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Current status and issues with the dosimetric assay of iodine-125 seed sources at medical facilities in Japan: a questionnaire-based survey†

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ABSTRACT

In conducting dosimetric assays of seed sources containing iodine-125 (^{125}I), several major guidelines require the medical physicist to verify the source strength before patient treatment. Japanese guidelines do not mandate dosimetric assays at medical facilities, but since 2017, three incidents have occurred in Japan wherein seeds with incorrect strengths were delivered to medical facilities. Therefore, this study aimed to survey the current situation and any barriers to conducting the dosimetric assay of iodine-125 seeds at medical facilities in Japan. We conducted a questionnaire-based survey from December 2020 to April 2021, to examine whether seed assay and verification of the number of seeds delivered were being performed. We found that only 9 facilities (16%) performed seed assay and 28 (52%) verified the number of seeds. None of the facilities used an assay method that ensured traceability. The reasons for not performing an assay were divided into two categories: lack of resources and legal issues. Lack of resources included lack of instruments, lack of knowledge of assay methods, shorthand, or all of the above, whereas legal issues included the inability to resterilize iodine-125 seeds distributed in Japan and/or purchase seeds dedicated to the assay. Dosimetric assays, including simple methods, are effective in detecting calibration date errors and non-radioactive seeds. The study findings suggest that familiarization of medical personnel with these assay methods and investigation of the associated costs of labor and equipment should be recommended, as these measures will lead to medical reimbursement for quality assurance.

Keywords: prostate cancer; low-dose-rate brachytherapy; low-energy source; iodine-125; seed assay

INTRODUCTION

In Japan, prostate brachytherapy with seed sources containing iodine-125 (^{125}I) began in 2003 and has been used to treat over 45 000 patients at >110 facilities [1]. Prostate brachytherapy plays an essential role in treating localized prostate cancer and is a highly effective treatment, with few side effects reported [2, 3]. The source strength of brachytherapy is directly proportional to the dose delivered to patients. Therefore, to accurately evaluate patient doses and determine the position and number of seed sources when planning treatment, it is necessary to use a source strength that is guaranteed by some method such as a dosimetric assay. For dosimetric assays of low-energy, low-dose-rate brachytherapy sources, European and North American guidelines state that the medical physicist is responsible for ensuring the source strength before treating a patient [4–9]. These guidelines describe the number of seeds to be assayed to ensure the required patient dose. However, for the reasons discussed below, the Japanese guidelines only introduced that 'Essentially, the source strength of iodine-125 seeds should be confirmed by dosimetric assay'. Therefore, seed assays were not included in the recommended practices in those guidelines [10, 11]. These domestic guidelines were issued in the mid-2000s and are still being referenced today.

When the guidelines were issued, the dosimetric traceability of iodine-125 seeds had not been established in Japan. Therefore, calibration of well-type ionization chambers required the use of overseas calibration services, such as the University of Wisconsin Accredited Dosimetry Calibration Laboratory (USA), making it difficult to perform dosimetric assays at medical facilities in Japan. Subsequently, the results of a single-seed assay for two types of sources distributed in Japan were reported and were found to correspond with the manufacturer-stated source strengths [12, 13]. A questionnaire survey of facilities performing seed brachytherapy in Japan found that seed assays were performed in 5% of the responding facilities [14]. Thereafter, major seed distributors in Japan reported that their quality assurance systems were well established [15]. In 2013, a study also reported that a batch assay of convenient sterile blister packs showed good agreement with the manufacturer-stated source strength [16]. Based on these reports, the source strengths of the iodine-125 seeds delivered in Japan are considered to be quality-assured. Therefore, many facilities do not measure source strength, and the manufacturer-stated source strength is used for treatment planning and dose calculation.

Since 2017, three incidents have occurred, including the delivery of the wrong source strength and non-radioactive seeds to medical facilities [17–19]. Such incidents potentially worsen the treatment outcomes of patients treated with iodine-125 seed brachytherapy. The errors in seed quality were reported within a short period, leading to loss of confidence in manufacturer-stated strengths. The status of seed assays in Japan was only surveyed once in 2008 [14]. Since then, the models of seed sources available in Japan have changed. In some cases, it is difficult to perform dosimetric assays because the seeds are preloaded in cartridges that cannot be resterilized. Therefore, the present study aimed to understand the current status of dosimetric assays for iodine-125 seeds in Japan by conducting a questionnaire survey.

Table 1. Source models and loading types used in brachytherapy

Source model	Loading type	Number[a]	%
STM1251	Mick/QuickLink Cartridge	48	67
STM1251	ReadyLink	1	1
AgX100	TheraStrand-SL	34	47
AgX100	Mick Cartridge	30	42

[a]Some facilities use two or more source models and/or source loading types.

MATERIALS AND METHODS

We distributed the questionnaire via Google Forms (Google, Mountain View, CA, USA) from December 2020 to April 2021. The survey request was sent to all facilities considered to be implementing iodine-125 seed brachytherapy in fiscal year 2020. The first section of the questionnaire requested details on the facility, such as the number of yearly treatments performed, the source model, the seed delivery type and the professions of persons administering seed brachytherapy. The next section inquired whether seed assays and verification of the number of seeds delivered were performed. The questions touched on details of the methods of dosimetric assay used, the number of seed assays performed, the number of seeds delivered and under whose supervision the assay was performed. In the last section, we enquired about reasons preventing respondents from performing seed assays and the possible improvements that could be made, using multiple-choice and open-ended questions. All questions are summarized in the Appendix.

RESULTS

Facility information

Sixty-seven of the 95 facilities currently providing iodine-125 seed brachytherapy in Japan responded to this survey. Figure 1 shows the annual number of patients treated with iodine-125 seed brachytherapy in the fiscal year 2019. The number of patients treated at the facilities was considered unbiased. The source models used in each facility are listed in Table 1. Two source models are available in Japan: STM1251 (product name: BARD® BRACHYSOURCE®, Becton, Dickinson and Company (BD), Franklin Lakes, NJ, USA) and TheraAgX100® (Theragenics Corporation, Buford, GA, USA). STM1251 is delivered encapsulated in sterilized cartridges of the Mick® and QuickLink® types, and is also delivered as a ReadyLink®, in which the seeds are connected by a bioabsorbable material to produce the source arrangement established in the pre-plan. According to Medicon, Inc, which markets the BARD® BRACHYSOURCE® in Japan, only two facilities use the ReadyLink® type. TheraAgX100® is delivered in sterilized Mick® cartridges, and either a bare source or a source covered with a stranded bioabsorbable material, TheraStrand-SL®, is loaded into the Mick cartridge.

Dosimetric assay

Figure 2 shows the proportion of facilities performing the dosimetric assay and verifying the number of seeds delivered. A dosimetric assay of iodine-125 seeds was performed in 18% of the responding facilities, which was slightly greater than the proportion in the 2007

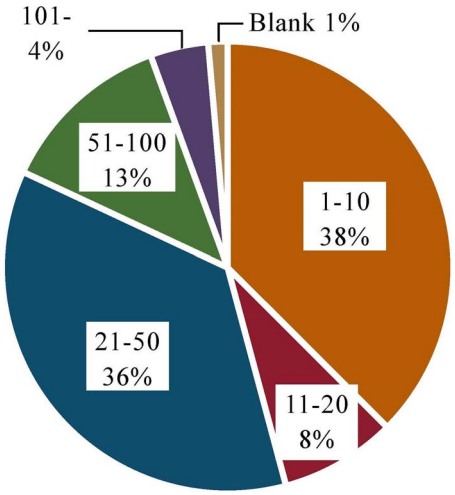

Fig. 1. Numbers of iodine-125 seed brachytherapy procedures in fiscal year 2019 at the responding facilities ($n = 67$).

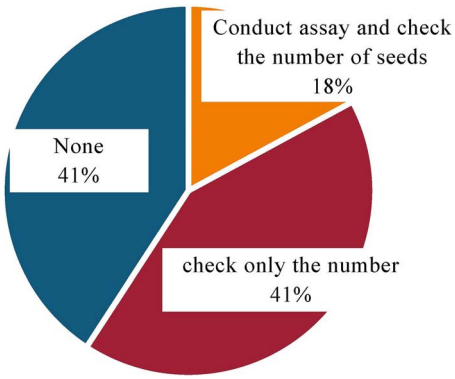

Fig. 2. Percentage of facilities performing seed dosimetric assays and checking the number of seeds delivered ($n = 67$).

survey (<10%). The number of seeds delivered was verified in 41% of the facilities. In the remaining 41%, neither the dosimetric assay was performed nor the number of seeds was verified. Table 2 shows the assay methods used by the responding facilities. One facility performed a single-seed assay using a well-type ionization chamber, seven facilities used well-type ionization chambers with sterilized cartridges (batch assays and/or grouped seed assays) and four facilities used survey meters or other simplified methods. One facility that performed single-seed assays examined leftover seeds not implanted during patient treatment, an after-the-fact assay that does not guarantee the dose delivered to the patient. Both the recommended single-seed and batched assays are traceable to the absolute value of the air kerma indicated by national standards. Therefore, for either assay method, the source strength can be indicated by the reference air kerma rate or air kerma strength. However, none of these facilities used an assay method that ensured traceability. It is believed that all facilities evaluated the relative source strength by comparing it with the previously measured value.

Reasons and issues for not conducting the assay

Table 3 shows the reasons given for facilities not performing seed assays. Many believed that the source strength stated by the manufacturer had already been established and was guaranteed. The results of the question on what improvements would be required to ensure that assays are performed are shown in Table 4. Many respondents cited problems with lack of resources, such as lack of measuring equipment, knowledge of measurement techniques and personnel. The other common answers included inability to charge the cost for performing the seed assay to patients, legal regulation of the assayed seeds and verification of the source strength before patient treatment, which are not recommended by the Japanese guidelines.

DISCUSSION

To ensure the quality of treatment of patients undergoing iodine-125 seed brachytherapy, a dosimetric assay of the seeds should be performed before treatment. Several guidelines have stated that all seed sources should ideally be measured before seed implantation [4–7, 9]. However, in Japan, assays are rarely performed at medical facilities. This is because the manufacturer's stated source strength is considered reliable, and a requirement for verification is not specified in the guidelines [10, 11]. This survey once again revealed that only 18% of the facilities performed the dosimetric assay.

The most common reason for not performing the assay was the inability to resterilize the source. Resterilization is time-consuming and requires dedicated personnel. Most iodine-125 seeds distributed in Japan cannot be resterilized because of regulations governing pharmaceutical products. The percentage of facilities performing dosimetric assays improved slightly from the 5% reported in 2008 [14], but the reasons for not performing the assay have not changed. This shows that the situation in Japan has not improved over the years. The use of seeds covered in a bioabsorbable material that ensures immobilization inside the prostate gland has become more common. These sources cannot be resterilized, which would cause deformation or dissolution of the bioabsorbable material. To calibrate source strength using a traceable method, it is necessary to purchase seeds dedicated to the assay. Furthermore, seeds that are not implanted in patients must be strictly managed in accordance with domestic laws, and the loss of custody of seeds is legally punishable. In addition, the cost of seeds used only for the assay and not for treating the patient cannot be billed to the patient or to medical insurance. Many respondents also cited reasons related to workload, such as insufficient staff and lack of time to perform assays. For the above reasons, seed assays based on the single-seed method using a well-type ionization chamber calibrated with a reference air kerma rate are not performed at all facilities. In 2009, a calibration service for iodine-125 seeds with traceability to the national standards was established in Japan. The number of calibration requests is extremely small: in the 10 years from the start of the calibration service in 2009 to 2018, there were 3 requests for the supply of a seed calibrated with reference air kerma rate and 11 requests for the calibration of well-type ionization chambers. Therefore, the calibration service has been temporarily suspended.

Several alternative assay methods have been developed in Japan that do not compromise the sterility of seeds or cartridges [20–23]. Reports

Table 2. Seed assay methods used by facilities (total number = 12)

	Single seed assay	Grouped seed assay	Alternatives ex. survey-meter
STM1251 Mick Cartridge	1	4	1
STM1251 QuickLink Cartridge	0	2	0
AgX100 TheraStrand-SL	1	1	0
AgX100 Mick Cartridge	1	1	0
STM1251 ReadyLink	0	0	0

Table 3. Reasons given for not performing seed dosimetric assays

	Number
Not resterilizable	59
Trust the manufacturer stated strength	50
Shorthanded	41
Lack of measurement time	32
Avoid radiation exposure	31
Lack of measuring devices	26
Unable to purchase measurement seeds	25
Avoid missing seed	25
No knowledge of how to measure	15
Considers measurement unnecessary	5

Table 4. Recommended improvements in the conduct of dosimetric assays at Japanese medical facilities

	Number
Installation of measuring devices	55
Learning of measurement techniques	50
Turn measurement into revenue for hospitals	50
Increase in personnel	46
Make measurement mandatory in guidelines	41
Exclude measured sources from legal control	34
Others	6
Extremely hard to measure under any circumstances	5

from overseas have used survey meters to validate the measurement results from third-party calibration services. All these reports agreed that alternative methods were effective in identifying erroneous source strengths and non-radioactive seeds. In Japan, alternative methods are not used in most facilities because of cost and workload problems. This situation has led to technical problems such as lack of measuring equipment in facilities and insufficient knowledge of measurement methods. In Japan, third-party calibration services have not been established, and the established calibration services are located in the USA and are thus not available. Therefore, in most facilities, treatment planning and post-planning dose calculations are performed without confirmation of the source strength stated by the manufacturer. Thus, this situation may lead to an incorrect assessment of the dose administered to the patient during seed brachytherapy.

This study has a few limitations. The response rate of this survey was 70% among the facilities that perform iodine-125 seed brachytherapy; therefore, we were unable to obtain information from all facilities in Japan. In addition, facilities that are proactive in quality assurance tend to respond more frequently to such questionnaire surveys. Thus, it is possible that only a few facilities actually perform seed assays.

CONCLUSION

In conclusion, technical, financial and legal issues remain barriers to implementing best seed assay practices at all facilities. To solve the technical problems, we should first make medical physicists and other technical personnel familiar with currently possible seed assay methods. This will help avoid major accidents, such as the use of multiple non-radioactive seeds for seed therapy. Several guidelines state that medical physicists are responsible for determining if the measured average source strength or the nominal source strength provided by the vendor is available [4–9]. The problem with the current seed assays in Japan is that the measurement methods are not standardized, traceability is not ensured and measurement uncertainty is not evaluated. Therefore, the authors believe that even if dosimetric assay can be performed at a medical facility, the application of source strengths as presently measured in clinical practice here should be avoided. Furthermore, it will be necessary to establish a dosimetric assay method that is suitable for the current situation in Japan, where seed resterilization is not possible and third-party seed calibration services are not available. We are currently developing a simple method of measurement using a survey meter or a well-type ionization chamber such as that used in nuclear medicine that preserves source sterility. We also recommend investigation of the cost of seed assays in both labor and measuring equipment, as well as linking quality assurance activities, including dosimetric assays, to medical reimbursement.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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None declared.

DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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