogeneous dose distribution by stepping-source optimization through computer simulations, (4) the absence of direct radiation exposure to the medical staff, and (5) better patient care using ordinary hospital wards. Three-dimensional image-guided HDR-ISBT has laid the groundwork for forming a stepping-source technology which offers the advantage of optimizing dose distribution by varying dwell times. Additionally, this technique allows for real dose optimization guidance to elicit homogeneous dose distribution to a planning target volume, thereby reducing dose spillover to the organ at risk. The current chapter will elucidate some of the (1) benefits of HDR-ISBT, (2) treatment methods, (3) results of the definitive treatment of HDR-ISBT for oral cancer patients, (4) a mold technique, and (v) a CT-compatible modular spacer with lead shield. In conclusion, HDR-ISBT is an important treatment option when dealing with oral cancer.

Keywords

High-dose-rate · Interstitial brachytherapy · Oral cancer · Tongue cancer Definitive treatment

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18.1 Introduction

Radiation therapy plays an important role in the treatment of the head and neck cancers as it provides high locoregional tumor control as well as significant preservation of organ functions. Low-dose-rate (LDR) and high-dose-rate (HDR) interstitial brachytherapy (ISBT) have historically been used to treat oral cavity cancers and offer high local control rates and low toxicity [1–3]. ISBT is an effective technique used in definitive, postoperative, recurrent, and salvage settings [4], and it offers an important way to apply an intense and localized radiation dose within the confines of a short treatment time, thereby minimizing unwanted exposure to normal tissue due to the rapid dose falloff around the source [5]. LDR-ISBT is being increasingly replaced by HDR-ISBT, as the stepping-source technology offers the advantage of optimizing the dose distribution by varying the dwell times. Importantly, HDR-ISBT for oral cancer appears to yield local control and complication rates equivalent to those of LDR-ISBT [1, 6–8]. One meta-analysis also showed that HDR-ISBT constituted a valid alternative to LDR-ISBT to treat early-stage oral cancers [9]. Consequently, this chapter aims to point out (1) the benefits, (2) treatment methods, (3) results of the definitive treatment of HDR-ISBT for oral cancer patients, (4) a mold technique, and (5) a CT-compatible modular spacer with lead shield to be used in HDR-ISBT.

18.2 Advantages of HDR-ISBT Within the Treatment of Oral Cancers (as Compared to LDR-ISBT)

Mobile tongue cancer is highly curable with radiation therapy, especially when employing ISBT. Many institutions have reported successful results when using LDR-ISBT [10–14]. However, there are also some shortcomings to LDR-ISBT, such as the unwanted radiation exposure to the medical staff and the absence of any dose optimization regimen. To solve these problems, several institutions adopted HDR-ISBT using a remote afterloading system for oral cancer patients. There are some advantages of HDR-ISBT, such as the absence of radiation exposure to the medical staff, and HDR-ISBT makes it possible to treat patients in an ordinary hospital where more optimal patient care can be provided.

Some other advantages of HDR-ISBT include (1) a more accurate dose calculation enabled by a complete fixation of the flexible treatment tubes, (2) an optimized parallel source arrangement by a linked double-button technique or custom-made vinyl template technique, and (3) a homogeneous dose distribution by stepping-source optimization using computer simulations [2].

Additionally, though it is relatively uncommon, in Japan, occasionally, there is a shortage of radioactive sources to be used in LDR-ISBT (as this depends on import from other countries). On the other hand, the radioactive sources being used in HDR-ISBT therapies are usually readily available without any problems, as HDR-ISBT has become widely accepted in treating many types of cancer [15].

18.3 Treatment Procedure and Planning at Osaka University Hospital

Catheter reconstruction is a very important step in the planning process of HDR-ISBT to treat oral cancers. In this section, the flexible tube implants to treat tongue cancer are shown in Fig. 18.1. This procedure takes place under local anesthesia in most cases, typically using a submandibular approach. First, an

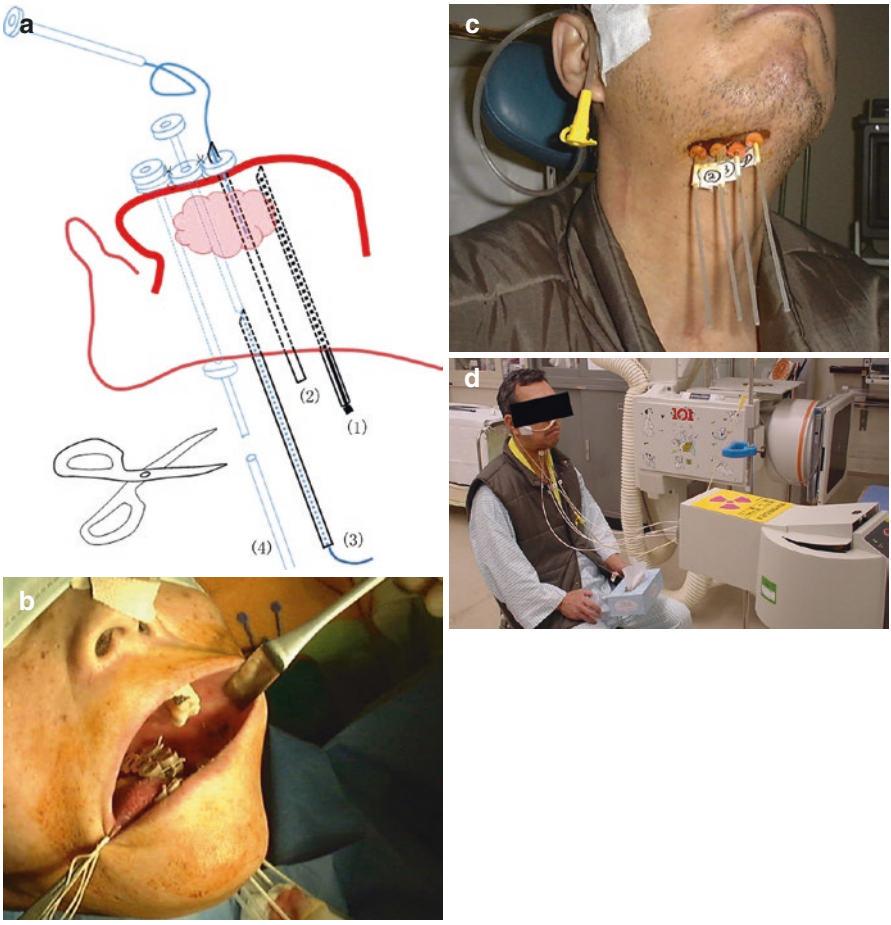

Fig. 18.1 Flexible plastic treatment applicator reconstruction. (**a**) Schematic depicting the linked double bottom technique to treat mobile tongue cancer (*1*). An open-end metal needle is implanted in the submandibular region (*2*) (*3*). Flexible plastic treatment applicator is replaced on the needle (*4*). Flexible plastic treatment applicators are cut in the place having identical length. (**b**) Flexible plastic tubes implanted in the right lateral border of the tongue. (**c**) The submandibular area with flexible plastic tubes attached. (**d**) Flexible plastic tubes were connected to the microSelectron HDR®

open-end metal needle is implanted in the submandibular region. Then, a linked double-button or custom-made vinyl template with double button on the tongue surface is used to determine the correct needle exit points. After the needles penetrated the surface of the tongue, flexible plastic treatment applicators are placed on the needle. These steps are repeated depending on the tumor size while keeping a parallel trajectory leaving 10 mm of space between needles. Next, an additional button is inserted in each flexible plastic tube to fix it to the submandibular skin. Then, flexible plastic treatment applicators are cut in the place each having an equal length to ensure adequate connection to the radioactive source dispenser. Double buttons are applied ensuring proper coverage of the prescribed dose to the dorsal surface of the tongue. Flexible plastic tubes are implanted on the edge of tumor, which are evaluated using palpation and MRI the day before treatment commences.

Before 2010, in Osaka University Hospital, dose-distribution curves and dose-volume histograms (DVH) were created using a conventional 2D planning method. Using this method, the reference point was set at 5 mm from the applicator position in the central plane of the clinical target volume (CTV). Computer simulations were performed using geometrical optimization of volume without any modifications. The prescribed dose was delivered to the reference point, and a DVH was established. However, from 2011, a CT-based 3D treatment planning system was installed in Osaka University Hospital (Fig. 18.2). This addition allowed us to perform 3D image-guided HDR-ISBT to better treat mobile tongue cancer using image-guided brachytherapy (IGBT). CT images were taken from patients with or without contrast media just after implantation to more precisely establish the gross tumor volume (GTV) contours. MR images which were taken just 1 day before implantation were used as a reference GTV contour. We defined the GTV, CTV, and a planning target volume (PTV) to be equivalent. The PTV delivered prescribed radiation doses up to 100% of the reference dose at first. However, after that, the isodose curves were modified manually to adequately cover the PTV through following the isodose line of the prescribed dose without imposing excessive doses to the organ at risk (OAR; i.e., the mandibular bone in most cases) as well as to avoid a large hyperdose sleeve. This 3D IGBT forms the stepping-source technology which offers the advantage of optimizing the dose distribution by varying the dwell times. Additionally, it is possible to guide the real dose optimization to establish a homogeneous dose distribution to the PTV as well as a dose reduction to OAR. Yoshida et al. reported the effectiveness of 3D IGBT in the treatment of mobile tongue cancer [16]. Additionally, to prevent any additional complications from radiotherapy, we devised a “modular spacer” in our lab. At the CT planning stage, we inserted this spacer (without lead to prevent metallic artifacts) while taking the CT scans. However, after CT planning, a lead shield was inserted, and the spacer was sealed. The specifics of this spacer and its valuable role in HDR-ISBT will be introduced later in this chapter.

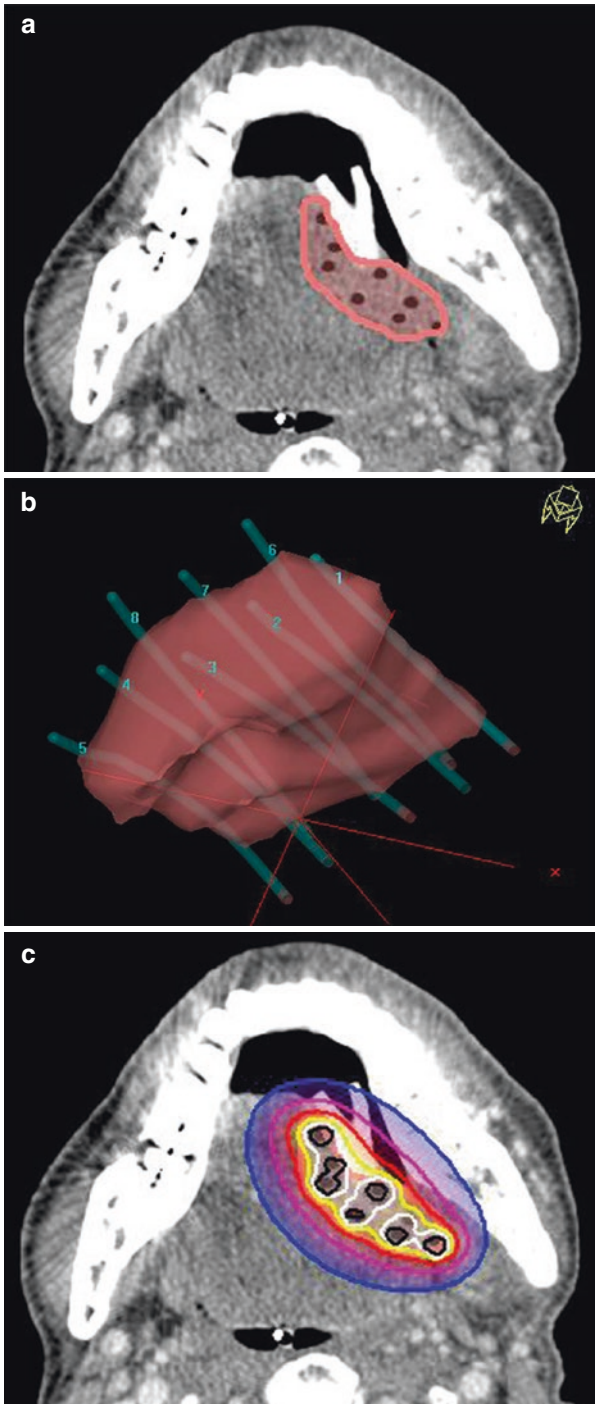

Fig. 18.2 Image-guided interstitial brachytherapy to treat tongue cancer. (**a**) Planning target volume (PTV) as shown on a CT image. (**b**) PTV and flexible plastic tubes are shown on 3D image. (**c**) Dose-distribution curves on axial CT image. The red line shows the 100% (6Gy/fraction) isodose curve

18.4 Treatment Dose and Schedule for Tongue Cancer

Occasionally, low local control rates when using HDR-ISBT in the treatment of tongue cancer are obtained. Lau et al. reported a 53% of the local control rate when using 45.5 Gy/7 fractions, based upon data of the linear-quadratic model [17]. This dose is lower than the typical treatment dose used at our hospital. We typically employ a 60 Gy/10 fractions/6–8-day dose, based on the data of a phase I/II study [18]. Our dose schedule when applying HDR-ISBT in a phase I/II study ranged from 35 Gy/10 fractions (bid)/week to 60 Gy/10 fractions/week [18]. Within this schedule no severe early complications were observed. Typically, spotted mucositis appeared starting 3 days after the end of HDR-ISBT, while confluent mucositis developed and approached its peak at around 10 days but gradually disappeared between the 4th and 8th week. Early mucosal reactions treated by using 60 Gy of HDR-ISBT were comparable to those observed when using 70 Gy of LDR-ISBT. This fits well with a phase III trial reported in the literature which was performed to compare the results and complications of 70 Gy of LDR-ISBT in the treatment of early tongue cancer with those of 60 Gy of HDR-ISBT [1, 6]. Additionally, this study reported no statistically significant differences between LDR-ISBT and HDR-ISBT concerning local control ratio, cause-specific survival ratio, and complications such as ulcer or mandibular bone exposure. Therefore, a prescribed radiation dose of 60 Gy in HDR-ISBT seems to be suitable to preserve local control and to avoid unnecessary complications.

For HDR-ISBT treatment, the aforementioned phase III trial study implemented a dose fractionation schedule of 60 Gy in 10 fractions over approximately 8 days at a distance of 5 mm from the radioactive source and achieved respectable treatment results, which were comparable to those of LDR-ISBT [1, 6]. However, it is still controversial, in terms of efficacy and safety, whether HDR-ISBT can actually replace LDR-ISBT in the treatment of oral cancer patients. The potential radiobiological disadvantage of HDR-ISBT can be compensated by using a twice-a-day fractionation schedule. With HDR-ISBT, a smaller dose per fraction may reduce tissue injury, but a higher number of fractions are required for the treatment. The Groupe Européen de Curiethérapie and the European Society for Radiotherapy and Oncology (ESTRO) recommend using a fraction dose of <3–4 Gy [19], and the American Brachytherapy Society (ABS) recommended around ≦6 Gy per fraction [20]. Some trials reported a modest local control rate when treating early tongue cancer with HDR-ISBT [17, 21]. However, HDR-ISBT is more technically demanding, and it is unknown whether this divergence may have been caused by technical issues, such as the precise delineation of GTV, usage of treatment planning software, remote afterloading devices, and the quality of radioactive sources. It seems safe to advise that HDR-ISBT should be applied with the support of well-informed technical staff and should preferably be administered by someone who has large amount of experience using HDR-ISBT to treat oral cancer patients.

Nevertheless, HDR-ISBT is an invasive and uncomfortable method and may pose a risk to patients, as maintaining applicators in the oral to submandibular region for a prolonged period may cause significant irritation and a risk of sputum

aspiration [22]. Therefore, alternative treatment schedules may be considered to reduce the dose amount and treatment period without compromising treatment outcomes. For example, it has been shown that applying 54 Gy in 9 fractions showed very similar outcomes compared to administering 60 Gy in 10 fractions [22, 23].

HDR-ISBT is always performed through hyperfractionation, for example, by administering two fractions per day with a time interval between fractions greater than 6 h. According to one paper, a non-irradiation day, such as a weekend or hospital holidays, can even be embedded in a 54–60 Gy/9–10 fractions regimen without affecting the treatment results. Therefore, overall treatment time can take place in a timespan of roughly 5–9 days containing 54–60 Gy/9–10 fractions of HDR-ISBT. However, it was reported that the overall treatment time from 5 days to 9 days of 54–60 Gy/9–10 fractions HDR-ISBT for early mobile tongue cancer did not significantly affect treatment results [24].

18.5 Definitive HDR-ISBT Treatment Results for Mobile Tongue Cancer

HDR-ISBT is used as a monotherapy or in conjunction with external beam radiotherapy (EBRT) for the treatment of mobile tongue cancer. For the smaller-sized tongue cancers such as the T1 or T2 categories using TNM classification, HDR-ISBT is mainly used as monotherapy (Fig. 18.3), but the combination therapy of HDR-ISBT with EBRT is used in larger or thicker tumor such as in the T3 or T4 categories (Fig. 18.4). In Table 18.1, the dose, the fractionation schedule, and the treatment results for HDR-ISBT as a monotherapy to treat mobile tongue cancer are outlined. The local control rates were shown to range from 53 to 100% [1, 2, 7, 17, 21–23, 25–27]. Looking at the early data, which were reported before 2000, the local control rates of HDR-ISBT were not particularly high; however, over the course of time, they are improving gradually except for Bansal's report [27]. This suggests that, indeed, when applying HDR-ISBT, a large amount of clinical experience is beneficial when treating oral cancer patients. With respect to T1 or T2 tongue cancer, six out of eight studies displayed a local control rate of over 80%, and two of them showed more than 90%. Concerning the T3 tongue cancer, both Lau et al. and Akiyama et al. reported that local control was achieved in all of their patients [17, 22]. Additionally, Kakimoto et al. reported a 71% local control rate (3 years) in 14 T3 tongue cancer patients treated with HDR-ISBT [24]. When using HDR-ISBT, there is no limit to the dose prescription for the superior-and-inferior directions as flexible tubes are applied using a submandibular approach. Therefore, it is possible for HDR-ISBT to treat an advanced and large tongue cancer such as a T3 cancer.

One particularly troubling problem when treating oral cancer is to maintain adequate nodal control (i.e., restrain lymph node metastasis). It has been reported that the 5-year nodal control rate of HDR-ISBT for early tongue cancer was 76% or 67% [1, 2]. Generally speaking, occult metastasis for regional lymph nodes occurs in about 30–40% in N0 tongue cancer patients. Although, clearly, regional control

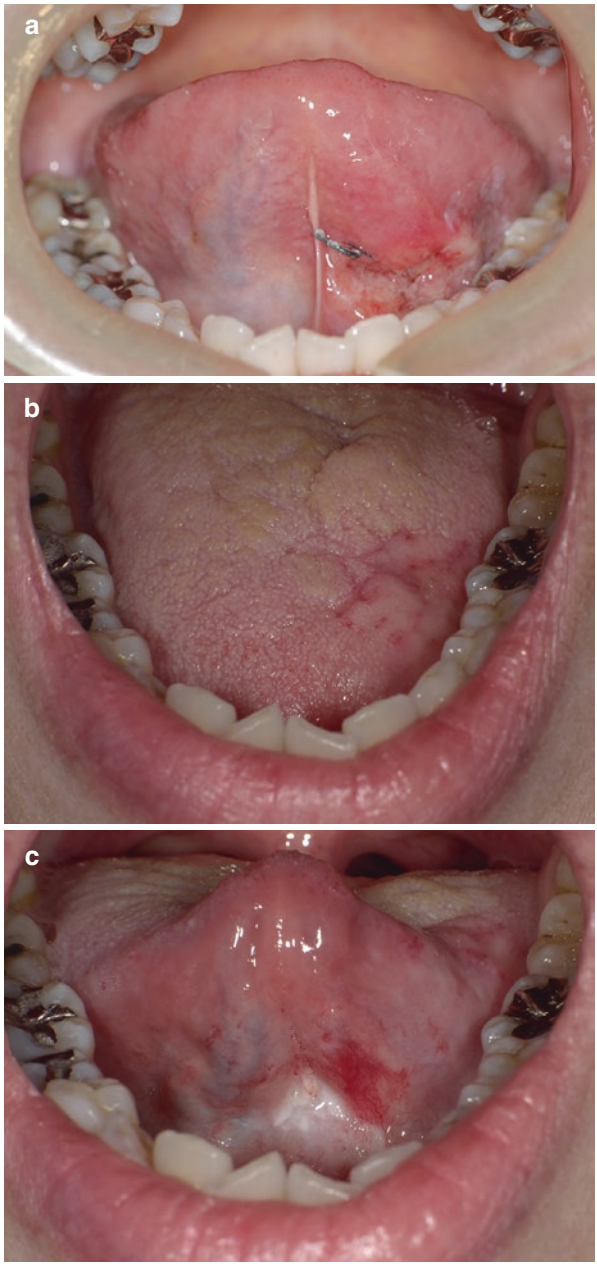

Fig. 18.3 Inferior surface tongue cancer patient (T1N0M0). (**a**) Tongue cancer located at the left side of the inferior surface of the tongue and close to the tongue tip and oral floor at the first visit. (**b**, **c**) Telangiectasia is confirmed, but no evidence of disease at the primary tumor site at 3 years and 5 months post-HDR-ISBT treatment

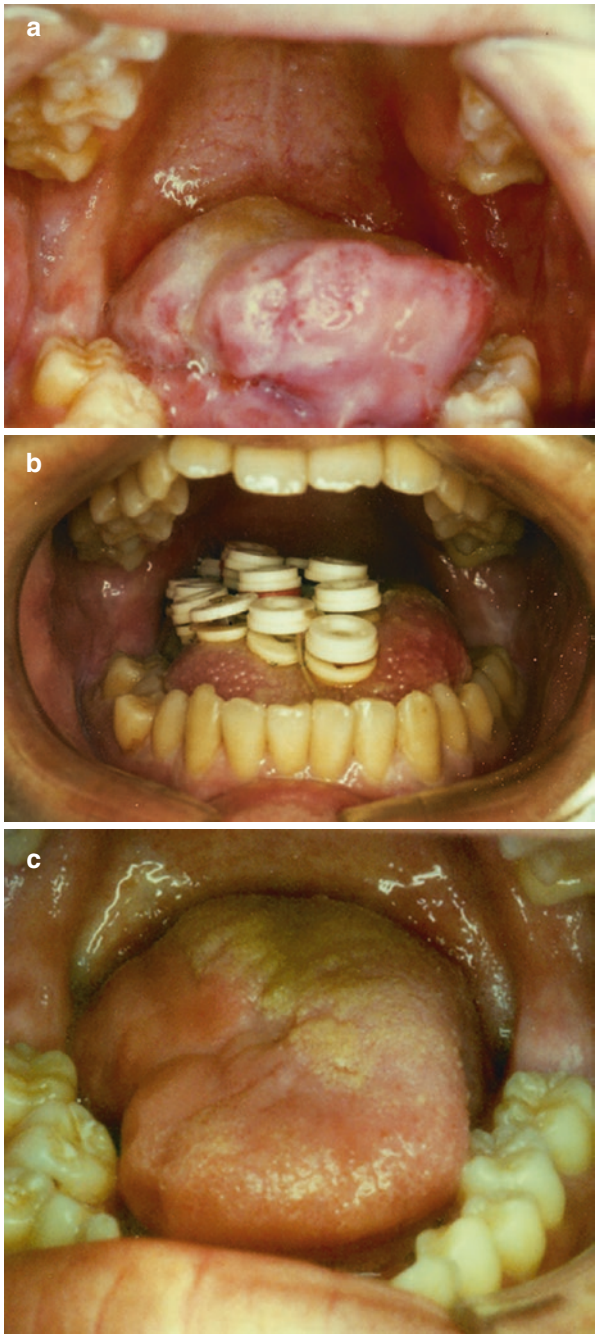

Fig. 18.4 Tongue cancer patient (T3N0M0). (**a**) Tongue cancer occupying most of the right half side of the tongue including the tongue tip at the first visit. (b) Twelve flexible plastic tubes were implanted at the right side of the tongue. (**c**) No evidence of disease at the primary tumor site is confirmed at 2 years and 9 months post-HDR-ISBT treatment

Table 18.1 Definitive HDR-ISBT treatment results for mobile tongue caner

Author	Year	Ref. no.	Case	T category	Therapy	Dose	LCR	OS	Complications
Lau HY	1996	17	27	T1:T2:T3 = 10:15:2	Br	6.5Gy x 7fr	53% (5y)	66% (5y)	Soft+Bone= 37%
Leung TW	1997	25	8	T1:T2 = 5:3	Br	6 Gy x 10 fr	100% (26 m)	7/8 (26 m)	Soft or Bone= 3 patients
Umeda M	2000	21	25	T1:T2 = 18:7	Br	6 Gy x 9–10 fr	T1:T2 = 72%:54% (3y)	T1:T2 = 64%:38% (2y)	Osteonecrosis = 5 patients
Inoue T	2001	1	25	T1:T2 = 14:11	Br	6 Gy x 10 fr	87% (5y)	88% (5y, CSS)	Soft or Bone= 3 patients
Kakimoto N	2001	7	14	T3 = 1	Br	6 Gy x 10 fr	71% (3y)	46% (3y)	Soft = 3 patients
				T3 = 13	EBRT+Br	EBRT: 36 Gy + Br: 6Gy x 8fr (median)			
Leung TW	2002	26	19	T1:T2 = 10:9	Br	5.5Gy x 10 fr	94% (4y)		Soft or Bone= 3 patients
Yamazaki H	2003	2	58	T1:T2 = 22:36	Br	6 Gy x 10 fr	84% (5y)	T1:T2 = 83%:82% (5y, CSS)	10%
Akiyama H	2012	23	34	T1:T2 = 16:18	Br	6 Gy x 10 fr	88% (3y)	88% (3y)	Soft and/or Bone= 4 patients (12%)
			17	T1:T2 = 7:10	Br	6 Gy x 9 fr	88% (3y)	82% (3y)	Soft and/or Bone= 3 patients (18%)
Akiyama H	2014	22	18	T1:T2:T3 = 3:11:4	Br	6 Gy x 9 fr	82% (2y)	83% (2y, CSS)	28%
Bansal A	2016	27	92[a]	T1:T2 = 47:45	Br	4 Gy x 10–13 fr	68.2% (5y)	78.8% (5y)	Osteonecrosis = 1 patient (1.1%)
					EBRT+Br	EBRT: 40 Gy + Br: 3Gy x 6-8fr	57.6% (5y)	61.1% (5y)	

Br brachytherapy, *EBRT* external beam radiotherapy, *fr* fractions, *LCR* local control rate, *OS* overall survival rate, *CSS* cause-specific survival rate, *Soft* soft tissue complication, *Bone* bone complication

[a]This study includes 8 cases with local excision of 92 patients

seems not to be the main treatment, as through the application of a submandibular approach in HDR-ISBT for tongue cancer, the occult metastasis rate is almost the same as for other treatment regimens such as surgery or LDR-ISBT. When lymph node involvement is detected, elective treatment of the neck with surgery and/or EBRT is recommended in most of the cases. Watchful waiting regarding the neck lymph node may be discussed in the tongue cancer patients who are treated with HDR-ISBT alone. Therefore, local and regional controls are still a necessary requirement even when only HDR-ISBT is performed in the treatment of tongue cancer.

When applying HDR-ISBT to treat tongue cancer patients, complications, such as soft tissue ulcers and osteonecrosis, constitute a serious problem for the quality of life in patients. For example, it has been reported that soft tissue and/or bone complications occurred in around 10–37.5% of all tongue cancer patients treated with HDR-ISBT (Table 18.1). Consequently, Akiyama et al. tried to reduce the total dose and duration from 60 Gy/10 fractions to 54 Gy/9 fractions [22, 23]. Bansal et al. reported that osteonecrosis in the mandible occurred in only 1.1% of patients with fraction size of 3–4 Gy in HDR-ISBT, although local control ratio and overall survival ratio were 64.2% and 73.2%, respectively [27]. It is therefore safe to assume that total dose reduction decreases the amount of complications when applying HDR-ISBT. Nowadays, 3D HDR-IGBT offers the advantage of optimizing dose distribution for homogeneous dose distribution to the PTV and dose reduction to the OAR, thereby significantly reducing complications [28].

18.6 Applying HDR-ISBT to Patients Who Have Cancer at the Floor of the Mouth or at the Lip

Patients with cancer at the floor of the mouth (FOM) are treated with radiation therapy for functional and cosmetic reasons. Inoue et al. reported the treatment results of HDR-ISBT alone and in combination with EBRT including the presence/absence of chemotherapy for 16 FOM cancer patients [29]. The treatment dose of 60 Gy/10 fractions was used in HDR-ISBT alone, and a total dose of 30–40 Gy of EBRT followed by a total dose of 48 Gy/8 fractions of HDR-ISBT was administered as a combination therapy. The 5-year local control rate and cause-specific survival rate of the FOM cancer patients both were 94%. As for complications, bone exposure and/or soft tissue ulcer occurred in 6 of 16 patients (37.5%).

In patients with lip cancer, which is not a superficial tumor, ISBT provides better cosmetic and functional results because tissue removal is typically avoided (Fig. 18.5). Guinot et al. reported the treatment results of HDR-ISBT alone (101 cases) and in combination with EBRT (3 cases) for lip cancer patients [3]. The treatment dose of 4.5–5.5 Gy/8–9 fractions (total 40.5–45 Gy) was used in HDR-ISBT. Local control was achieved in 99 of 104 patients (95.2%) with no complications such as bone or soft tissue necrosis. Feldman et al. reported T2 lip cancer patient treatment employing a Customized Mold Sandwich technique using a combination of interstitial sleeve catheters and a surface mold with embedded sleeve catheters [30]. In this paper seven patients were treated with this method, and all achieved

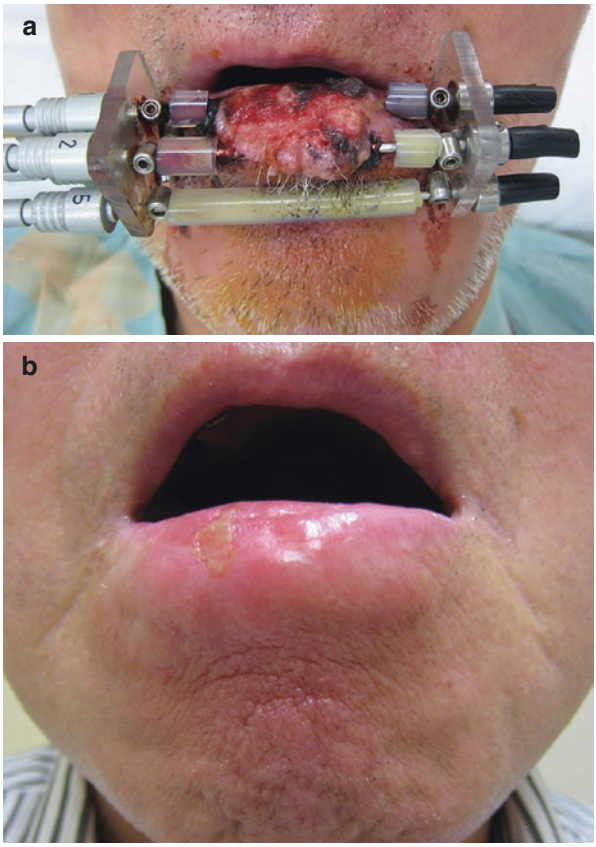

Fig. 18.5 Lip cancer patient (T2N0M0). (**a**) The treatment applicators implanted in the tumor and adjacent to tumor (i.e., the lowest applicator). (**b**) Lip cancer disappeared leaving some small mucositis on the lower lip at 2 months post-HDR-ISBT treatment

local control with excellent esthetic and functional results in median 47-month follow-up periods. Therefore, although, with respect to oral cancers, HDR-ISBT is mostly used in treating tongue cancers, its usefulness can be extended to other types of oral cancers as well.

18.7 HDR Brachytherapy Using a Mold Technique

For superficial carcinoma within the oral cavity, some authors reported the effectiveness of HDR brachytherapy using a mold, without the need for invasive needles [31–33]. It was reported that the carcinoma of lips, buccal mucosa, hard palate, gingiva, and the FOM could be treated with this technique. The local control rates were reported to range from 54.1 to 100%. Skillful dental techniques play a very important role in construction of the mold. An impression determining the tumor margins may prove to be very useful when the location of the catheters in or around the mold is to be decided and the adequate dose distribution is to be planned. This technique constitutes a minimally invasive treatment for superficial lip and oral cavity cancer patients.

18.8 Modular Lead-Lined Spacer for HDR-ISBT

HDR-ISBT is an important treatment option for oral cancer patients as this method is able to administer a very high strength dose directly to the cancer (the same as the PTV) during a very short time (usually less than 10 min). However, the mandible and gingiva may inadvertently also receive a strong radiation dose as well. This could lead to severe complications such as osteonecrosis. Therefore, it is recommended, whenever possible, to apply a spacer during HDR-ISBT. This device increases the distance between the irradiation source and healthy tissue such as the mandible and gingiva. A recent report, however, has gone one step further and applied a modular lead shield to be inserted in the spacer during the post-planning stage [34]. That is, it is now possible to construct a spacer (Fig. 18.6) which contains a groove which can hold a lead shield. As lead causes severe artifacts when planning the treatment using a CT scan, the fact that the lead can be later inserted presents an ideal solution as CT images can be taken just after implantation with spacer, and

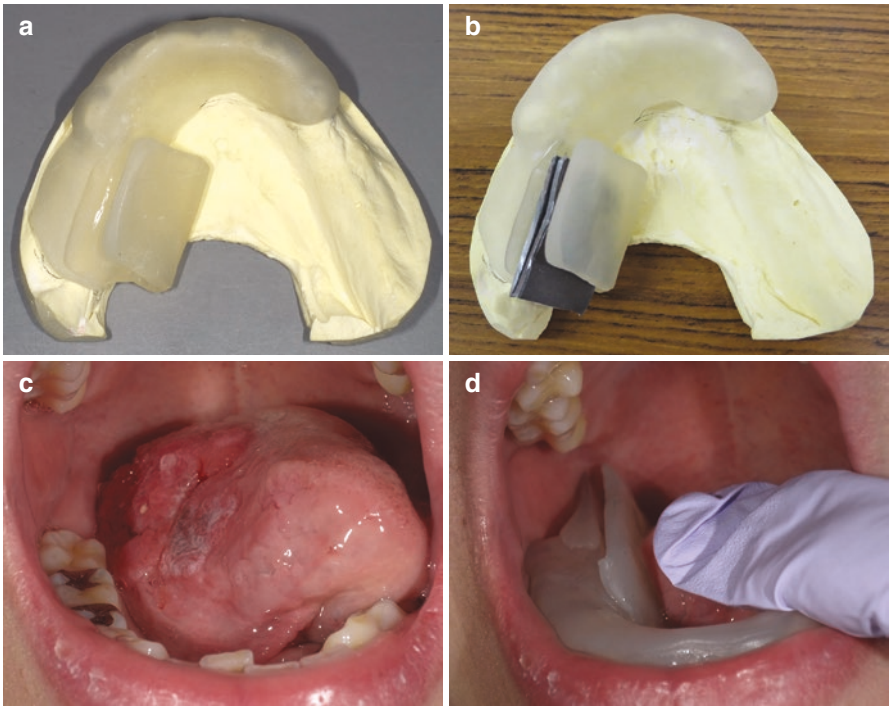

Fig. 18.6 CT-compatible modular spacer with lead shield. (**a**) Spacer was made by light photopolymerization-cured resin on the plaster model. (**b**) The lead shield when inserted in the groove. (**c**) Tongue cancer was confirmed at the right-side border of the tongue. (**d**) Spacer without lead shield is fixed in the mouth and teeth before flexible tube implantation. After this, the patient will be implanted with flexible tubes and examined by CT using the spacer without lead. (**e**) After CT examination for IGBT, the lead shield is inserted and covered with resin inside the spacer. (**f**) The spacer with lead shield is applied during the radiotherapy treatment

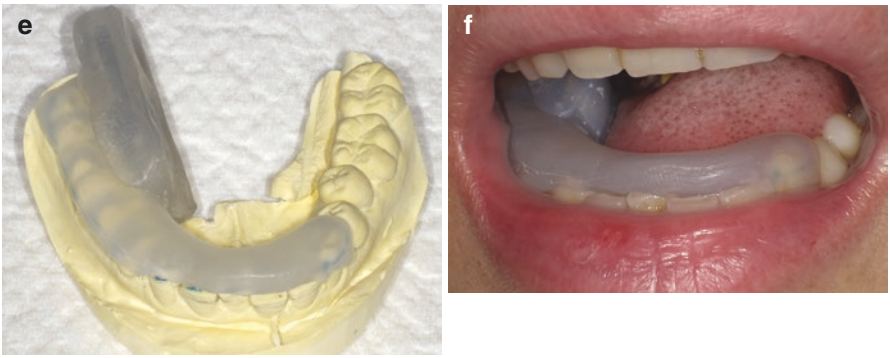

Fig. 18.6 (continued)

accurate GTV and CTV contours can be drawn for IGBT. In other words, the planning stage accurately presents the treatment stage using completely the same thickness to evaluate the real dose administered to the PTV and OAR. Although this type of spacer has yet only be used within a small patient group for a relatively short period, osteoradionecrosis and acute complication such as redness, erosion, or gingival ulcers have not been observed.

Conclusion

Although reports in the clinical literature on the usage of HDR-ISBT to treat oral cancer patients are relatively sparse, this chapter points out that it is an effective method for accurately delivering high-dosage radiotherapy to the oral and maxillofacial region. HDR-ISBT includes the application of dose optimization methods to the tumor and avoids radiation exposure to medical staff. As HDR-IGBT planning allows for accurate dose estimations to the tumor, as well as healthy tissue, it also leads to more precise and quantitatively reliable estimations of the likely treatment outcomes. This chapter has reported on the (1) benefits, (2) treatment methods, and (3) clinical results of the definitive treatment of HDR-ISBT for oral cancer patients and (4) a mold technique for superficial tumors and also (5) presents a CT-compatible modular spacer with lead to be used in IGBT. In all, this chapter concludes that HDR-ISBT constitutes a viable and important treatment option to treat oral cancer patients.

References

1. Inoue T, Inoue T, Yoshida K, Yoshioka Y, Shimamoto S, Tanaka E, et al. Phase III trial of high- vs. low-dose-rate interstitial radiotherapy for early mobile tongue cancer. Int J Radiat Oncol Biol Phys. 2001;51(1):171–5.
2. Yamazaki H, Inoue T, Yoshida K, Yoshioka Y, Furukawa S, Kakimoto N, et al. Brachytherapy for early oral tongue cancer: low dose rate to high dose rate. J Radiat Res. 2003;44(1):37–40.
3. Guinot JL, Arribas L, Tortajada MI, Crispin V, Carrascosa M, Santos M, et al. From low-dose-rate to high-dose-rate brachytherapy in lip carcinoma: equivalent results but fewer complications. Brachytherapy. 2013;12(6):528–34.

4. Kovacs G. Modern head and neck brachytherapy: from radium towards intensity modulated interventional brachytherapy. J Contemp Brachytherapy. 2015;6(4):404–16.
5. Takacsi-Nagy Z, Martinez-Mongue R, Mazeron JJ, Anker CJ, Harrison LB. American brachytherapy society task group report: combined external beam irradiation and interstitial brachytherapy for base of tongue tumors and other head and neck sites in the era of new technologies. Brachytherapy. 2017;16(1):44–58.
6. Inoue T, Inoue T, Teshima T, Murayama S, Shimizutani K, Fuchihata H, et al. Phase III trial of high and low dose rate interstitial radiotherapy for early oral tongue cancer. Int J Radiat Oncol Biol Phys. 1996;36(5):1201–4.
7. Kakimoto N, Inoue T, Inoue T, Murakami S, Furukawa S, Yoshida K, et al. Results of low- and high-dose-rate interstitial brachytherapy for T3 mobile tongue cancer. Radiother Oncol. 2003;68(2):123–8.
8. Yamazaki H, Yoshida K, Yoshioka Y, Shimizutani K, Furukawa S, Koizumi M, et al. High dose rate brachytherapy for oral cancer. J Radiat Res. 2013;54(1):1–17.
9. Liu Z, Huang S, Zhang D. High dose rate versus low dose rate brachytherapy for oral cancer--a meta-analysis of clinical trials. PLoS One. 2013;8(6):e65423.
10. Mazeron JJ, Crook JM, Benck V, Marinello G, Martin M, Raynal M, et al. Iridium 192 implantation of T1 and T2 carcinomas of the mobile tongue. Int J Radiat Oncol Biol Phys. 1990;19(6):1369–76.
11. Hareyama M, Nishio M, Saito A, Kagami Y, Asano K, Oouchi A, et al. Results of cesium needle interstitial implantation for carcinoma of the oral tongue. Int J Radiat Oncol Biol Phys. 1993;25(1):29–34.
12. Shibuya H, Hoshina M, Takeda M, Matsumoto S, Suzuki S, Okada N. Brachytherapy for stage I & II oral tongue cancer: an analysis of past cases focusing on control and complications. Int J Radiat Oncol Biol Phys. 1993;26(1):51–8.
13. Pernot M, Malissard L, Hoffstetter S, Luporsi E, Peiffert D, Aletti P, et al. The study of tumoral, radiobiological, and general health factors that influence results and complications in a series of 448 oral tongue carcinomas treated exclusively by irradiation. Int J Radiat Oncol Biol Phys. 1994;29(4):673–9.
14. Fein DA, Mendenhall WM, Parsons JT, McCarty PJ, Stringer SP, Million RR, et al. Carcinoma of the oral tongue: a comparison of results and complications of treatment with radiotherapy and/or surgery. Head Neck. 1994;16(4):358–65.
15. Erickson BA, Demanes DJ, Ibbott GS, Hayes JK, Hsu IC, Morris DE, et al. American society for radiation oncology (ASTRO) and American college of radiology (ACR) practice guideline for the performance of high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys. 2011;79(3):641–9.
16. Yoshida K, Takenaka T, Akiyama H, Yamazaki H, Yoshida M, Masui K, et al. Three-dimensional image-based high-dose-rate interstitial brachytherapy for mobile tongue cancer. J Radiat Res. 2014;55(1):154–61.
17. Lau HY, Hay JH, Flores AD, Threlfall WJ. Seven fractions of twice daily high dose-rate brachytherapy for node-negative carcinoma of the mobile tongue results in loss of therapeutic ratio. Radiother Oncol. 1996;39(1):15–8.
18. Teshima T, Inoue T, Ikeda H, Murayama S, Furukawa S, Shimizutani K. Phase I/II study of high-dose rate interstitial radiotherapy for head and neck cancer. Strahlenther Onkol. 1992;168(11):617–21.
19. Mazeron JJ, Ardiet JM, Haie-Meder C, Kovacs G, Levendag P, Peiffert D, et al. GEC-ESTRO recommendations for brachytherapy for head and neck squamous cell carcinomas. Radiother Oncol. 2009;91(2):150–6.
20. Nag S, Cano ER, Demanes DJ, Puthawala AA, Vikram B, American Brachytherapy S. The American brachytherapy society recommendations for high-dose-rate brachytherapy for head-and-neck carcinoma. Int J Radiat Oncol Biol Phys. 2001;50(5):1190–8.
21. Umeda M, Komatsubara H, Nishimatsu N, Yokoo S, Shibuya Y, Komori T. High-dose rate interstitial brachytherapy for stage I-II tongue cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;90(5):667–70.

22. Akiyama H, Yoshida K, Yamazaki H, Takenaka T, Kotsuma T, Masui K, et al. High-dose-rate interstitial brachytherapy for mobile tongue cancer: preliminary results of a dose reduction trial. J Contemp Brachytherapy. 2014;6(1):10–4.
23. Akiyama H, Yoshida K, Shimizutani K, Yamazaki H, Koizumi M, Yoshioka Y, et al. Dose reduction trial from 60 Gy in 10 fractions to 54 Gy in 9 fractions schedule in high-dose-rate interstitial brachytherapy for early oral tongue cancer. J Radiat Res. 2012;53(5):722–6.
24. Kakimoto N, Inoue T, Inoue T, Murakami S, Furukawa S, Yoshida K, et al. High-dose-rate interstitial brachytherapy for mobile tongue cancer: influence of the non-irradiated period. Anticancer Res. 2006;26(5B):3933–7.
25. Leung TW, Wong VY, Wong CM, Tung SY, Lui CM, Leung LC, et al. High dose rate brachytherapy for carcinoma of the oral tongue. Int J Radiat Oncol Biol Phys. 1997;39(5):1113–20.
26. Leung TW, Wong VY, Kwan KH, Ng TY, Wong CM, Tung SY, et al. High dose rate brachytherapy for early stage oral tongue cancer. Head Neck. 2002;24(3):274–81.
27. Bansal A, Ghoshal S, Oinam AS, Sharma SC, Dhanireddy B, Kapoor R. High-dose-rate interstitial brachytherapy in early stage oral tongue cancer - 15 year experience from a tertiary care institute. J Contemp Brachytherapy. 2016;8(1):56–65.
28. Kovacs G, Martinez-Monge R, Budrukkar A, Guinot JL, Johansson B, Strnad V, et al. GEC-ESTRO ACROP recommendations for head & neck brachytherapy in squamous cell carcinomas: 1st update–improvement by cross sectional imaging based treatment planning and stepping source technology. Radiother Oncol. 2017;122(2):248–54.
29. Inoue T, Inoue T, Yamazaki H, Koizumi M, Kagawa K, Yoshida K, et al. High dose rate versus low dose rate interstitial radiotherapy for carcinoma of the floor of mouth. Int J Radiat Oncol Biol Phys. 1998;41(1):53–8.
30. Feldman J, Appelbaum L, Sela M, Voskoboinik N, Kadouri S, Weinberger J, et al. Novel high dose rate lip brachytherapy technique to improve dose homogeneity and reduce toxicity by customized mold. Radiat Oncol. 2014;9:271.
31. Ariji E, Hayashi N, Kimura Y, Uchida T, Hayashi K, Nakamura T. Customized mold brachytherapy for oral carcinomas through use of high-dose-rate remote afterloading apparatus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999;87(4):508–12.
32. Chatani M, Tsuboi K, Yagi M, Fujiwara K, Tachimoto R, Yoshioka H. High dose rate brachytherapy using molds after chemoradiotherapy for oral cavity cancer. Jpn J Radiol. 2012;30(1):40–4.
33. Unetsubo T, Matsuzaki H, Takemoto M, Katsui K, Hara M, Katayama N, et al. High-dose-rate brachytherapy using molds for lip and oral cavity tumors. Radiat Oncol. 2015;10:81.
34. Murakami S, Verdonschot RG, Kakimoto N, Sumida I, Fujiwara M, Ogawa K, et al. Preventing complications from high-dose rate brachytherapy when treating mobile tongue cancer via the application of a modular lead-lined spacer. PLoS One. 2016;11(4):e0154226.

Ocular Plaque Brachytherapy for Uveal Melanoma and Retinoblastoma

19

Naoya Murakami, Shigenobu Suzuki, and Jun Itami

Abstract

The main topic of this chapter is brachytherapy for ocular tumor. A small dish-shaped applicator is temporarily attached outside of the eyeball where the tumor is located, and after adequate irradiation time, it is removed. Because generally eyeball moves quickly and frequently, it is difficult to irradiate intraocular tumor with external beam technique. When big dose is delivered with adequate margin to compensate the organ motion, it is difficult to preserve visual function. On the other hand, when the applicator is accurately attached to the location of the tumor, the applicator moves together with the eyeball, and it is possible to perform very conformal irradiation. Therefore, ocular plaque brachytherapy is very important for the management of ocular tumors such as uveal melanoma and retinoblastoma.

Keywords

Plaque brachytherapy · Ocular tumors · Uveal melanoma · Retinoblastoma

19.1 Uveal Melanoma

19.1.1 Introduction

Uveal melanoma is the most common type of primary ocular melanoma in adult, accounting for approximately 79–81% of ocular melanoma cases [1]. Similar to skin melanoma, incidence of uveal melanoma has racial difference: incidence of

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uveal melanoma was reported to be 6.02 cases in 1 million population in non-Hispanic white [2] while 0.25 cases in 1 million population in Japanese [3]. Although local control of the tumor is generally excellent, because up to 20–50% of patients will eventually develop distant metastasis, its mortality is relatively high. Because the eyeball has no regional lymph node, typical mode of metastasis is hematogenous metastasis, and the liver is the most commonly affected organ (89%) followed by the lung (29%) and bone (17%) [4]. UV-B radiation exposure and wearing no sunglasses in the daylight have reported to be associated with the development of uveal melanoma [5].

Typically uveal melanoma patients present with visual symptoms such as visual field defect, floaters in vision, photopsia, and blurred vision. On the other hand, approximately 30% of patients are asymptomatic and are diagnosed by chance. Different from other malignancies, diagnosis of uveal melanoma may often be made by no pathological confirmation because of the possibility of developing extraocular dissemination, intraocular bleeding, or retinal detachment through biopsy procedure. Most diagnoses are made by normal funduscopic examination with or without ultrasonography and fluorescein angiography. The major differential diagnosis for uveal tumors would be metastasis from other sites of origin and pigmented nevi. It is difficult to distinguish small-sized melanoma from pigmented nevi, and Shields et al. reported that possibility of progressing malignant melanoma from pigmented nevi was 2%, 9%, and 13% at 1, 5, and 10 years of follow-up, respectively [6]. Therefore, pigmented nevi which look similar to melanoma need to be closely followed for potential malignant transformation.

Risk factors which relate to poor prognosis of uveal melanoma include advanced age at presentation, male gender, large tumor size, extraocular extension, involvement of the ciliary body, and uncontrolled tumor after initial local treatment. One of the most important prognostic factors of uveal melanoma is tumor size (largest basal diameter (LBD) and thickness). The Collaborative Ocular Melanoma Study (COMS) group created staging system according to tumor size (Table 19.1) and conducted a series of prospective clinical trials according to the tumor categories [7–10]. The 5-, 10-, and 12-year mortalities of medium-sized tumor were 10%, 18%, and 21%, respectively, for patients treated by I-125 plaque brachytherapy and 11%, 17%, and 17% for patients treated by enucleation, showing no inferiority of plaque brachytherapy [7]. In the COMS large tumor trial, disease-associated mortality at 5 and 10 years was 28% and 40% for patients treated by enucleation [8]. Monosomy of chromosome 3 in the tumor cell is reported to be prone to distant metastasis and associated with a worse prognosis [11]. BAP1 (BRCA1-associated protein 1 gene) mutations are reported to be present in about 1.6% of uveal melanoma patients and are also associated with

Table 19.1 The Collaborative Ocular Melanoma Study (COMS) staging of melanoma of the eye

Small	Between 1 mm and 3 mm in height and between 5 mm and 16 mm LBD
Medium	Between 3.1 mm and 8 mm in height and no more than 16 mm LBD
Large	More than 8 mm in height or more than 16 mm LBD

LBD: largest basal diameter

larger tumor diameters, more frequently ciliary body involvement, and higher rate of distant metastasis resulting in poor prognosis [12]. However, if the tumor is localized, no biopsy will be performed due to the possibility of development of iatrogenic dissemination as written above, and no treatment strategy based on tumor biology is currently performed for localized disease in daily practice. On the other hand, in the United States or European countries, because of high prevalence of this disease and existence of well-experienced ocular pathologists, needle biopsy is incorporated into diagnostic work-up in dedicated institutions using very thin needles (25–27 G needles). Because no adequate tissue specimen can be obtained by needle biopsies, to compensate its weakness, there is a primary tumor gene expression profile (GEP) testing which can categorize patients into two groups: low-risk Class 1 group with low metastatic potential and high-risk Class 2 group [13]. In terms of local management of uveal melanoma, there is no difference between these two groups. After local treatment, high-risk Class 2 group patients could be monitored frequently for distant metastasis and can be offered a clinical trial trying to prevent development of distant metastasis.

19.1.2 Diagnosis

As described above, normally biopsy is avoided due to the possibility of developing extraocular dissemination, intraocular bleeding, and retinal detachment; patient history and physical examination taken by conventional slit lamp and ophthalmoscopy are very important for the diagnosis of uveal melanoma. High accuracy of diagnosis without pathological confirmation was demonstrated by one of COMS [10]. In addition to these, photography, fundus autofluorescence imaging, MRI, and I-123 IMP SPECT (123N-isopropyl-p-[123I]-iodoamphetamine single photon emission computed tomography) are also used in the diagnostic procedure. Although I-123 IMP SPECT has high sensitivity and specificity, it is not popular in the United States and Europe because they perform needle biopsy and GEP as described above. When it is difficult to make diagnosis, especially for small tumors, treatment will be started after confirmation of disease progression.

19.1.3 Local Treatment for Uveal Melanoma

Treatment of the primary tumor depends upon tumor size, location, general condition of the patient, and patient preference. Historically, enucleation had been the treatment of choice. Since equal effectiveness of local control and overall survival between surgical resection and plaque brachytherapy with I-125 were demonstrated for medium-sized uveal melanoma (<8 mm in height and <16 mm in diameter) by COMS phase III clinical trial [7], the majority of medium-sized localized disease are treated with plaque brachytherapy to spare vision in the United States. On the contrary, only one institution, the National Cancer Center Hospital, can perform plaque brachytherapy using Ru-106 in Japan, and the number of patients

who can be treated within a certain period of time by Ru-106 is strictly limited by the law; majority of patients treated by plaque brachytherapy are retinoblastoma patients, and unfortunately patients who are good candidate for plaque brachytherapy are usually treated with external beam radiation therapy such as stereotactic radiation therapy or particle beam with which it is difficult to preserve adequate visual function. I-125, which can treat thicker tumor than Ru-106, is not allowed to be used for ocular plaque brachytherapy in Japan; therefore, urgent introduction of I-125 in the management of ocular tumor is warranted in Japan. Exclusion criteria for plaque brachytherapy described in the American Brachytherapy Society consensus guideline include tumors with extraocular extension more than 5 mm in diameter (T4e), blind painful eyes, and patients with no light perception vision [14]. Enucleation is still the treatment of option in selected cases when there is little probability of preserving eyesight, the tumor is too large to be treated by other local therapies, a tumor causes extensive bleeding necessitating urgent resection, or the patients feel anxious for eye-preservation treatment. The COMS quality-of-life study found that although patients treated with brachytherapy enjoyed significantly better visual function than patients treated with enucleation, patients treated with brachytherapy were more likely to have anxiety during follow-up than patients treated with enucleation [15].

Twelve-year results of COMS phase III clinical trial for medium-sized tumor of I-125 brachytherapy vs enucleation found that cumulative all-cause mortality rates and death with histopathologically confirmed melanoma metastasis were 43% and 21% in I-125 brachytherapy arm and 41% and 17% in enucleation arm, respectively [7]. Among brachytherapy patients, the most common complications during the first 5 years after treatment were loss of visual acuity and local recurrence [16]. Five-year visual acuity of 20/200 or worse was 63%, and 5-year cumulative rate of enucleation was 12%. Long-term results of carbon ion radiation therapy for locally advanced (UICC T2–T3) uveal melanoma were reported, and 5-year overall survival and local control were 80.4% and 92.8% with 35.9% of neovascular glaucoma incidence rate [17].

If the tumor is small enough to be treated with plaque brachytherapy, brachytherapy should be considered in terms of both local control and organ function preservation.

19.1.4 Treatment-Related Complications

Radiation maculopathy or radiation optic neuropathy could be occurred especially posteriorly located tumors. These late complications related with plaque brachytherapy generally occur within 3 years after treatment. Toxic tumor syndrome can occur after large melanomas treated by radiotherapy either with plaque brachytherapy or proton beam radiation by inducing cytokines and cause ischemia of the retina and exudative retinal detachment. This radiation maculopathy is the primary cause of irreversible visual loss. Even if the tumor is controlled, enucleation is needed when toxic tumor syndrome is developed.

19.2 Retinoblastoma

19.2.1 Introduction

Retinoblastoma is a disease for neonatal infant or baby and is the most frequent intraocular malignancy in children. There is no difference of incidence according to race or sex. In Japan, about 70–90 patients are diagnosed with retinoblastoma every year [18], and 95% of them are diagnosed until they become 5 years old. About 60% of the patients are non-hereditary and unilateral, 25% are hereditary and bilateral, and 15% are hereditary and unilateral. Patients with the genetic diathesis are prone to develop secondary malignancies, especially soft tissue sarcomas and osteosarcomas.

19.2.2 Diagnosis

Typical symptom for retinoblastoma for sporadic cases is leukocoria or strabismus. Because infants cannot complain about visual disturbance by themselves, most cases are found in locally advanced stage. When relatives have family history of retinoblastoma, early fundus examination occasionally finds early-stage disease. Same as uveal melanoma, because of concern for developing dissemination, needle biopsy is thought to be a contraindication. Diagnosis is generally done by ocular examination, detecting whitish tumors with typical calcification. Differential diagnoses are persistent hyperplastic primary vitreous (PHPV), Coats disease, retinal dysplasia, ocular toxocariasis, congenital cataract, and retinal detachment. Reese-Ellsworth classification had been used to predict prognosis when external beam radiation therapy was the main treatment modality, but now that chemotherapy became the main player for retinoblastoma [19], it does not correlate well with prognosis. The International Classification of Retinoblastoma (ICRB) categorizes (Table 19.2) intraocular tumor very well and correlates with clinical results [20]. Since the 7th edition of UICC TNM, the concept of ICRB category has been adhered fundamentally; therefore the succeeding 8th edition of TNM staging system [21] also correlates well with prognosis of retinoblastoma.

Table 19.2 The International Classification of Retinoblastoma (ICRB)

Group A	Small intraretinal tumors (<3 mm) away from fovea and disc
Group B	Tumors >3 mm, macular or juxtapapillary location, or with subretinal fluid
Group C	Tumor with focal subretinal or vitreous seeding within 3 mm of tumor
Group D	Tumor with diffuse subretinal or vitreous seeding >3 mm from tumor
Group E	Extensive retinoblastoma occupying >50% of the globe with or without neovascular glaucoma, hemorrhage, extension of tumor to optic nerve or anterior chamber

19.2.3 Treatment

When tumor is localized in the retina, ocular preservation probability is very high, and the ultimate goal of the treatment is visual preservation. Localized tumor thickness of which is less than 3 mm can be well controlled by laser or cryotherapy, and approximately 90% local control will be expected. Moderately large tumor thickness of which is less than 5 mm can be well controlled by Ru-106 brachytherapy and less than 8 mm by I-125. Tumors thicker than 5 mm or tumors having retinal or vitreous dissemination require induction chemotherapy followed by local therapy, and organ preservation rate for such tumors is about 50% with poor visual function. There exists controversy whether to preserve the eyeball which has no adequate visual function. Even without visual function, if the eyeball is preserved, the orbital growth will be encouraged, and better cosmetic result will be expected. Even though tumor is found in locally advanced stage, only if the tumor is localized within the eye, 95% of patients can expect long-term survival. On the other hand, when tumor develops extraocular spread, prognosis becomes very poor and requires multidisciplinary modalities to save the life.

19.2.4 Tumors with Less Than 3 mm Thickness (TNM(7th) T1, TNM(8th) T1)

Either laser or cryotherapy can control such small tumors. The tumors located in peripheral part of the retina are good candidate for periscleral cryotherapy. Both techniques can achieve approximately 90% of local control.

19.2.5 Tumors with Less Than 5 mm Thickness or Limited Vitreous Dissemination (TNM(7th) T2a, TNM(8th) T2a)

This category of tumors is good candidate for plaque brachytherapy, and 94% of 5-year tumor control is reported by Ru-106 plaque brachytherapy [22].

19.2.6 Tumors Larger Than 5 mm and/or Widespread Dissemination (TNM(7th) T2b–T3, TNM(8th) T2b)

Several decades ago, external beam radiation therapy (EBRT) had been given for such locally advanced patients. However, because of the possibility of development of secondary malignancies, especially in patients with hereditary disease, and concern for facial bone growth obstruction, chemotherapy has replaced the position of EBRT [20]. Typical agents used as systemic chemotherapy are combination of vincristine, carboplatin, and etoposide. After achievement of optimal tumor shrinkage, which is so-called chemoreduction, local therapies described above are applied because chemotherapy alone is not strong enough to completely destroy the tumor. To reduce the toxicity associated with systemic chemotherapy such as

myelosuppression, infection, nausea and vomiting, renal dysfunction, ototoxicity, reproductive organ damage, and secondary malignancies, selective ophthalmic arterial injection (SOAI) was introduced [23]. Suzuki et al. reported long-term clinical result of retinoblastoma patients treated by SOAI using melphalan [24]. Eyes with active vitreous seeding >3 mm from tumor are also treated with vitreous injection of melphalan. Although plaque brachytherapy is not suitable for such large and disseminated tumor, combined with systemic chemotherapy, SOAI, or vitreous injection of chemotherapy and if favorable tumor shrinkage is obtained, plaque brachytherapy is also applied [25].

19.2.7 Tumor with Glaucoma, Massive Intraocular Bleeding, or Orbital Inflammatory Disease (TNM(7th) T3b, TNM(8th) T3)

Primarily eyes with such complications should be enucleated. If pathologic report revealed the risk factor of metastasis such as massive choroidal involvement, optic nerve invasion, or extrascleral spread, adjuvant chemotherapy will be given to prevent hematogenous metastasis, central nervous system metastasis, or orbital recurrence, respectively. Chemotherapy agents given are similar to those used in treatment for neuroblastoma or regimen according to those used for limited stage Retinoblastoma such as VEC (vincristine, etoposide, and carboplatin).

19.2.8 Complications

Radiation retinopathy/maculopathy and optic neuropathy represent late-onset complications of plaque brachytherapy and are characterized by a slowly progressing occlusive vasculopathy, which produces variable ischemic changes and subsequent visual loss [26]. Other types of complications include exudative retinal detachment, radiation cataract, neovascular glaucoma, and retinal bleeding.

19.3 Plaque Brachytherapy Procedure

Application of brachytherapy in the management of intraocular tumor has been started since 1930 [27]. Various types of isotopes have been used as plaque sources including Co-60, Ru-106, I-125, Cs-131, Sr-90, and Pd-103 [17]. Ru-106 emits beta ray and, therefore, can only treat thin tumors less than 5–6 mm in apical thickness. In contrast, I-125 emits gamma ray and can treat up to 8-mm-thick tumors. Because dose distribution created by Ru-106 is more conformal than I-125, when the tumor apical dose is the same, radiation dose to the contralateral side of the eyeball is far less in Ru-106 compared to I-125 (Fig. 19.1). Ru-106 plaque applicators (BEBIG Isotopen und Medizintechnik GmbH, Berlin, Germany) stocked in the National Cancer Center Hospital are shown in Fig. 19.2. Round shaped applicators, so-called CCA and CCB, are used to treat tumors away

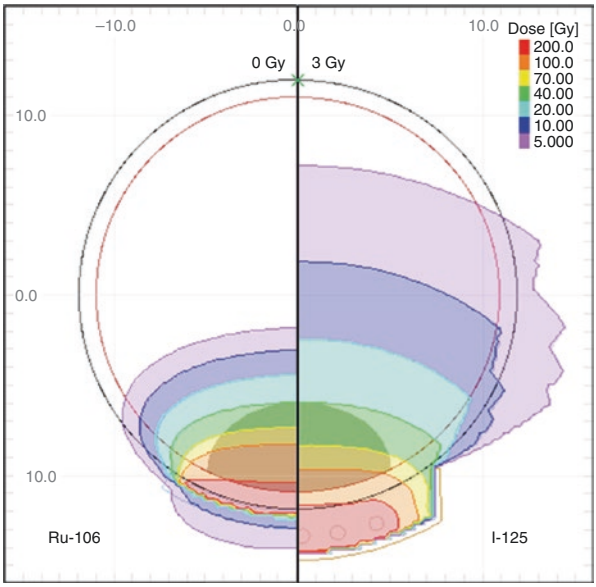

Fig. 19.1 Comparison of dose distribution for Ru-106 and I-125 plaque brachytherapy. The round represents the eyeball and the brown object at the bottom of the eyeball represents a tumor. Dose is normalized to the apex of the tumor (40 Gy). While contralateral side dose with Ru-106 is 0 Gy, it is 3 Gy in I-125

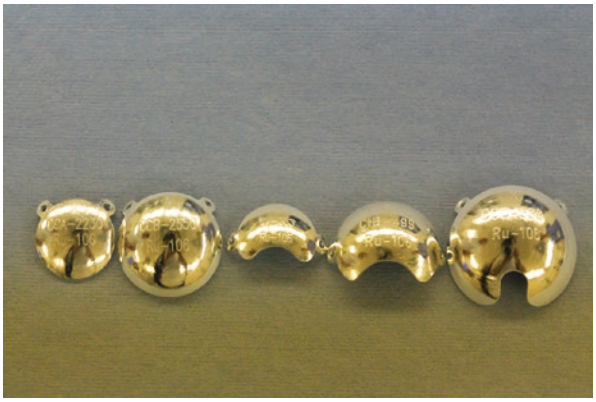

Fig. 19.2 Five different types of applicator are shown. Small applicators are used for small tumors and large applicators for large tumors. The notched applicators are used for anteriorly located tumor to avoid cornea and lens as shown in Fig. 19.3. Applicator, which has deep notch, COC, is used to treat juxtapapillary tumor. Because of the presence of the optic nerve, which connects the eyeball to the brain, it is impossible to put a plaque applicator just behind of a tumor which locates just next to the optic nerve. Therefore, by using such an applicator which has deep notch surrounding the optic nerve, the β rays emitted by Ru-106 turn around, and it can be expected to secure dose of the surface of the optic nerve

from normal structures such as optic nerve, lens, or cornea. Applicators which have shallow notch, CIA and CIB, are used to treat periphery located tumors to avoid high dose to the lens and cornea. Applicator which has deep notch, COC, is used to treat juxtapapillary tumor to ensure the dose which locates very close to

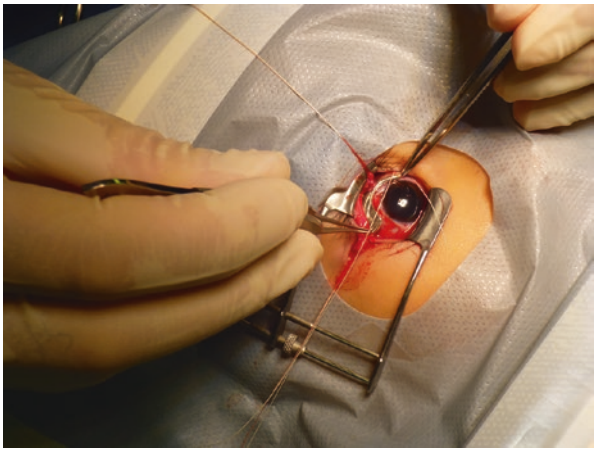

Fig. 19.3 After conjunctival incision, the external ocular muscle is temporarily detached to make applicator as close to the tumor as possible. Applicator is sutured to the eyeball by the surgical thread through eyelets

the optic nerve. Because of the presence of the optic nerve, which connects the eyeball to the brain, it is impossible to put a plaque applicator just behind of a tumor which locates just next to the optic nerve. Therefore, by using an applicator which has deep notch surrounding the optic nerve, the β rays emitted by Ru-106 will turn around, and it can be expected to secure dose of the surface of the optic nerve. Tumor localization is determined by indirect ophthalmoscopy. After conjunctival incision external ocular muscle is temporarily detached to make applicator as close to the tumor as possible. Tumor margins are marked on the sclera by indentation of the sclera using illuminator, and applicator is inserted (Fig. 19.3). Applicator is sutured to the eyeball by the surgical thread through eyelets. Because the thickness of Ru-106 plaque applicator is only 1 mm, it is suitable for children. Prescription dose at the apex of the tumor is 85 Gy and 40 Gy for uveal melanoma and retinoblastoma, respectively.

References

1. Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. Ophthalmology. 2011;118:1881–5.
2. Hu DN, Yu GP, McCormick SA, et al. Population based incidence of uveal melanoma in various races and ethnic groups. Am J Ophthalmol. 1996;76:784–96.
3. Kaneko A. Incidence of malignant melanoma of the eye in Japan, 1977–1979. Nippon Ganka Gakkai Zasshi. 1982;86:1042–5.
4. Diener-West M, Reynolds SM, Agugliaro DJ, et al. Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: collaborative ocular melanoma study group report no 26. Arch Ophthalmol. 2005;123:1639–43.
5. Mainster MA, Turner PL. Ultraviolet-B phototoxicity and hypothetical photomelanomagenesis: intraocular and crystalline lens photoprotection. Am J Ophthalmol. 2010;149:543–9.
6. Shields CL, Furuta M, Berman EL, et al. Choroidal nevus transformation into melanoma:analysis of 2514 consecutive cases. Arch Ophthalmol. 2009;127:981–7.
7. Collaborative Ocular Melanoma Study Group. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: V. Twelve-year mortality rates and prognostic factors: COMS report no 28. Arch Ophthalmol. 2006;124:1684–93.

8. Hawkins BS, Collaborative Ocular Melanoma Study Group. The collaborative ocular melanoma study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma: IV. Ten-year mortality findings and prognostic factors. COMS report number 24. Am J Ophthalmol. 2004;138:936–51.
9. The Collaborative Ocular Melanoma Study Group. Factors predictive of growth and treatment of small choroidal melanoma:COMS report no. 5. Arch Ophthalmol. 1997;115:1537–44.
10. The Collaborative Ocular Melanoma Study Group. Accuracy of diagnosis of choroidal melanomas in the collaborative ocular melanoma study. COMS report no. 1. Arch Ophthalmol. 1990;108:1268–73.
11. Sandinha MT, Farquharson MA. McKay IC et al: Monosomy 3 predicts death but not time until death in choroidal melanoma. Invest Ophthalmol Vis Sci. 2005;46:3497–501.
12. Gupta MP, Lane AM, DeAngelis MM, et al. Clinical characteristics of uveal melanoma in patients with germline BAP1 mutations. JAMA Ophthalmol. 2015;133:881–7.
13. Plasseraud KM, Cook RW, Tsai T, et al. Clinical performance and management outcomes with the DecisionDx-UM gene expression profile test in a prospective multicenter study. J Oncol. 2016;2016:5325762.
14. American Brachytherapy Society–Ophthalmic Oncology Task Force. The American brachytherapy society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma. Brachytherapy. 2014;13:1–14.
15. Melia M, Moy CS, Reynolds SM, et al. Quality of life after iodine 125 brachytherapy vs enucleation for choroidal melanoma: 5-year results from the collaborative ocular melanoma study: COMS QOLS report no. 3. Arch Ophthalmol. 2006;124:226–38.
16. Collaborative Ocular Melanoma Study Group. Collaborative ocular melanoma study (COMS) randomized trial of I-125 brachytherapy for medium choroidal melanoma, I: visual acuity 3 years following I-125 brachytherapy for choroidal melanoma: COMS report no. 16. Ophthalmology. 2001;108:348–66.
17. Toyama S, Tsuji H, Mizoguchi N, et al. Long-term results of carbon ion radiation therapy for locally advanced or unfavorably located choroidal melanoma: usefulness of CT-based 2-port orthogonal therapy for reducing the incidence of neovascular glaucoma. Int J Radiat Oncol Biol Phys. 2013;86:270–6.
18. Survival rate and risk factors for patients with retinoblastoma in Japan. The Committee for the National Registry of retinoblastoma. Jpn J Ophthalmol. 1992;36:121–31.
19. Shields CL, De Potter P, Himelstein BP, et al. Chemoreduction in the initial management of intraocular retinoblastoma. Arch Ophthalmol. 1996;114:1330–8.
20. Shields CL, Mashayekhi A, Au AK, et al. The international classification of retinoblastoma predicts chemoreduction success. Ophthalmology. 2006;113:2276–80.
21. Brierley JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumors. 8th ed. Hoboken, New Jersey: Wiley-Blackwell; 2017. 978-1-119-26357-9
22. Schueler AO, Fluhs D, Anastassiou G, et al. Beta-ray brachytherapy with 106Ru plaques for retinoblastoma. Int J Radiat Oncol Biol Phys. 2006;64:1212–21.
23. Shields CL, Shields JA. Retinoblastoma management: advances in enucleation, intravenous chemoreduction, and intra-arterial chemotherapy. Curr Opin Ophthalmol. 2010;21:203–12.
24. Suzuki S, Yamane T, Mohri M, et al. Selective ophthalmic arterial injection therapy for intraocular retinoblastoma: the long-term prognosis. Ophthalmology. 2011;118:2081–7.
25. Murakami N, Suzuki S, Ito Y, et al. ^{106}Ruthenium plaque therapy (RPT) for retinoblastoma. Int J Radiat Oncol Biol Phys. 2012;84:59–65.
26. Krema H, Xu W, Payne D, et al. Factors predictive of radiation retinopathy post 125 iodine brachytherapy for uveal melanoma. Can J Ophthalmol. 2011;46:158–63.
27. Moore R. Choroidal sarcoma treated by the intraocular insertion of radon seeds. Br J Ophthalmol. 1930;14:145e156.

Part VI

Intraluminal

Intraluminal Brachytherapy for Endobronchial Cancer

20

Yoshihito Nomoto

Abstract

Endobronchial brachytherapy can be used with curative or palliative intent in patients with lung cancer. However, the radiation dose and fraction and the setting of the reference dose point differ according to the intent of treatment. When used with palliative intent, endobronchial brachytherapy is effective for removal of endobronchial obstruction and is recognized as a useful treatment for rapid improvement of clinical status. However, for a relatively small tumor that is limited to the bronchial lumen, endobronchial brachytherapy can be used with curative intent to eradicate the tumor. Given that there have been many reports on palliative endobronchial brachytherapy and a guideline has already been published, this chapter focuses on the indications for which this treatment can be used with curative intent.

Keywords

Lung cancer · Endobronchial brachytherapy · Curative intent · Reference dose point · Applicator

20.1 Introduction

Lung cancer is a major health problem and a leading cause of cancer mortality worldwide. Many patients with lung cancer have advanced disease at diagnosis and are not candidates for surgery. Such patients often suffer with symptoms of airway obstruction, including cough and dyspnea. Endobronchial brachytherapy plays an important role in the palliative treatment of obstructive symptoms. Removal of

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bronchial obstruction helps to improve the patient's clinical status. In the palliative setting, there have been many reports demonstrating the efficacy of endobronchial brachytherapy [1–7], and the American Brachytherapy Society (ABS) has published a guideline with recommendations for the radiation dose and fractionation [8]. However, there are relatively few reports on curative intent endobronchial brachytherapy, and the ABS guideline generally recommends that radical endobronchial brachytherapy (alone or as a boost) should be used within the confines of clinical trials. However, there are reports of an excellent treatment effect when endobronchial brachytherapy is in patients with superficial centrally located endobronchial tumors. For example, Saito et al. [9] reported impressive results of curative endobronchial brachytherapy using a low-dose-rate Ir-192 source.

Endobronchial brachytherapy for curative treatment of an endobronchial tumor needs to be compared with other available therapeutic modalities, such as stereotactic body radiotherapy or photodynamic therapy. Unlike with stereotactic body radiotherapy, movement of the clinical target volume during respiration does not need to be taken into account when using brachytherapy. Further, the safety of stereotactic body radiotherapy when used to treat centrally located bronchial tumors has not been confirmed. Photodynamic therapy has been demonstrated to have an excellent therapeutic effect in patients with centrally located early-stage lung cancer and tumor invasion limited to a small area (≤1 cm) [10], but the local control rate decreased when the tumor size exceeded 1 cm. In addition, the indication for photodynamic therapy is limited to patients in whom the tumor does not infiltrate deeper than the submucosal layer.

The beneficial outcomes of palliative endobronchial brachytherapy have been widely described, so the focus of this chapter is on the use of endobronchial brachytherapy with curative intent.

20.2 Indications for Curative Endobronchial Brachytherapy

It is recognized that endobronchial brachytherapy achieves good results in patients with centrally located superficial tumors without extension to the outside of the bronchial wall. Such cases are identified on bronchoscopic examination for hemoptysis in the absence of evidence of a tumor on imaging studies and on bronchoscopic follow-up after surgery for lung cancer. Other candidates for endobronchial brachytherapy are patients who have undergone surgery for lung cancer in whom pathologic evidence of residual tumor is found at the anastomotic site. In most such cases, the tumor is limited to the bronchial wall. An endobronchial tumor without extension beyond the bronchial wall is a good indication for endobronchial brachytherapy in terms of dose distribution.

20.3 Need for an Applicator

When using endobronchial brachytherapy, especially with curative intent, it is important to use an applicator to centralize the radioactive source in the bronchial lumen. Otherwise, the source-delivering catheter is located on one side of the lumen,

and this eccentric position of the catheter might result in inappropriate distribution of the dose to the bronchial mucosa. An uneven dose distribution means that certain areas in the bronchial mucosa receive an excessive dose, which leads to bronchial necrosis. The use of an applicator is not necessary for palliative endobronchial brachytherapy because the bronchus lumen is narrow and irregular by a tumor but is necessary when this treatment modality is used with curative intent because of the need of even dose distribution for the bronchial lumen and the expectation of longer patient survival.

To prevent eccentric positioning of the catheter, we developed an applicator in 1997 that has two "wings" to centralize the radioactive source in the bronchial lumen [11] (Fig. 20.1a, b). This applicator can hold the source-delivering catheter because the wings open according to the bronchial diameter (Fig. 20.1c) and the reference dose point can be set accordingly. The source-centralizing applicator is necessary for curative endobronchial brachytherapy to avoid eccentric distribution

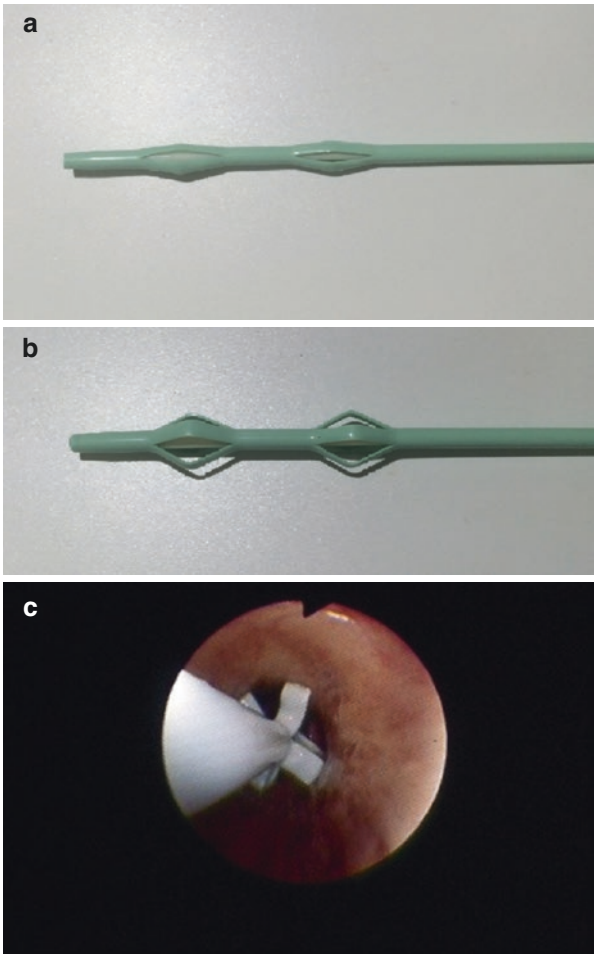

Fig. 20.1 (**a**) Closed wing state at the time of insertion. (**b**) Open wing state at the tumor site. (**c**) Source-centralizing applicator positioned in the bronchial lumen

of the radiation dose and to protect the mucosal membrane of the bronchus from high-dose irradiation, as well as to set the reference dose point according to the bronchial diameter.

20.4 Radiation Dose and Fractionation

In many reports on curative endobronchial brachytherapy, the fraction size was 5–7 Gy (Table 20.1). Although there are still no internationally recognized recommendations for endobronchial brachytherapy with curative intent, the present Japanese guideline for curative endobronchial brachytherapy recommends a radiation schedule consisting of 40 Gy of external irradiation and 18 Gy in three fractions of brachytherapy. The fraction size of 6 Gy in this guideline is based on a study by Saito et al. [9], who reported that a combination of external radiotherapy at 40 Gy and low-dose-rate endobronchial brachytherapy at 25 Gy achieved excellent outcomes in patients with centrally located endobronchial cancer. The treatment schedule in the Japanese guideline was designed in the same manner, and the recommended endobronchial brachytherapy dose is comparable with conversion of low-dose-rate brachytherapy to high-dose-rate brachytherapy.

The aim of external irradiation prior to brachytherapy is to reduce the tumor size and to obtain a uniform distribution of the dose to the bronchial wall. It is advantageous to have a smaller target volume and adequately encompass the residual disease within the high-dose field of endobronchial brachytherapy after external beam radiotherapy. However, for a patient with limited respiratory function, external beam irradiation might be omitted to preserve pulmonary function. In a study by Hennequin et al. [13], endobronchial brachytherapy consisting of six fractions of 5 Gy or 7 Gy achieved a local control rate of 52% and a 5-year overall survival rate of 24%.

20.5 Reference Dose Point

In most studies of endobronchial brachytherapy, the reference dose point was set to 10 mm from the source axis, especially when this treatment was used with palliative intent. In this setting, the actual radiation dose to the bronchial mucosa

Table 20.1 Fraction size and Reference dose points

Author	Year	Fraction size (Gy)	Reference dose points (mm)
Perol et al. [12]	1997	7	10
Hennequin et al. [13]	1998	5 or 7	10
Guilcher et al. [14]	2011	5, 6, 7	10
Rochet et al. [15]	2014	5 ~ 7	10
Kawamura et al. [16]	2012	5	10, 7, 5, 3
Hosni et al. [17]	2016	8 or 5	10, 7, 5
Nomoto et al. [18]	2017	6	7, 5

might be higher than the prescription dose because the radius of the main bronchus is 7–8 mm or smaller on the distal side of the bronchial tree. This situation is thought to cause bronchial necrosis and leads to massive hemoptysis. To prevent overdosing of the bronchial mucosa, it is recommended that the reference points for curative endobronchial brachytherapy be set according to the anatomic bronchial diameter. Saito et al. [9] reported that the reference dose point was 9 mm from the source axis at the trachea, 7 mm at the main bronchus, 5 mm at the lobe bronchus, and 3 mm at the segmental bronchus. In the reports published by Kawamura et al. [16] and Hosni et al. [17], who used high-dose-rate Ir-192, the reference dose point was 10 mm at the trachea, and the other points were the same as those in the report by Saito et al. [9]. At our institution, we obtain computed tomography (CT) scans at every session and measure the distance between the source axis and the bronchial wall surface on the CT image. The reference dose points are set according to the bronchial diameter at the bronchial site of irradiation.

20.6 Brachytherapy Procedure

Endobronchial brachytherapy includes bronchoscopy, so it should be performed in cooperation with a pulmonologist. The endobronchial applicator (Create Medic Co. Ltd., Japan) has two "wings" on the tip side of the applicator. The first step in the application procedure is to insert the source-delivering catheter via the operating channel of a bronchoscope with a nasal approach. When the source-delivering catheter reaches the treatment position, the bronchoscope is removed, leaving behind the source-delivering catheter. After retracting the bronchoscope, the endobronchial applicator is inserted under fluoro-roentgenographic guidance with the wings closed and overlaying the source-delivering catheter. When the applicator reaches the treatment position, the two wings open (Fig. 20.2). The "wings" are self-expandable and adjustable according to the diameter of the bronchial lumen. The applicator is adjusted to the optimal position such that the tumor is located between the two wings (Fig. 20.3), and the position is confirmed by bronchoscopy via an oral approach. After placement of the applicator, CT scans are obtained at every treatment session to confirm the applicator's position and to measure the distance between the source axis and the bronchial wall (Fig. 20.4).

Brachytherapy is performed with a fractional dose of 5 Gy or 6 Gy using a high-dose-rate Ir-192 after-loading machine. Generally, three fractions of brachytherapy are performed once per week in combination with 40 Gy of external beam irradiation. The reference dose points vary from patient to patient depending on the bronchial diameter. The distance from the source axis to the bronchial wall is measured on the planning CT image. When the irradiation length is long, multiple dose prescription points are set, for example, 7 mm on the central side and 5 mm on the peripheral side (Fig. 20.5). The irradiation length is defined according to the length of the tumor with 2 cm proximal and distal margins.

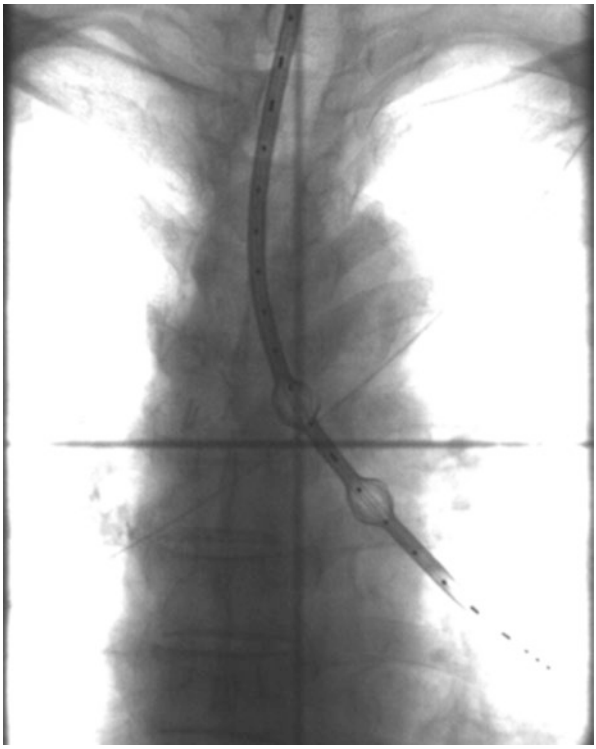

Fig. 20.2 Insertion of the applicator. The wings are self-expandable and adjustable according to the diameter of the bronchial lumen

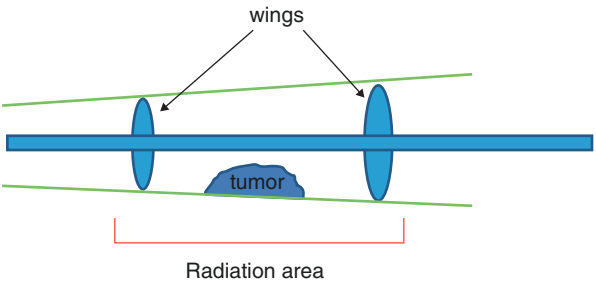

Fig. 20.3 The tumor is located between the two wings. Measurement of the distance between the source axis and the bronchial wall on a computed tomographic image

At every session, dose-volume histograms should be examined for the bronchial wall and other organs at risk using the treatment planning system (Fig. 20.6a, b). Murakami et al. [19] reported that a D2cc >85 Gy in EQD2 for the trachea and main bronchus was a strong risk factor for severe late respiratory complications after

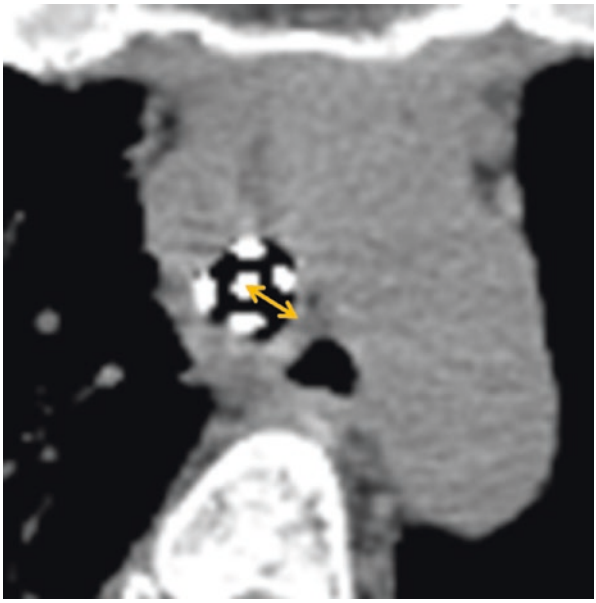

Fig. 20.4 Measurement of the distance between the source axis and the bronchial wall on a computed tomographic image. The reference dose points are adjusted according to the bronchial diameter

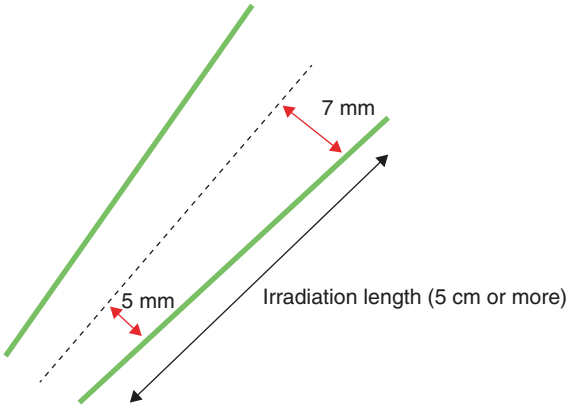

Fig. 20.5 (**a**) The reference dose points are adjusted according to the bronchial diameter. Dose distribution seen on the treatment planning system. (**b**) Reference dose points vary according to the site in the bronchus

endobronchial brachytherapy. In our study, the mean values for D0.1 cm^3, D1cm^3, and D2cm^3 to the bronchial wall were 155.2% (118.5%–202.0%), 105.4% (77.4%–119.2%), and 83.6% (65.5%–104.3%), respectively, confirming that there was no hyper-dose area or hot spot in the bronchial wall.

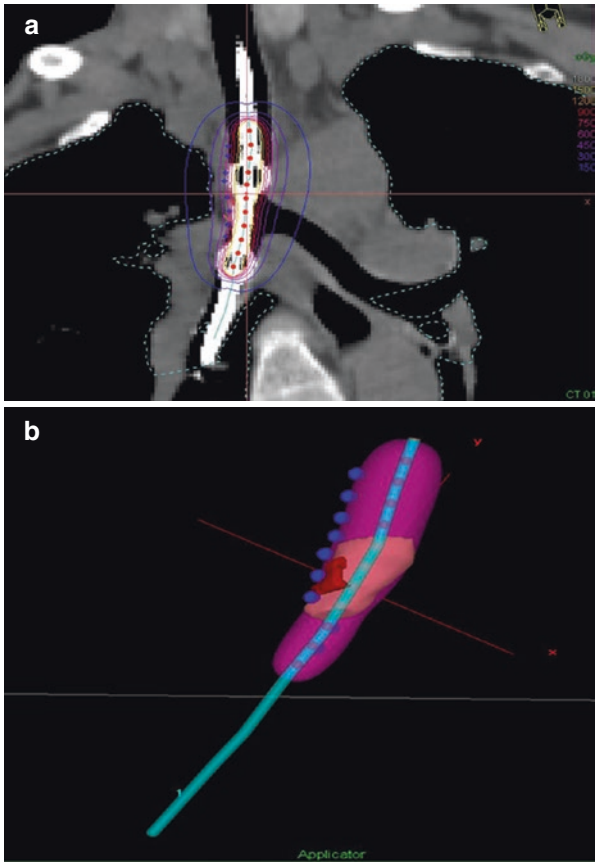

Fig. 20.6 (**a**) Dose distribution seen on the treatment planning system. (**b**) Reference dose points vary according to the site in the bronchus

20.7 Treatment Outcomes and Complications

The treatment outcomes and complications in several studies of curative endobronchial brachytherapy are shown in Table 20.2 [12–15, 18]. In these studies, the overall survival rate was in the range of 47.4%–92.3%, and the local control rate was 56%–100%.

Hemoptysis and severe bronchitis are known to be the major toxicities of endobronchial brachytherapy. Although hemoptysis likely relates to tumor recurrence, it has been suggested that its presence after endobronchial brachytherapy is a complication of the treatment itself. Such complications may be partly explained by the placement of the radioactive source-delivering catheter at eccentric locations in the bronchial lumen, which can lead to localized hot spots on the mucous membrane of the bronchus. An applicator was used to protect the bronchial mucosa from high-dose irradiation in the reports of Kawamura et al. [16], Hosni et al. [17], and Nomoto et al. [18]. In most studies of endobronchial brachytherapy, the reference dose point was set to 10 mm from the source axis regardless of the site of the bronchial tree.

Table 20.2 Treatment outcome and complication

Authors	Cases (n)	Overall survival rate	Local control rate	Hemoptysis
Perol et al. [12]	19	58%, 2 years	75%, 2 years	13.3%
Hennequin et al. [13]	149	47.4%, 3 years	60.3%, 3 years	7.4%
Guilcher et al. [14]	226	57%, 2 years	68%, 2 years	6.6%
Rochet et al. [15]	35	61%, 2 years	56%, 5 years	8.6%
Kawamura et al. [16]	16	92.3%, 2 years	86.2%, 2 years	0%
Hosni et al. [17]	10	67%, 2 years	89%, 2 years	0%
Nomoto et al. [18]	15	79%, 3 years	100%, 3 years	0%

In this setting, the actual radiation dose to the bronchial mucosa might be higher than the prescription dose because the bronchial radius is 7–8 mm or smaller at the distal side of the main bronchus. There was no mention of hemoptysis in the reports by Kawamura et al. [16], Hosni et al. [17], and Nomoto et al. [18]. Varying the reference dose points according to bronchial diameter might be one of the reasons for the lesser toxicity in those studies.

References

1. Mehta M, Shahabi S, Jarjour N, Steinmetz M, Kubsad S. Effect of endobronchial radiation therapy on malignant bronchial obstruction. Chest. 1990;97:662–5.
2. de Aquino Gorayeb MM, Gregorio MG, de Oliveira EQ, Aisen S, Carvalho Hde A. High-dose-rate brachytherapy in symptom palliation due to malignant endobronchial obstruction: a quantitative assessment. Brachytherapy. 2013;12:471–8.
3. Skowronek J, Kubaszewska M, Kanikowski M, Chichel A, Mlynarczyk W. HDR endobronchial brachytherapy (HDRBT) in the management of advanced lung cancer–comparison of two different dose schedules. Radiother Oncol. 2009;93:436–40.
4. Zorlu AF, Selek U, Emri S, Gurkaynak M, Akyol FH. Second line palliative endobronchial radiotherapy with HDR Ir 192 in recurrent lung carcinoma. Yonsei Med J. 2008;49(4):620.
5. Kubaszewska M, Skowronek J, Chichel A, Kanikowski M. The use of high dose rate endobronchial brachytherapy to palliate symptomatic recurrence of previously irriadiated lung cancer. Neoplasma. 2008;55:239–45.
6. Kelly JF, Delclos ME, Morice RC, Huaringa A, Allen PK, Komaki R. High-dose-rate endobronchial brachytherapy effectively palliates symptoms due to airway tumors: the 10-year M. D. Anderson cancer center experience. Int J Radiat Oncol Biol Phys. 2000;48:697–702.
7. Macha HN, Wahlers B, Reichle C, von Zwehl D. Endobronchial radiation therapy for obstructing malignancies: ten years' experience with iridium-192 high-dose radiation brachytherapy afterloading technique in 365 patients. Lung. 1995;173:271–80.
8. Hepel JT, Arthur D, Shaitelman S, Polgar C, Todor D, Zoberi I, et al. American brachytherapy society consensus report for accelerated partial breast irradiation using interstitial multicatheter brachytherapy. Brachytherapy. 2017;16:919–28.
9. Saito M, Yokoyama A, Kurita Y, Uematsu T, Tsukada H, Yamanoi T. Treatment of roentgenographically occult endobronchial carcinoma with external beam radiotherapy and intraluminal low-dose-rate brachytherapy: second report. Int J Radiat Oncol Biol Phys. 2000;47:673–80.
10. Furuse K, Fukuoka M, Kato H, Horai T, Kubota K, Kodama N, et al. A prospective phase II study on photodynamic therapy with photofrin II for centrally located early-stage lung cancer. The Japan lung cancer photodynamic therapy study group. J Clin Oncol. 1993;11:1852–7.

11. Nomoto Y, Shouji K, Toyota S, Sasaoka M, Murashima S, Ooi M, et al. High dose rate endobronchial brachytherapy using a new applicator. Radiother Oncol. 1997;45:33–7.
12. Perol M, Caliandro R, Pommier P, Malet C, Montbarbon X, Carrie C, et al. Curative irradiation of limited endobronchial carcinomas with high-dose rate brachytherapy. Results of a pilot study. Chest. 1997;111:1417–23.
13. Hennequin C, Bleichner O, Tredaniel J, Quero L, Sergent G, Zalcman G, et al. Long-term results of endobronchial brachytherapy: a curative treatment? Int J Radiat Oncol Biol Phys. 2007;67:425–30.
14. Aumont-le Guilcher M, Prevost B, Sunyach MP, Peiffert D, Maingon P, Thomas L, et al. High-dose-rate brachytherapy for non-small-cell lung carcinoma: a retrospective study of 226 patients. Int J Radiat Oncol Biol Phys. 2011;79:1112–6.
15. Rochet N, Hauswald H, Stoiber EM, Hensley FW, Becker HD, Debus J, et al. Primary radiotherapy with endobronchial high-dose-rate brachytherapy boost for inoperable lung cancer: long-term results. Tumori. 2013;99:183–90.
16. Kawamura H, Ebara T, Katoh H, Tamaki T, Ishikawa H, Sakurai H, et al. Long-term results of curative intraluminal high dose rate brachytherapy for endobronchial carcinoma. Radiat Oncol. 2012;7:112.
17. Hosni A, Bezjak A, Rink A, Czarnecka K, McPartlin A, Patterson S, et al. High dose rate brachytherapy as a treatment option in endobronchial tumors. Lung Cancer Int. 2016;2016:3086148.
18. Nomoto Y, Ii N, Murashima S, Yamashita Y, Ochiai S, Takada A, et al. Endobronchial brachytherapy with curative intent: the impact of reference points setting according to the bronchial diameter. J Radiat Res. 2017;58(6):849–53. (in press)
19. Murakami N, Kobayashi K, Nakamura S, Wakita A, Okamoto H, Tsuchida K, et al. A total EQD2 greater than 85 Gy for trachea and main bronchus D2cc being associated with severe late complications after definitive endobronchial brachytherapy. J Contemp Brachytherapy. 2015;7:363–8.

Brachytherapy for Esophageal Cancer: Optimum Dose and Indications in the Modern Era

21

Atsunori Yorozu and Takushi Dokiya

Abstract

Endoluminal brachytherapy (BT) is an effective means of delivering high doses to esophageal lesions while delivering much lower doses to surrounding tissues. In the 1980s and 1990s, esophageal BT was a common treatment option. However, some influential studies suggested that dose escalation with BT resulted in significant and devastating toxicity. The cause for this relatively high rate of severe complications could be the high total biological radiation dose to the mucosa. In a wide esophageal lumen, larger applicators should be used, whereas applicators with small diameters are limited to obstructing lesions. The important dosimetry and esophageal BT emphasizes lumen diameter, applicator diameter, wall thickness, dose at 5 mm from the applicator surface into the esophageal wall, and dose at the applicator surface. Different treatment geometries can achieve positive oncologic and palliative outcomes without excessive toxicity. To optimize BT, it is beneficial to perform 3D CT-based treatment planning, especially in curative settings. Modern BT could play a role in the management of locally advanced, recurrent, or superficial cancer in patients without surgical options. Herein, we recommend some optimum regimens for superficial and advanced tumors based on published literature and our long-term follow-up data over 20 years.

Keywords

Endoluminal · Brachytherapy · Esophagus · Superficial · Complication Applicator · Balloon · Mucosa · Optimum dose

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21.1 Introduction

Current treatment options for localized esophageal cancer are chemoradiotherapy or a trimodality combining chemoradiotherapy followed by surgery. Historically, definitive radiotherapy was a major option. Endoluminal brachytherapy (BT) is an effective means of delivering high doses to esophageal lesions while delivering much lower doses to surrounding tissues, such as the lung, heart, and spinal cord. For decades, Japan has been a leader in the implementation of endoluminal BT for esophageal cancer especially as a curative treatment. In the 1980s and 1990s, esophageal brachytherapy was a common treatment option in Japan. In 1980, Hishikawa performed endoluminal high-dose-rate (HDR) BT for the first time and published many highly regarded papers [1]. Hareyama reported excellent results in 277 patients treated with low-dose-rate (LDR) brachytherapy (BT) combined with external beam radiotherapy (EBRT) between 1974 and 1988 [2]. Dokiya developed a balloon-type applicator for esophageal HDR BT in 1989, which has been the standard applicator in Japan since then [3]. We showed a dose-response relationship in esophageal toxicity after HDR BT combined with EBRT and suggested some effects of concurrent chemoradiotherapy [4]. Okawa conducted a multi-institutional randomized trial of EBRT with or without BT for esophageal cancer in Japan [5]. In patients with a tumor length of 5 cm or less, the cause-specific survival rate was significantly higher in the brachytherapy boost group. Thereafter, clinical outcomes of BT for superficial esophageal cancer were reported from several institutions in Japan [6–10]. Unexpectedly, treatment-related deaths from late esophageal ulceration were reported in some patients with superficial tumors treated with a BT boost. An influential study suggested that dose escalation with BT resulted in significant toxicity with no survival benefit [11]. Thus, the use of esophageal BT has gradually declined and has been abandoned in some institutions in Japan [12]. However, several studies suggest BT may play a role in the management of locally advanced, recurrent, or early-stage cancer in patients without surgical options [13]. Moreover, there is evidence that different treatment geometries can achieve positive oncologic and palliative outcomes without excessive toxicity [14, 15]. In addition to dosimetry, the procedure emphasizes lumen diameter, applicator diameter, wall thickness, dose at 5 mm from the applicator/lumen surface into the esophageal wall, and dose at the applicator/lumen surface [16]. We had 400 cases that experienced esophageal BT and managed the long-term morbidity. Our long-term follow-up data over 20 years may clarify the effect of esophageal BT to determine the optimal BT regimen. We will highlight the clinical results of superficial tumors.

21.2 Long-Term Clinical Outcomes at Tokyo Medical Center

21.2.1 Materials and Methods

21.2.1.1 Study Patients

The study population comprised 364 patients with histologically confirmed esophageal cancer treated with BT and EBRT at Tokyo Medical Center between 1988

and 2008. Our retrospective analysis used information from patient medical records and databases. Most patients (80%) were deemed medically unfit due to frailty and/or comorbidity, and 45% had extensive and unresectable disease. All patients were staged according to the classification of malignant tumors of the UICC 1987 staging system. For the toxicity analysis, we included 22 patients who were treated with salvage BT for local disease.

21.2.1.2 Treatment

All patients received EBRT followed by an HDR BT boost. Until 2000, patients receiving EBRT underwent 2D radiation treatment planning. Since 2001, computed tomography scans have been carried out routinely. Margins of 2 cm laterally and 3–5 cm craniocaudally were applied to create the treatment field. EBRT was delivered using a 6 or 10 MV photon beam using anteroposterior and oblique fields prescribed to the midplane dose. A dose of 40–60 Gy was given, and the median dose was 50 Gy. The daily fractional dose was 180 or 200 Gy given 5 days a week.

HDR BT was typically given 2 weeks after the last EBRT treatment. We localized the tumor with a mouthful of contrast medium. For small or superficial tumors, we localized by verifying with metal clips using endoscopy. A 1–2 cm margin craniocaudally was used to define the total treatment volume. An esophageal applicator was placed through the mouth and positioned under slight sedation. A plastic applicator, 7 mm in diameter, was used for 95 patients before 1989, and the double-balloon applicator we developed was used after 1990. The inner balloon was used for centering and the outer balloon for adhering to the esophageal mucosa by injecting water and contrast medium. The length of the outer balloon was 10–20 cm. In most cases, the balloons were inflated to a diameter of 15 mm with water. For dose specification, we typically used a point 12.5 mm from the mid-dwell position, which was originally defined as 5 mm beyond the balloon surface. The median prescribed dose per fraction was 4 Gy (2–6 Gy). The application was twice per week, one to five times in total. The median BT dose was 16 Gy in 4 fractions, ranging from 4 to 24 Gy in total. We performed a CT scan after treatment planning and measured the dose at the balloon surface or esophageal mucosa of each case after 1996. A recent dose prescription is 50 Gy via EBRT followed by a BT of 12 Gy in 2 fractions at the mucosa, and the surface of the balloon applicator diameter is 20 mm for superficial tumors, i.e., 10 mm from the source axis.

A total of 116 patients received chemotherapy concurrently with EBRT after 1990. Fluorouracil (600 mg/m^2 of body surface per day) was given for the first 4 days of weeks 1 and 4, and cisplatin (60 mg/m^2) was given on day 1 of each course.

21.2.1.3 Follow-Up

The study end points were overall survival and late toxicities. Most patients were assessed for recurrence symptomatically, radiologically, and endoscopically, at intervals of 3 months for 2 years at minimum. Subsequent follow-up was individualized. Radiotherapy toxicity was graded using the RTOG toxicity scoring criteria. The survival curve was calculated from the start of radiotherapy using the

Kaplan-Meier method. Statistical analysis was performed using a chi-square test, log-rank test, and Cox regression analysis.

21.2.2 Results

21.2.2.1 Survival

Patient and disease characteristics are summarized in Table 21.1. At the time of this analysis, 31 patients (8.5%) were still alive. The median follow-up was 9 years and 4 months. The causes of death were esophageal cancer (77.8%), intercurrent disease (17.1%), treatment-related toxicity (4.2%), and unknown (0.9%).

The median overall survival of treated patients was 13.7 months. The 2-, 5-, 10-, and 15-year survival rates were 31.5%, 17.4%, 9.0%, and 5.5%, respectively. The 2-, 5-, 10-, and 15-year disease-specific survival rates were 34.4%, 24.2%, 15.4%, and 11.4%, respectively. For 22 patients treated with salvage BT for locally recurrent tumors, the median survival was 7.7 months, and the 2- and 5-year overall survival rates were 13.6% and 4.5%, respectively (Fig. 21.1).

Selected prognostic variables were analyzed. Overall survival was significantly associated with age, stage, tumor length, performance status, applicator types, treatment periods, and total dose. Patients with stage I disease had a 5-year survival rate of 53.2% compared with 21.0%, 3.5%, and 1.9% for patients with stage II, III, and IV diseases, respectively ($p < 0.001$), in Fig. 21.1. In the univariate analysis, patients receiving a total dose of 66 Gy or less (sum of a prescribed dose of BT and EBRT) had a longer median survival compared with patients receiving a total dose higher than 66 Gy ($p < 0.001$). In the multivariate analysis, stage, tumor length, performance status, and chemotherapy were significant variables.

21.2.2.2 Treatment Failure and Cause of Death

Clinically, local recurrence or persistence occurred in 56.6% (206/364) of patients. Repeated biopsy confirmed local control in 38.5% (140/364) of patients. The main causes of death were distant metastases (39.8%) and local tumor progression (33.8%), followed by intercurrent disease (15.6%). Treatment-related death was seen in 14 patients (3.8%). Fistula and massive bleeding including tumor progression occurred in 29 patients (8.0%) and 19 patients (5.8%) of the whole cohort, respectively.

21.2.2.3 Late Toxicity of the Esophagus

We found radiation ulcers in 51 patients (14.0%) and strictures in 26 patients (7.1%). The interval from completion of treatment to esophageal ulcer ranged from 1 to 15 months with a median of 7 months. Esophageal ulcers were categorized as grade 2 in 19 patients (5.2%), grade 3 in 9 (2.5%), grade 4 in 2 (0.5%), and grade 5 in 7 (1.9%). Esophageal strictures were categorized as grade 2 in 11 patients (11.0%), grade 3 in 5 (1.4%), and grade 4 in 1 (0.3%). All benign esophageal strictures occurred from esophageal ulceration.

Table 21.1 Patient and disease characteristics and analysis of prognostic factors for survival

Characteristics		Number	%	Median overall survival (months)	Univariate analysis p-value	Multivariate analysis p-value	Exp(B) 95% CI
Gender	Males	281	82.2%	13.8	0.249		
	Females	61	17.8%	15.2			
Age	Median, range	71 years (39–92)					
	<=70 years	164	48.0%	14.6	0.027	0.201	
	>70 years	178	52.0%	15.2			
Stage	1	62	18.1%	64.1	0.000	0.000	Ref
	2	111	32.5%	20.4		0.000	0.691 (0.498–0.960)
	3	115	33.6%	10.0		0.000	0.331 (0.229–0.479)
	4	54	15.8%	6.8		0.028	0.158 (0.097–0.256)
Localization	Upper	65	18.0%	13.7	0.891		
	Middle	216	63.1%	14.1			
	Lower	61	17.8%	13.8			
Histology	Squamous cell	331	96.8%	13.8	0.553		
	Non-squamous cell	11	3.2%	21.8			
Tumor length	Median, range	6 cm (1–18)					
	5 cm>=	143	41.8%	32.3	0.000	0.011	Ref
	>5 cm	199	58.2%	10.0			0.684 (0.511–0.915)
Performance status	0–1	158	46.2%	24.3	0.000	0.008	Ref
	2–4	184	53.8%	10.0			0.716 (0.560–0.916)

(continued)

Table 21.1 (continued)

Characteristics		Number	%	Median overall survival (months)	Univariate analysis p-value	Multivariate analysis p-value	Exp(B) 95% CI
Chemotherapy	No	230	67.3%	12.8	0.061	0.000	Ref
	Yes	112	32.7%	16.0			1.844 (1.403–2.422)
Applicator	Narrow, 7 mm diameter	86	25.1%	9.3	0.002	0.712	
	Double-balloon type	256	74.9%	14.4			
Treatment periods	–1993	158	46.2%	10.2	0.000	0.243	
	1994–	184	53.8%	15.3			
Total dose	<=66 Gy	112	32.7%	16.0	0.003	0.066	
	>66 Gy	230	67.3%	11.6			
Response of EBRT	No regression	82	24.0%	7.4	0.000	0.000	0.470 (0.352–0.628)
	Tumor regression	260	76.0%	18.3			Ref

EBRT external beam radiotherapy

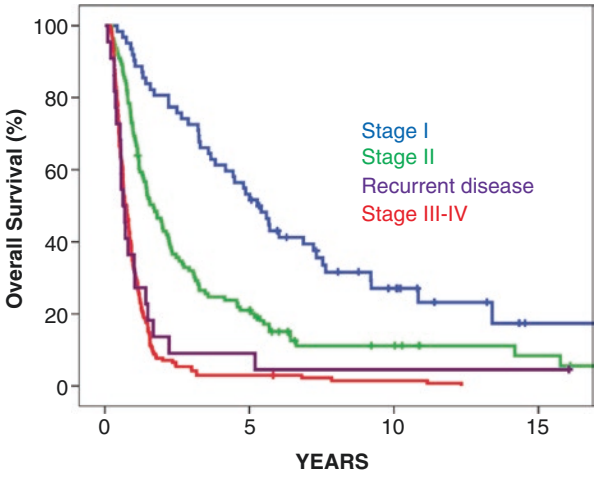

Fig. 21.1 Overall survival curves according to clinical stages for all 364 patients

Table 21.2 Toxicity according to doses for superficial tumors ($n = 62$)

Total dose of BT and EBRT	*n*	Ulcer grade 2+	Ulcer grade 3+	Ulcer grade 4+	Stricture grade 2+
<66 Gy	25	1 (4%)	0	0	0
66 Gy	20	2 (10%)	0	0	0
>66 Gy	17	6(35.3%)	3(17.6%)	2 (11.8%)	3 (17.6%)
p-value		0.014	0.015	0.065	0.015

BT dose	*n*	Ulcer	Ulcer grade 2+	Local recurrence
<16 Gy	20	1 (5.0%)	1 (5.0%)	5 (25.0%)
>=16 Gy	42	14 (33.3%)	8 (19.0%)	13(31.0%)
p-value		$p = 0.012$	$p = 0.138$	$p = 0.433$

BT brachytherapy, *EBRT* external beam radiotherapy

21.2.2.4 Outcomes for Superficial Tumors

A total of 62 patients had stage I (UICC T1N0M0) cancer. The 5- and 10-year disease-specific survival rates were 75.5% and 48.1%, respectively. The 5- and 10-year local control rates were 70.2% and 54.5%, respectively. Nine patients had mucosal lesions and 53 had submucosal lesions. The 5-year overall survival rate was 66.7% for mucosal cases and 50.9% for submucosal cases ($p = 0.033$). The 5-year disease-specific survival rate was 85.7% for mucosal cases and 73.5% for submucosal cases ($p = 0.066$). There was no significant difference in the local control rate between mucosal cases and submucosal cases. The local control rate was not dependent on total doses or BT doses. In regard to late toxicity, esophageal ulcer occurred in 15 patients (24.2%) including 6 in grade 2 (9.7%), 1 in grade 3 (1.6%), and 2 in grade 5 (3.2%) with massive bleeding leading to death. Esophageal strictures occurred in 4 patients (6.5%): 1 in grade 1 (1.6%), 2 in grade 2 (3.2%), and 1 in grade 3 (1.6%). We examined the relationship between dose and ulceration (Table 21.2). Esophageal ulcers of grades 2+ or 3+ were significantly higher in patients receiving total doses

higher than 66 Gy compared with patients receiving lesser doses. Esophageal ulcers occurred significantly more in patients receiving BT doses of 16 Gy or higher compared with patients receiving lesser doses.

21.3 Discussion

21.3.1 Overview

This study showed the long-term outcomes of a BT boost-based approach in a population unsuited to surgical treatment. To our knowledge, this is the largest and longest series. The 5- and 10-year overall survival rates were 17.4% and 9.0%, respectively, for the whole cohort including early to advanced disease. Our results compare favorably with the survival results from a published series delivering a combination treatment [1–15]. Many prospective clinical trials including meta-analyses support the use of BT for symptomatic patients with advanced incurable cancer as palliative setting [14, 17, 18]. In contrast, as curative setting, the use of BT as boost has been evaluated in several retrospective studies providing data on feasibility, tumor control, and toxicity with some methodological limitations, such as wide variations of techniques, doses, and fractionation [1–16]. In 1999, Okawa reported outcomes of a multi-institutional randomized trial: 103 patients were randomly assigned to receive BT or EBRT to deliver a 10 Gy boost to their primary tumor, following EBRT to a total dose of 60 Gy. The overall survival rate was 20.3% at 5 years for all patients [5]. The cause-specific survival was 27% in the EBRT alone group and 38% in the BT boost group (p = 0.385). There was no survival benefit overall; however, in a subgroup of patients with small tumors less than 5 cm in length, cause-specific survival at 5 years was 64% in the BT boost group as opposed to 31.5% in the EBRT alone group (p = 0.025). At present, we should select good candidates for BT carefully because chemoradiotherapy with or without surgery is a standard treatment.

21.3.2 Applicators

There are several variations in the applicators [16]. The common applicators are single catheters. The diameters of these cylindrical applicators vary greatly, up to 20 mm. In a wide esophageal lumen, larger applicators are used preferentially, whereas applicators with small diameters are limited to obstructing lesions. Attention must be paid to irregular contact with the mucosa. To reduce the overdose volume in the esophageal wall in applicators with a large diameter, a smaller tube fitting the inner diameter of the applicator is inserted to center the source carrying a small catheter within the applicator tube. We needed bougie dilatation before BT in 7.1% of patients. As obstructive tumors are sometimes rather rigid in recurrent lesions, it is difficult to dilate the lumen mechanically. If no dilation is possible, an applicator with a small diameter catheter is introduced, and the high dose to the

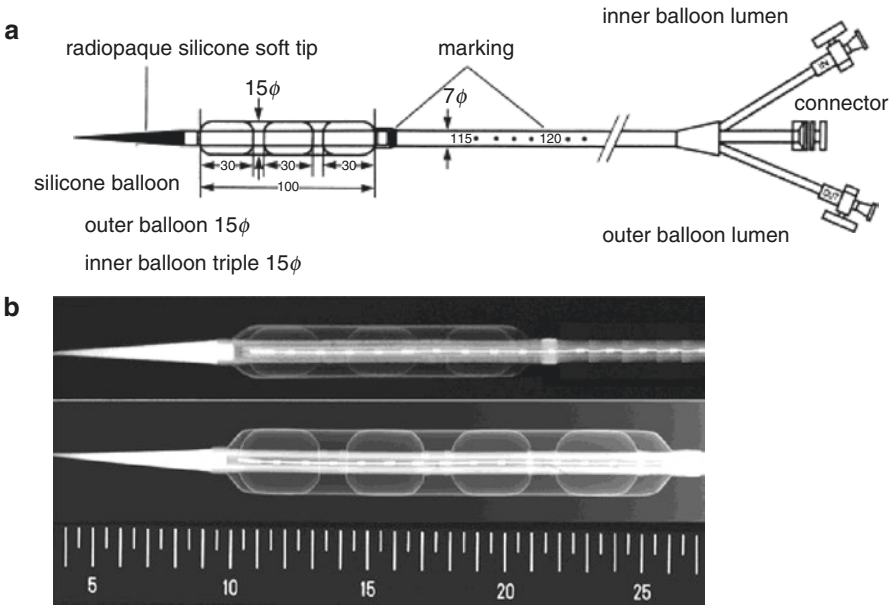

Fig. 21.2 (**a**) Schematic of the Japanese double-balloon applicator. (**b**) Inflated balloon diameters 15 mm and 20 mm

tumor surface and a significant overdose to the mucosa/submucosa are considered in dose prescription. Bougie applicators have been constructed to gradually dilate the esophageal lumen [3]. Dilation by bougies must be carried out with taking care of perforation and bleeding. If there is a wide esophageal lumen, the diameter of even a large diameter applicator (14–16 mm) may not be sufficient to fill the entire lumen. The applicator with the largest diameter should always be used. In certain situations, balloon applicators with double balloon lumens may be used, which allows for a better fit with larger diameters. The balloon can be filled with a dilute contrast medium up to a diameter of 20 mm leading to a large distance (up to 10 mm) between the source and the surface of the balloon for superficial tumors (Fig. 21.2).

21.3.3 Dose Specification and Applicators

Dose escalation with BT boost has a significant potential for esophageal toxicity as well as local control [3]. We found esophageal ulcer of grade 3+ in 4.9% and grade 4+ in 2.4% in 364 patients. In 2000, Gaspar reported a high incidence of fistula formation following a BT boost in 49 patients undergoing chemoradiotherapy in a randomized trial (RTOG 9207) [11]. In the trial, the HDR boost was given at doses of 10–15 Gy in fractions of 5 Gy, following EBRT up to a total dose of 50 Gy. The HDR was delivered with an applicator of 4–6 mm diameter, and dose was specified

at a 1 cm depth. Life-threatening toxicity (grade 4) or treatment-related death (grade 5) occurred in 24% and 10% of cases, respectively. Treatment-related esophageal fistulas occurred in 14% of patients. The development of fistulas was strongly associated with a higher boost dose (15 Gy), a smaller applicator diameter, and chemotherapy being applied concomitantly with the BT boost. The use of narrow catheters leads to a remarkably high dose on the applicator surface, and decentering of thin catheters may result in regions of very high doses directly to the esophageal mucosa. Cause for the relatively high rate of severe complications could be the high total radiation dose to the mucosa and the high biological effective dose (BED) that was given in a high dose fraction. Dokiya invented the double-balloon applicator (inflating outside diameter, 15–20 mm) to solve these issues (Fig. 21.2). The inner balloon is used for centering and the outer balloon for adhering to the esophageal mucosa. The applicator can be expanded to a circle of 18–20 mm diameter for small tumors by injecting appropriate amount of water into the balloons to avoid 150% or higher dose spots in the mucosa. After implementing this applicator, we reported that increasing incidence of esophageal ulcers was related to the prescribed dose in BT, and doses more than 16 Gy lead to a significant risk of ulceration in 124 patients with T1–2 tumors [3]. There were 15 patients (12%) with a fistula or massive bleeding after treatment, of which 11 patients had a local recurrence. Except superficial tumors, many of these complicated fistulas were associated with tumor recurrence or were explained by T4 under staging. ESTRO recommends recording and reporting the dose at 5 mm tissue depth (reference depth) from the lumen/applicator surface (lumen/applicator radius + 5 mm) and at the lumen/applicator surface, indicating the dose gradient in the tumor and the normal tissue and the dose at the lumen/tumor surface [16]. This reporting at 5 mm tissue depth is independent of the prescription strategy chosen (e.g., at 10 mm from the source axis).

21.3.4 Optimum Regimen for Superficial Tumors

In our experiences for superficial tumors, the 5-year survival rate was 53.2% in 62 patients. We found a dose-response relationship between ulceration and total doses or BT doses. In Japanese studies for superficial tumors, several authors reported that severe ulcers commonly encountered when large fractions as high as 5 Gy at 5 mm below the mucosa were given using this balloon-type applicator [6, 9, 12]. Superficial esophageal tumors are different anatomically from advanced cancer, because cancer cells spread in the normal mucosa or submucosa without invasion deep into the muscular layer. Normal tissues and cancer cells mixing up lie in very thin tissue of the esophageal surface. Therefore, we could estimate normal tissue tolerance dose after HDR boost for superficial tumors from several literatures. In Table 21.3, projected mucosal doses and observed toxicity in historic studies are shown. Mucosal doses were reported or calculated with methods proposed by Folkert [15]. Total

Table 21.3 Projected mucosal doses and historic studies and reported toxicity for superficial tumors

Reference	*n*	EBRT dose (Gy) median	Dose prescription of HDR BT	Applicator outer diameter (mm)	Prescription depth from surface of applicator (mm)	Reported mucosal dose (Gy)/fr	Calculated mucosal dose (Gy), central	Total mucosal dose, BED (Gy3)	Grade 2+ toxicity	Grade 3+ toxicity	Grade 4+ toxicity	Fistula	Local control rate	Overall survival
Akagi [6]	35	60	10 Gy/2–5 fr	16/20	5	3.24–8.7	NS	133.7–167.9	20.0%	11.4%	2.9%	0%	75%, 5 years	38%, 5 years
Murakami [10]	60	60	10 Gy/2–5 fr	16/20	5	3.24–8.7	NS	133.7–167.9	18.3%	8.3%	3.3%	5.0%	63%, 5 years	58%, 5 years
Kodaira [12]	27	50	10 Gy/3–5 fr	16/20	5	NS	6.47–9.6	144.6–164	44.4%	25.9%	14.8%	11.1%	84%, 3 years	85%, 3 years
Ishikawa [9]	17	60	10 Gy/2 fr–9 Gy/3 fr	16/20	5	NS	4.8–8.0	137.4–158.7	17.7%	11.8%	5.9%	5.9%	82%, 5 years	81%, 5 years
Nishimura [7]	19	50/56	8 Gy/2 fr–12 Gy/3 fr	20	5	6.5	NS	130.4–145.1	23.1%	0%	0%	0%	85%, 3 years	85%, 3 years
Nemoto [8]	46	56	10 Gy/2 fr–10 Gy/5 fr	20	5	NS	4–8.1	140–153.3	9.0%	0%	0%	0%	NS	60%, 5 years
Maington [19]	25	50	10 Gy/2 fr–15 Gy/3 fr	13	0–5	6.2–8.8	NS	121.4–140.4	8.0%	0%	0%	4%	56%	22%, 3 years
Pasquier [20]	66	60	7 Gy/2 fr	13	0/5	4.41	NS	121.8	18.2%	9.0%	0%	0%	55%, 5 years	36%, 5 years
This study	62	50	8 Gy/2 fr–24 Gy/4 fr	16–20	0–5	5.4–6	NS	119.3–155.3	14.5%	4.8%	3.2%	3.2%	70.2%, 5 years	53%, 5 years

EBRT external beam radiotherapy, *HDR BT* high-dose-rate brachytherapy, *BED* biologically equivalent dose, *NS* not specified

mucosal dose as BED was between 119 and 168 Gy3, late toxicity of grade 2+ from 8% to 44.4%, and grade 4+ from 0% to 11.1%. Wide ranges of mucosal doses and EBRT doses make difficult to define clear threshold of normal tissue tolerance of esophageal mucosa. However, grade 3+ or 4+ toxicity occurred more frequently in the total mucosal doses between 133.7 Gy3 and 167.9 Gy3, compared to doses less than 153.3 Gy3. Akagi showed BED > 134 Gy3 and a fraction size was associated with late complications of grade 2+ [6]. In our study, total doses of 66 Gy or higher and BT dose of 16 Gy or higher were associated with ulceration for superficial tumors, and dose calculations based on sectional CT imaging in 34 in 62 patients lead to a precise assessment of dose in the esophagus. An outside diameter of the balloon applicator to 18–20 mm allowed the delivery of 4 Gy to the prescription depth while limiting the mucosal surfaces to 5–6 Gy (Fig. 21.3). Ishikawa and Akagi recommended 2.5–3 Gy per fraction prescribed at 5 mm below the mucosa after 60 Gy of EBRT. Higher doses between 119 Gy3 and 168 Gy3 at the mucosa could not improve local control or survival in any studies (Table 21.3). From Japanese experiences, smaller fraction sizes of 6 Gy or less at the mucosa should be considered with the aim of lowering late morbidity [6–9, 11]. Overall, we can recommend balloon-type applicators or bougie-type applicators with 16–20 mm diameters, especially for superficial tumors. Consequently, we recommend 12 Gy in 2 fractions or 15 Gy in 3 fractions specified at the applicator surface, i.e., 10 mm from the mid-axis, following 50 Gy of EBRT, equivalent with 119.3 Gy3 or 123.3 Gy3 of total mucosal BED, respectively. Moreover, to optimize BT, we suggest performing 3D CT-based treatment planning; the size and shape of the reference isodose may be changed accordingly in all directions, thus improving the tumor coverage and sparing of close organs at risk.

21.3.5 Modern Indications for Superficial Tumors

Recently, chemoradiotherapy with or without surgery has been a standard treatment, and indications of the BT boost are rather limited in our institution. However, new indications of BT boost are emerging. For instance, a patient with interstitial lung disease unable to receive a full dose of EBRT should be a good candidate of BT boost; a patient with a persistent superficial tumor several months after receiving 60 Gy of EBRT or a patient with the local recurrence as a superficial tumor several years after receiving 50.4 Gy in 28 fractions of EBRT given with concurrent chemotherapy. Some recommended doses are listed in Table 21.4, in which reference dose points at the esophageal mucosa are specified. For patients with locally recurrent, small esophageal cancer after EBRT (median dose 60 Gy), Nonoshita gave HDR BT of 20 Gy with 4 or 5 fractions prescribed at the mucosa with the balloon applicator of 20 mm diameter [21]. No severe late complications were observed with a median survival of 30 months, even between 146.7 Gy3 and 153.3 Gy3. Esophageal tissue takes 6 months or longer following EBRT to recover.

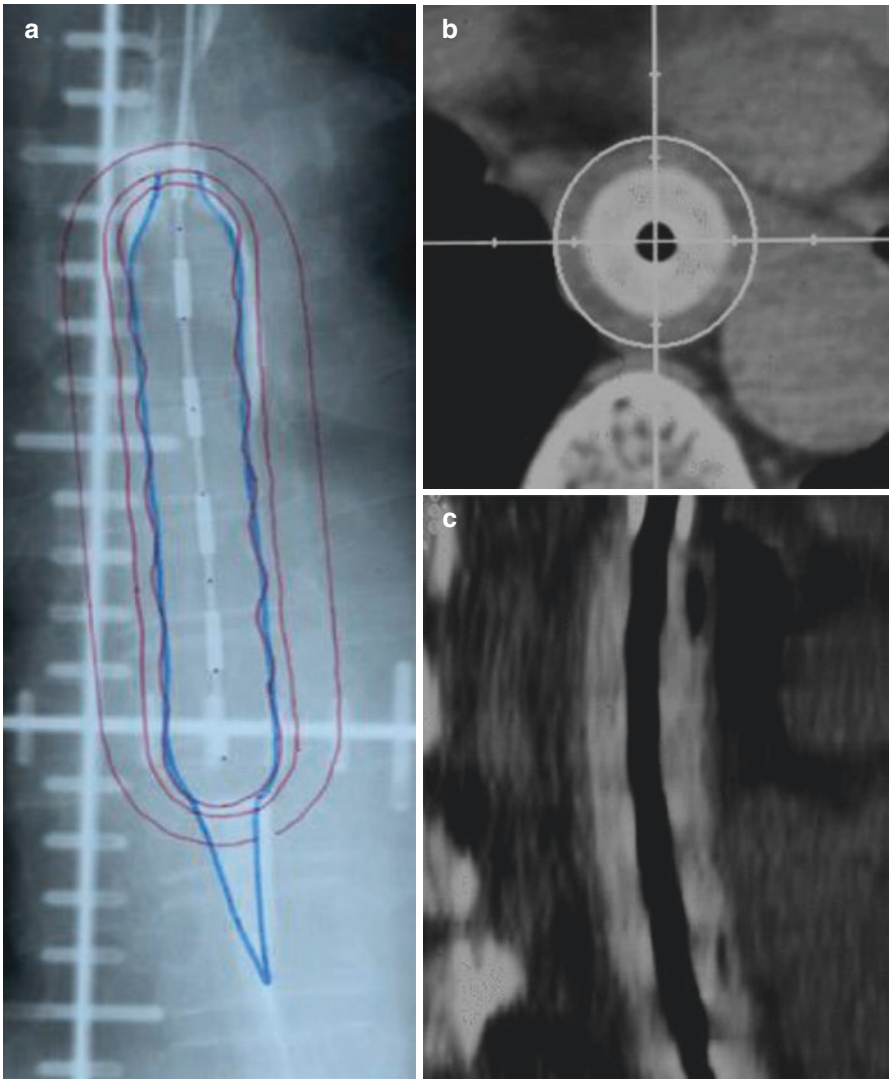

Fig. 21.3 (**a**) Superficial esophageal cancer: inflated balloons and isodose curves. (**b**) Limited thickness of the tumor esophageal wall (3 mm). The prescribed dose of 4 Gy at 12.5 mm from the source axis corresponds to the reference dose at 5 mm for balloon diameter 15 mm. In this case, as the balloon is inflated to diameter 18 mm, the dose at the luminal surface (mucosa) is 5 Gy, and the minimum peripheral tumor dose is 4 Gy. (**c**) The balloon inflated without decentering can be seen in the sagittal image

Table 21.4 BED/EQD for acute and late effects for recently used radiotherapy schedules for superficial tumors

EBRT dose	HDR at mucosa	BED Gy3	BED Gy10	EQD2 Gy3	EQD2 Gy10
50 Gy/25 fractions	12 Gy/2 fractions	119.3	79.2	71.6	66.0
40 Gy/20 fractions	18 Gy/3 fractions	120.7	76.8	72.4	64.0
Persistent superficial tumors in 6 months after EBRT					
60 Gy/30 fractions	10 Gy/2 fractions	126.7	87.0	76.0	72.5
Recurrent superficial tumors 1 year after EBRT					
Previous 50.4 Gy/28 fractions	18 Gy/3 fractions	134.6	88.3	80.8	73.6

EBRT external beam radiotherapy, *HDR* high-dose-rate brachytherapy, *BED* biologically equivalent dose, *EQD2* equivalent total dose in 2 Gy fractions

21.3.6 Dose Specification for Non-superficial Tumors

Our study showed that clinical stages I–II, tumor length <5 cm, performance status (PS 0–1), good tumor regression after EBRT, and concurrent chemotherapy were significant variables in the multivariate analysis. For patients with tumor length <5 cm, T2–3 lesions with good regression after EBRT, or chemoradiotherapy with good performance status, a BT boost could have important roles for better local control [22]. In these settings, the two major methods of dose prescription and dose reporting are 10 mm from the source axis and 5 mm from the applicator surface. Especially for non-superficial tumors, the significant dose variations at the mucosa/tumor surface and within the esophageal wall depend on the applicator diameter, lumen diameter, thickness of the tumor, and prescription point (Fig. 21.4). We use the balloon-type applicator and prescribe at 5 mm from the applicator surface at the narrowest lumen or 10 mm from the source axis for non-superficial tumors. Table 21.1 shows that the survival of patients treated with the narrow applicator of 7 mm diameter was significantly inferior to patients treated with the balloon applicator. Patients receiving a total dose of 66 Gy or less had longer median survival compared with patients receiving a total dose higher than 66 Gy. Muijs analyzed 62 patients with esophageal cancer who were treated with curative-intended radiotherapy consisting of EBRT (60 Gy in 30 fractions) followed by intraluminal BT (12 Gy in 2 fractions) [23]. They reported severe treatment-related toxicities in ten patients (16%). A narrow applicator diameter of 6 mm was used, and the dose was prescribed at 1 cm from the source. The median dose at the catheter surface was calculated at 207.6 Gy3 as the isoeffective dose with HDR. They cautioned about the relationship between the high rate of severe complications and BT at high surface doses. Aggarwal reported the median survival was independently related to the HDR BT dose following EBRT of 30 Gy/10 fractions, with patients receiving a 10 Gy boost showing superior median survival compared with patients receiving a 15 Gy boost [24]. The BED for esophageal mucosa is significantly higher for the

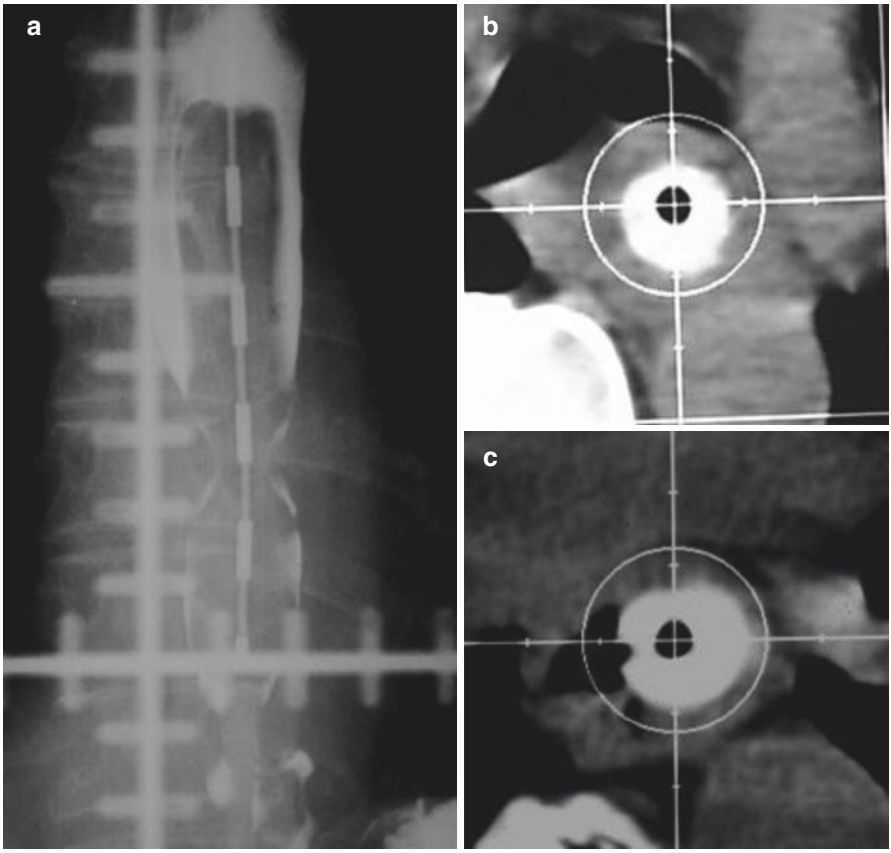

Fig. 21.4 (**a**) T3 esophageal cancer: severe stenosis remains even after 60 Gy of EBRT. (**b**) At extensive stricture, the smallest distance between the source axis and the anterior mucosa/tumor surface is 4 mm, and a dose of 3 Gy is prescribed at 10 mm from the source axis. Report dose of 3.6 Gy at 9 mm (4 + 5) from the source axis, the maximum anterior mucosa/tumor surface dose of 7.5 Gy, and the minimum peripheral tumor dose of 2 Gy at 14 mm from the source axis. Only 1 fraction is given in this case, and the maximum mucosal dose is 126.2 Gy3. (**c**) On this slice, tumor distances from the source axis range from 8 mm to 14 mm, and the doses are between 4 Gy and 2 Gy

15 Gy HDRBT schedule (150–157.5 Gy3) compared with the 10 Gy HDRBT schedule (103–111 Gy3). They concluded that the inferior survival outcomes could be related to increased normal tissue toxicity in patients receiving the 15 Gy regimen. These figures are comparable with the threshold dose derived from the superficial tumor series. At present, we prefer to prescribe doses at 10 mm from the source axis and specify maximum doses at the applicator surface and minimal tumor doses. For advanced tumors, esophageal stenosis usually remains after EBRT when the balloon does not inflate the esophageal lumen sufficiently (Fig. 21.4). To minimize toxicity, we recommend 12 Gy in 2 fractions to 15 Gy in

3 fractions specified at the applicator surface at the most stenotic lumen following 50 Gy of EBRT for advanced tumors as well. Again, 3D CT-based treatment planning offers all the advantages of an individualized treatment to achieve the optimum dosimetry. In addition, HDRBT with or without chemotherapy could be safe and beneficial for local control in the radical treatment of patients with esophageal cancer [4, 25].

21.3.7 Palliative Setting

Whether the combination of HDRBT and EBRT is superior to HDRBT alone for the palliation of esophageal cancer was examined in an International Atomic Energy Agency randomized trial [14]. A total of 219 patients were randomized to adding EBRT or not, after receiving 2 fractions of HDRBT. Each HDRBT consisted of 8 Gy prescribed at 1 cm from the source center. Patients randomized to EBRT received 30 Gy in 10 fractions. The primary outcome was dysphagia relief. A median survival was 188 days and an 18% survival rate at 1 year. Dysphagia relief was significantly improved with combined therapy. In contrast, weight, toxicities, and overall survival were not different between study arms. They concluded symptom improvement occurred with the addition of EBRT to standard HDRBT.

21.3.8 Dose for Palliation

For the management of dysphagia owing to incurable esophageal cancer, BT alone has been proposed as an alternative to stent placement. In a phase 3 trial, single-dose brachytherapy gave better long-term relief of dysphagia than metal stent placement [17]. Since brachytherapy was also associated with fewer complications than stent placement, Homs recommended it as the primary treatment for palliation of dysphagia from esophageal cancer. A systematic review was reported to examine its efficacy and safety in the resolution of dysphagia [18]. Six studies for a total of 9 treatment arms (623 patients) were eligible. BT was performed in the studies using a single catheter diameter 4–10 mm, with doses specified at 1 cm from the source axis of the applicator. After 1 month since treatment, the dysphagia-free survival rate was 86.9%; after 3 months, it was 67.2%; after 6 months, it was 47.4%; and after 12 months, it was 29.4%. The meta-regression analysis showed total radiation dose and number of fractions as the only positively influencing factors. The severe adverse event rate was 22.6%, and the main reported adverse events were brachytherapy-related stenosis (12.2%) and fistula development (8.3%). Two cases (0.3%) of deaths due to esophageal perforation were reported. It seems that a higher total radiation dose (i.e., 18 Gy or 21 Gy) delivered in 2 or 3 fractions could be more efficient than a single session of 12 Gy. In conclusion, BT is a highly effective and relatively safe treatment option; therefore, its underuse is no longer justified.

Conclusions

Intraluminal BT plays an important role in the treatment of esophageal tumors. BT should be established as an integral part of radiotherapy treatment schedules, both in curative and in palliative treatment settings. Selection of patients, applicators, dose specifications, and dose prescriptions are very important issues depending on the treatment aims. This treatment should be limited to facilities where sufficient clinical experience has accumulated to allow its safe application.

References

1. Hishikawa Y, Kamikonya N, Tanaka S, Miura T. Radiotherapy of esophageal carcinoma: role of high-dose-rate intracavitary irradiation. Radiother Oncol. 1987;9(1):13–20.
2. Hareyama M, Nishio M, Kagami Y, Narimatsu N, Saito A, Sakurai T. Intracavitary brachytherapy combined with external-beam irradiation for squamous cell carcinoma of the thoracic esophagus. Int J Radiat Oncol Biol Phys. 1992;24(2):235–40.
3. Yorozu A, Dokiya T, Oki Y, Suzuki T. Curative radiotherapy with high-dose-rate brachytherapy boost for localized esophageal carcinoma: dose-effect relationship of brachytherapy with the balloon type applicator system. Radiother Oncol. 1999;51(2):133–9.
4. Yorozu A, Dokiya T, Oki Y. High-dose-rate brachytherapy boost following concurrent chemoradiotherapy for esophageal carcinoma. Int J Radiat Oncol Biol Phys. 1999;45(2):271–5.
5. Okawa T, Dokiya T, Nishio M, Hishikawa Y, Morita K. Multi-institutional randomized trial of external radiotherapy with and without intraluminal brachytherapy for esophageal cancer in Japan. Japanese Society of Therapeutic Radiology and Oncology (JASTRO) study group. Int J Radiat Oncol Biol Phys. 1999;45(3):623–8.
6. Akagi Y, Hirokawa Y, Kagemoto M, Matsuura K, Ito A, Fujita K, Kenjo M, Kiriu H, Ito K. Optimum fractionation for high-dose-rate endoesophageal brachytherapy following external irradiation of early stage esophageal cancer. Int J Radiat Oncol Biol Phys. 1999;43(3):525–30.
7. Nishimura Y, Okuno Y, Ono K, Mitsumori M, Nagata Y, Hiraoka M. External beam radiation therapy with or without high-dose-rate intraluminal brachytherapy for patients with superficial esophageal carcinoma. Cancer. 1999;86(2):220–8.
8. Nemoto K, Yamada S, Hareyama M, Nagakura H, Hirokawa Y. Radiation therapy for superficial esophageal cancer: a comparison of radiotherapy methods. Int J Radiat Oncol Biol Phys. 2001;50(3):639–44.
9. Ishikawa H, Sakurai H, Tamaki Y, Nonaka T, Yamakawa M, Saito Y, Kitamoto Y, Higuchi K, Hasegawa M, Nakano T. Radiation therapy alone for stage I (UICC T1N0M0) squamous cell carcinoma of the esophagus: indications for surgery or combined chemoradiotherapy. J Gastroenterol Hepatol. 2006;21(8):1290–6.
10. Murakami Y, Nagata Y, Nishibuchi I, Kimura T, Kenjo M, Kaneyasu Y, Okabe T, Hashimoto Y, Akagi Y. Long-term outcomes of intraluminal brachytherapy in combination with external beam radiotherapy for superficial esophageal cancer. Int J Clin Oncol. 2012;17(3):263–71. https://doi.org/10.1007/s10147-011-0285-4. Epub 2011 Jul 12. PubMed PMID: 21748259
11. Gaspar LE, Winter K, Kocha WI, Coia LR, Herskovic A, Graham M. A phase I/II study of external beam radiation, brachytherapy, and concurrent chemotherapy for patients with localized carcinoma of the esophagus (radiation therapy oncology group study 9207): final report. Cancer. 2000;88:985–95.
12. Kodaira T, Fuwa N, Tachibana H, Nakamura T, Tomita N, Nakahara R, Inokuchi H, Mizoguchi N, Takada A. Retrospective analysis of definitive radiotherapy for patients with superficial esophageal carcinoma: consideration of the optimal treatment method with a focus on late morbidity. Radiother Oncol. 2010;95(2):234–9. https://doi.org/10.1016/j.radonc.2010.01.005. Epub 2010 Feb 12. PubMed PMID: 20153906

13. Gaspar LE, Nag S, Herskovic A, Mantravadi R, Speiser B. American brachytherapy society (ABS) consensus guidelines for brachytherapy of esophageal cancer. Clinical research committee, American brachytherapy society, Philadelphia, PA. Int J Radiat Oncol Biol Phys. 1997;38(1):127–32.
14. Sur RK, Levin CV, Donde B, Sharma V, Miszczyk L, Nag S. Prospective randomized trial of HDR brachytherapy as a sole modality in palliation of advanced esophageal carcinoma–an international atomic energy agency study. Int J Radiat Oncol Biol Phys. 2002;53(1):127–33.
15. Folkert MR, Cohen GN, Wu AJ, Gerdes H, Schattner MA, Markowitz AJ, Ludwig E, Ilson DH, Bains MS, Zelefsky MJ, Goodman KA. Endoluminal high-dose-rate brachytherapy for early stage and recurrent esophageal cancer in medically inoperable patients. Brachytherapy. 2013;12(5):463–70. https://doi.org/10.1016/j.brachy.2012.12.001. Epub 2013 Feb 20. PubMed PMID: 23434221.
16. Poetter R, Limbergen EV. Esophagus. In: Gerbaulet A, Petter R, Mazeron JJ, editors. The GEC ESTRO handbook of brachytherapy. Brussel: ACCO: ESTRO; 2002. p. p515–38.
17. Homs MY, Steyerberg EW, Eijkenboom WM, Tilanus HW, Stalpers LJ, Bartelsman JF, van Lanschot JJ, Wijrdeman HK, Mulder CJ, Reinders JG, Boot H, Aleman BM, Kuipers EJ, Siersema PD. Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial. Lancet. 2004;364(9444):1497–504.
18. Fuccio L, Mandolesi D, Farioli A, Hassan C, Frazzoni L, Guido A, de Bortoli N, Cilla S, Pierantoni C, Violante FS, Bazzoli F, Repici A, Morganti AG. Brachytherapy for the palliation of dysphagia owing to esophageal cancer: a systematic review and meta-analysis of prospective studies. Radiother Oncol. 2017;122(3):332–9. https://doi.org/10.1016/j.radonc.2016.12.034. Epub 2017 Jan 16. PubMed PMID: 28104297.
19. Maingon P, d'Hombres A, Truc G, Barillot I, Michiels C, Bedenne L, Horiot JC. High dose rate brachytherapy for superficial cancer of the esophagus. Int J Radiat Oncol Biol Phys. 2000;46(1):71–6.
20. Pasquier D, Mirabel X, Adenis A, Rezvoy N, Hecquet G, Fournier C, Coche-Dequeant B, Prevost B, Castelain B, Lartigau E. External beam radiation therapy followed by high-dose-rate brachytherapy for inoperable superficial esophageal carcinoma. Int J Radiat Oncol Biol Phys. 2006;65(5):1456–61.
21. Nonoshita T, Sasaki T, Hirata H, Toh Y, Shioyama Y, Nakamura K, Honda H. High-dose-rate brachytherapy for previously irradiated patients with recurrent esophageal cancer. Radiat Med. 2007;25(8):373–7.
22. Yorozu A, Toya K, Dokiya T. Long-term results of concurrent chemoradiotherapy followed by high dose rate brachytherapy for T2-3N0-1M0 esophageal carcinoma. Esopahgus. 2006;3(1):1–5.
23. Muijs CT, Beukema JC, Mul VE, Plukker JT, Sijtsema NM, Langendijk JA. External beam radiotherapy combined with intraluminal brachytherapy in esophageal carcinoma. Radiother Oncol. 2012;102(2):303–8. https://doi.org/10.1016/j.radonc.2011.07.021. Epub 2011 Aug 30
24. Aggarwal A, Harrison M, Glynne-Jones R, Sinha-ray R, Cooper D, Hoskin PJ. Combination external beam radiotherapy and intraluminal brachytherapy for non-radical treatment of oesophageal carcinoma in patients not suitable for surgery or chemoradiation. Clin Oncol (R Coll Radiol). 2015;27(1):56–64. https://doi.org/10.1016/j.clon.2014.09.001. Epub 2014 Oct 11
25. Vuong T, Szego P, David M, Evans M, Parent J, Mayrand S, Corns R, Burtin P, Faria S, Devic S. The safety and usefulness of high-dose-rate endoluminal brachytherapy as a boost in the treatment of patients with esophageal cancer with external beam radiation with or without chemotherapy. Int J Radiat Oncol Biol Phys. 2005;63(3):758–64.

Intraluminal Brachytherapy for Biliary Tract Cancer

22

Naoya Murakami and Jun Itami

Abstract

In this chapter, intraluminal brachytherapy (ILBT) for biliary tract cancer is discussed. Because of its rarity and poor prognosis and generally it is difficult to cover whole tumor with intraluminal brachytherapy, there exists no prospective study showing survival benefit of ILBT for biliary tract cancer. However, large retrospective study showed effectiveness of ILBT in local control for unresectable biliary tract cancer patients. Local control of the disease holds great significance for such patients; therefore, ILBT could be considered when applicable.

Keywords

Biliary tract cancer · Intraluminal brachytherapy

Biliary tract cancer is a relatively rare disease and 11,205 cases are newly diagnosed in 2013 in Japan [1]. The clinical outcome in patients with biliary tract cancer is generally poor. Main curative treatment method of this disease is surgical resection; however, unfortunately, because vast majority of patients are found with locally advanced or metastatic disease, only small part of patients are candidate for curative resection. Therefore, overall 5-year survival rates of only 10% or less have been reported [2]. So far many attempts have been performed to improve the outcomes for unresectable biliary tract cancer with definitive radiation therapy. Intraluminal brachytherapy (ILBT) for biliary tract cancer patients using low-dose-rate brachytherapy using 192-Ir wire was first reported in the late 1970s [3], and ILBT with

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high-dose rate after loading system was started in the early 1980s with or without external beam radiation therapy (EBRT) [4, 5]. While some researchers reported improvement of survival with the use of ILBT [6, 7], others did not [8]. Because of its rareness, to the best of our knowledge, no randomized control clinical trial with enough statistical power has been performed to determine the effectiveness of ILBT on survival outcomes for biliary tract cancers. Yoshioka et al. performed a multi-institutional retrospective study throughout Japan involving 31 institutions with 209 unresectable biliary tract cancer patients and compared clinical results between external beam radiation therapy with and without ILBT for unresectable biliary tract cancer using a propensity score matched-pair analysis [9]. They found that although the addition of ILBT had no impact on overall survival nor disease-specific survival, it was associated with better local control which has very important meaning for patient's quality of life. In this multi-institutional retrospective study, ILBT was performed by transpercutaneous route with use of percutaneous transhepatic cholangiography. The median of the ILBT total dose was 18 Gy, with a median fraction of 6 Gy. Generally, the ILBT dose was prescribed at a point 5–10 mm from the center of the source.

22.1 Brachytherapy Procedure

Before brachytherapy, biliary drainage is performed by either transduodenal or percutaneous transhepatic technique, and a drainage catheter is placed. Through the drainage catheter, a 5–6 Fr intraluminal radiation catheter is inserted as a carrier for the Ir-192 source under cholangiography. Occasionally, two catheters are inserted when disease spreads over two branches. Because transduodenal drainage catheter usually has strong flexure, when using transduodenal drainage catheter, it is important to make sure that dummy source can pass through the flexure beforehand. Generally the dose is prescribed 1 cm from the source axis (Figs. 22.1 and 22.2). Because extrahepatic bile duct is usually situated close to the intestine, especially the duodenum, dose distribution calculation should be based on CT image, and delivering high dose to the intestine should be avoided. Toxicities associated with ILBT are cholangitis, cholecystitis, gastroduodenitis, duodenal ulcer, and liver dysfunction.

22.2 Future Direction

There exists a phase I study for determining recommended dose of ILBT alone as a palliative treatment in extrahepatic biliary tract cancer [10], and they reported that recommended dose was defined as 25 Gy in five fractions prescribed 1 cm from the source axis. However, there exists no clinical trial for unresectable biliary tract cancers as a curative intent using combined EBRT and ILBT. Recently, with the

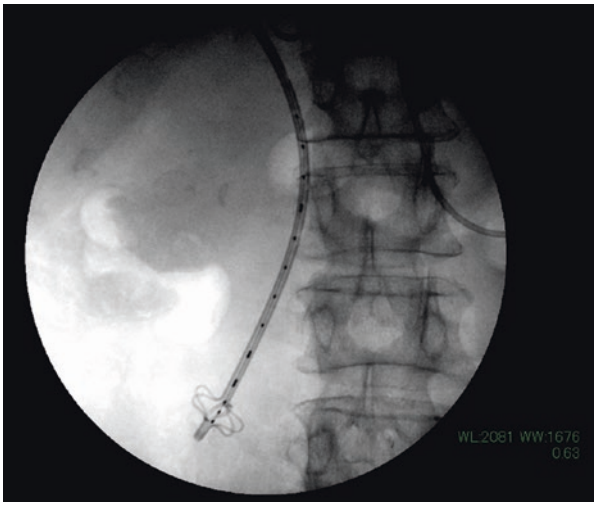

Fig. 22.1 An abdominal X-ray showing a 6 Fr intraluminal radiation catheter inserted through percutaneous transhepatic cholangiodrainage tube

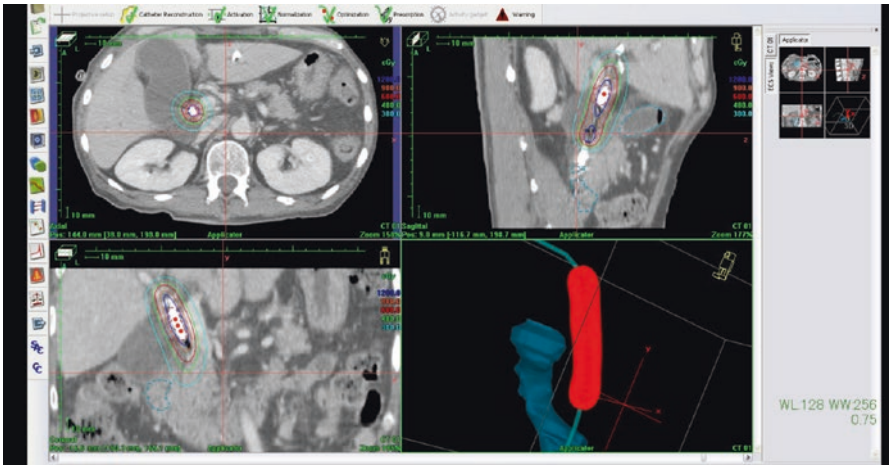

Fig. 22.2 Dose distribution of intraluminal brachytherapy for biliary tract cancer. The dose is prescribed 1 cm from the source axis. To avoid large dose to the duodenum or small intestine, CT-based dose calculation is mandatory

advancement of the image technique and introduction of intensity-modulated radiation therapy (IMRT), more accurate visualization of disease extent is possible, and delivering high dose while sparing surrounding normal tissue is also possible. Therefore, combined with these advanced techniques, a prospective clinical trial trying to find optimal combination of dosage of EBRT and ILBT and to show its role in the management of biliary tract cancer is warranted.

References

1. Cancer Registry and Statistics. Cancer Information Service, National Cancer Center, Japan.
2. Anderson CD, Pinson CW, Berlin J, et al. Diagnosis and treatment of cholangiocarcinoma. Oncologist. 2004;9:43–57.
3. Ikeda K, Kuroda C, Uchida H, et al. Intraluminal irradiation with Ir-192 wires for extrahepatic bile duct carcinoma. Nihon Igaku Houshasen Gakkai Zasshi. 1979;39:1356–8.
4. Koster R, Schmidt H, Greuel H, et al. Bestrahlung von malignen Gallengangsverschlüssen in Afterloading-Technik. Strahlentherapie. 1982;158:678–80.
5. Itami J, Saegusa Y, Tsuchiya T, et al. Intrakavitaere high-dose-rate-afterloading-Bestrahlung beim inoperablen malignen Gallengangsverschluss. Strahlenther Onkol. 1986;162:105–10.
6. Montemaggi O, Costamagna G, Dobelbower R, et al. Intraluminal brachytherapy in the treatment of pancreas and bile duct carcinoma. Int J Radiat Oncol Biol Phys. 1995;32:437–43.
7. Kamada T, Saitou H, Takamura A, et al. The role of radiotherapy in the management of extrahepatic bile duct cancer: an analysis of 145 consecutive patients treated with intraluminal and/or external beam radiotherapy. Int J Radiat Oncol Biol Phys. 1996;34:767–74.
8. Gonzalez D, Gouma D, Rauws E, et al. Role of radiotherapy, in particular intraluminal brachytherapy, in the treatment of proximal bile duct carcinoma. Ann Oncol. 1999;10:215–20.
9. Yoshioka Y, Ogawa K, Oikawa H, et al. Impact of intraluminal brachytherapy on survival outcome for radiation therapy for unresectable biliary tract cancer: a propensity score matched-pair analysis. Int J Radiation Oncol Biol Phys. 2014;89(4):822e829.
10. Mattiucci GC, Autorino R, Tringali A, et al. A phase I study of high-dose-rate intraluminal brachytherapy as palliative treatment in extrahepatic biliary tract cancer. Brachytherapy. 2015;14:401–4.