Objective: We aimed to propose a set of quality indicators (QIs) based on the clinical guidelines for cervical cancer treatment published by The Japan Society of Gynecologic Oncology, and to assess adherence to standard-of-care as an index of the quality of care for cervical cancer in Japan.

Methods: A panel of clinical experts devised the QIs using a modified Delphi method. Adherence to each QI was evaluated using data from a hospital-based cancer registry of patients diagnosed in 2013, linked with insurance claims data, between October 1, 2012, and December 31, 2014. All patients who received first-line treatment at the participating facility were included. The QI scores were communicated to participating hospitals, and additional data about the reasons for non-adherence were collected.

Results: In total, 297 hospitals participated, and the care provided to 15,163 cervical cancer patients was examined using 10 measurable QIs. The adherence rate ranged from 50.0% for ‘cystoscope or proctoscope for stage IV A’ to 98.8% for ‘chemotherapy using platinum for stage IVB’. Despite the variation in care, hospitals reported clinically valid reasons for more than half of the non-adherent cases. Clinically valid reasons accounted for 75%, 90.9%, 73.4%, 44.5%, and 88.1% of presented non-adherent cases respectively.

Conclusion: Our study revealed variations in pattern of care as well as adherence to standards-of-care across Japan. Further assessment of the causes of variation and non-adherence can help identify areas where improvements are needed in patient care.

Keywords: Quality Indicators; Uterine Cervical Neoplasms; Standard of Care; Guideline Adherence; Practice Guideline
INTRODUCTION

Cervical cancer is one of the most common gynecological cancers globally. Each year, more than 500,000 women are diagnosed with cervical cancer [1]. Although its incidence has been decreasing worldwide, cervical cancer is still common, especially in the developing regions. In contrast to most developed countries [2], the incidence of this cancer is on the rise in Japan, especially among the younger generation, casting a deep shadow over the Japanese cancer demography. According to statistics, the number of patients in their 20s has more than doubled annually over the last two decades [3]; a similar trend has also been observed for women in their 30s and 40s. With current 5-year survival rates of 92.6% for stage I, 75.2% for stage II, 59.3% for stage III, and 22.2% for stage IV [4], cervical cancer continues to exhibit high mortality and morbidity among gynecologic malignant tumors in Japan [5]. In addition, urologic complications such as bladder dysfunction, which are associated with treatments, can significantly lower patients’ quality of life [6,7].

Despite the growing number of patients, the quality of care for cervical cancer has remained unexamined. Quality of care (efficiency and effectiveness of care), is widely believed to help minimize disease aggravation, thus improving survival as well as quality of life [8]. Since the Japanese Diet passed the Cancer Control Act in 2007, ensuring, monitoring, and evaluating quality of patient care has gained attention at the national level [9]. Propelled by the national mandate for cancer control, The Japan Society of Gynecologic Oncology published its first treatment guideline for cervical cancer in 2007, which was revised in 2011, in order to promote standardized high-quality care in Japan [10,11]. To ensure that all patients receive high-quality care, it is thus imperative to evaluate the adherence of treatment centers to the recommendations outlined in these clinical guidelines.

Therefore, we aimed to propose a set of quality indicators (QIs) based on the clinical guidelines for cervical cancer treatment and to assess adherence to standard-of-care as an index of the quality of care for cervical cancer in Japan.

MATERIALS AND METHODS

1. Development of QIs

We developed a set of process-of-care QIs for cervical cancer care. QIs describe the care processes that a specific group of patients should receive as the standard-of-care treatment. The QIs serve to translate guideline recommendations into measurable indices with clear specifications of target patients and care processes. The QIs were devised by a panel of nationally renowned clinical experts in cervical cancer, using the Research ANd Development (RAND)/University of California, Los Angeles (UCLA) modified Delphi method [12]. Each expert initially proposed QI candidates based on relevant literature and clinical practice guidelines. Then, the QI candidates were individually and anonymously rated for QI validity and significance of the measurement by each expert, on a scale of 1–9 (1=extremely invalid/not significant; 9=extremely valid/significant). The expert panel discussed each potential QI candidate after the initial rating, and introduced any modifications that were agreed upon, by consensus. Each QI candidate was then rated again. The QIs were considered valid if the median ratings for both QI validity and the significance of measurement were 7 or higher (i.e., more than half of the panel members rated a QI ≥7, and 2 or fewer members rated a QI ≤3). The QI candidates that were considered worth measuring (i.e., median rating for significance-in-measurement was 7 or higher), but not valid
as QIs (i.e., median rating for validity being lower than 6), were considered pattern-of-care items (PCIs). Measurability was assessed using the available data.

2. Data
We used a database that linked the national database of the Hospital-Based Cancer Registry (HBCR) [13] and health insurance claims data from the Diagnosis Procedure Combination (DPC) survey. The HBCR is a compulsory cancer incidence reporting system for all designated cancer care hospitals, and is also voluntarily operated in several non-designated hospitals that play similar roles in their respective communities. The HBCR data contains clinical information such as clinical and pathological stages, tumor-node-metastasis (TNM) classifications, tumor location, and histopathological findings based on the International Classification of Diseases Oncology 3rd edition (ICD-O-3). All patients with cervical cancer (ICD-O morphology: C53.0–53.9) were included in the analyses. The DPC survey data contains information on all health services provided. While the DPC itself is a grouping system used to determine the global amount of per-day health insurance reimbursement to hospitals, the DPC survey data have the equivalent data for fee-for-service claims which code individual tests, images, procedures, and prescription drugs, along with the dates and unit costs of the services from both inpatient and outpatient settings.

Designated cancer care hospitals across Japan were invited to participate in the study. We collected claims data from October 2012 to December 2014, and linked them to the HBCR data. The time period for DPC data collection was selected to allow inclusion of all treatments performed for cancers diagnosed during 2013. The details of the data collection process are described elsewhere [14].

During implementation, several QI specifications which required data not included in the current version of HBCR were adjusted. For example, several QIs use sub-classifications of TNM, such as T1a and T2b, which is information that is mandated to be coded for all cases from the year 2016 onwards. Because the subclassifications of TNM will soon be available, the QIs that required this information were accepted in the development phase. For this reason, calculability of each QI was evaluated prior to analysis. The HBCR has adopted the Union for International Cancer Control (UICC) cancer staging system. However, as the International Federation of Gynecology and Obstetrics (FIGO) staging system is widely used in Japan, the T classification was resolved to correspond with the FIGO staging, while the cases presenting with metastasis were included in FIGO stage IV.

3. Data analysis
Adherence to each QI and its 95% confidence interval (CI) were calculated. The analysis included all patients who received first-line treatment at the participating facility. Three QIs pertained to treatment for cervical intraepithelial neoplasia 3 (CIN3), 3 for stage III or IVA disease, and one QI for stage IVB cancer. One QI addressed the examination of the extent of cancer and another QI pertained to brachytherapy regardless of the stage.

All analyses were performed on Stata version 13.2 (StataCorp LP, College Station, TX, USA). This study protocol was approved by the Institutional Review Board of the National Cancer Center, Japan (approval No. 2013-081).

4. Reasons for non-adherence to QIs
The analysis results were communicated to participating hospitals, which were requested to report back on the reasons for non-implementation of the care guidelines outlined as per the
QIs. The reasons cited were recorded and the frequency with which each reason was cited was examined. The reasons cited for less than 10 patients were not reported. Clinically valid reasons were categorized as ‘sufficient reasons’ and those that were not clinically valid as ‘insufficient reasons’.

Non-adherent cases were examined also from a different point of view. After the result of QI calculation was aggregated, limited use of radiation-based therapy has been particularly discussed amongst the expert panel. Therefore, we looked into the types of alternative treatments that were performed in patients who would otherwise have been treated with radiation-based therapy such as concurrent chemotherapy and radiation therapy (CCRT).

RESULTS

1. QI development
The panel of experts proposed 43 QI candidates in total. Among them, only 10 QIs were considered measurable, due to the lack of sub-stage information in the HBCR. Four candidates were designated as PCIs. For example, when the QI targeted patients with high-recurrence risks — such as in ‘post-surgery CCRT for pN1/pT2b patients without preoperative chemotherapy’ — we only included pN1 stage patients. Although QIs generally describe the care that should be provided, 3 QIs describe care not recommended for the target patient population — suggesting lower score (i.e., QI1 and QI10).

2. QI adherence scores
In total, 297 hospitals participated, and the care received by 15,163 cervical cancer patients was examined using 10 measurable QIs. Patient characteristics are presented in Table 1. The adherence data are shown in Tables 2 and 3. The adherence rate ranged from 50.0% for ‘cystoscope or proctoscope for stage IV A’ (QI8) to 99.1% for ‘chemotherapy using platinum for stage IVB’ (QI7). The adherence rate varied across facilities. Apart from the 4 PCIs, the greatest inter-facility variation was seen for ‘radical hysterectomy for stage II adenocarcinoma’ (QI3) and for ‘cystoscope or proctoscope for stage IV A’ (QI8), with adherence rates of 67.7% (standard deviation [SD]=41.6) and 50.0% (SD=45.6), respectively. The smallest variation was seen for ‘chemotherapy using platinum for stage IVB’ (QI7) and for ‘post-treatment maintenance therapy using oral chemotherapy’ (QI10), with adherence rates of 98.7% (SD=2.3) and 1.2% (SD=4.9), respectively.

3. Reasons for non-adherence to QI
Forty-seven hospitals submitted data pertaining to non-adherence to QIs. The frequency and the reasons for non-adherence to QIs are shown in Table 4. Overall, more than half of patients had clinically valid reasons for not receiving the specified care. Comorbidities accounted for more than 60% of the reasons listed for non-adherence to the guideline recommending the use of CCRT as the first-line treatment among stage III and IVA patients (QI4). Kidney failure (14%) and poor general condition due to age (38%) were the major comorbidities reported. Four patients (26%) were reported to have been treated with nedaplatin, though cisplatin was recommended for CCRT among stage III and IVA patients (QI5). Kidney failure was the only comorbidity reported in these patients. Among the reasons listed as ‘unknown’ in QI8, 70% of patients were reported to have been evaluated by computed tomography (CT) and magnetic resonance imaging (MRI) to determine the degree
of tumor invasion. The category ‘other’ for QI9 included ‘insertion difficulty’ and ‘large tumor size’.

Since the results elucidated that the use of CCRT remained conservative across the QIs and PCIs, we looked into the alternative first-line treatment provided to these patients. They were: chemotherapy only (5.7%), radiotherapy only (32.9%), surgery (1.1%), and others (5.1%). In patients aged below 70 years, the first-line treatment was CCRT in 74.7% of patients, chemotherapy in 8.3%, radiation therapy in 12.8%, surgery in 1.5%, and other in 2.8% of patients.

**DISCUSSION**

We developed 43 QI candidates, among which 10 QIs were measured using the nationwide hospital-based cancer registry and insurance claims data. Practice patterns were also measured using 4 PCIs to provide reference data to discuss the current status and the development of future standards. Variations in providing standard care were observed among participating facilities. In general, adherence rate for QIs describing care that is not...
Table 2. Adherence rates for various QIs

| QI | Target patients (denominator) | Specified care (numerator) | No. | Adherence rate (95% CI) |
|----|-------------------------------|-----------------------------|-----|-------------------------|
| QI1* | Conization for CIN3 | CIN3 patients who are under age 43 years | Patients who had total hysterectomy without conization | 242/6,256 | 3.9% (3.4–4.4) |
| QI2 | Total hysterectomy for adenocarcinoma in situ | Patients who had adenocarcinoma in situ over age 44 years | Patients who had total hysterectomy as the last treatment | 81/93 | 87.2% (78.5–93.2) |
| QI3 | Radical hysterectomy for stage II adenocarcinoma | Stage II adenocarcinoma patients | Patients who had radical hysterectomy | 115/170 | 67.6% (60.1–74.6) |
| QI4 | CCRT as the first-line treatment for stage III or IVA | Stage III or IVA patients | Patients who had CCRT as the first-line treatment | 397/720 | 55.1% (51.4–58.8) |
| QI5 | CCRT using cisplatin for stage III or IVA | Stage III or IVA patients who had CCRT | Patients who had cisplatin-based regimen for CCRT | 333/417 | 79.9% (75.7–83.6) |
| QI6* | Chemotherapy for stage III or IVA | Stage III or IVA patients who had curative radiation therapy or CCRT as main treatment | Patients who had chemotherapy before the main treatment | 8/663 | 1.2% (0.5–2.4) |
| QI7 | Chemotherapy using platinum for stage IVB | Stage IVB patients who had chemotherapy | Patients who had platinum-based chemotherapy | 422/426 | 99.1% (97.6–99.7) |
| QI8 | Cystoscope or proctoscope for stage IVA | Stage IVA patients | Patients who had cystoscope or proctoscope before the treatment | 87/174 | 50.0% (42.3–57.7) |
| QI9 | Curative radiation therapy using brachytherapy | Patients who had curative radiation therapy without surgery | Patients who had brachytherapy | 1,211/1,536 | 78.8% (76.7–80.9) |
| QI10* | Post-treatment maintenance therapy using oral chemotherapy | Stage I or II patients who had surgery, radiation or CCRT for the first time. | Patients who used oral chemotherapy | 28/2,313 | 1.2% (0.8–1.7) |

CI, confidence interval; CIN3, cervical intraepithelial neoplasia 3; CCRT, concurrent chemotherapy and radiation therapy; QI, quality indicator.

*Treatment modality defined as not recommended.

Table 3. Adherence rates for PCIs

| PCIs | Target patients (denominator) | Specified care (numerator) | No. | Adherence rate (95% CI) |
|------|-------------------------------|-----------------------------|-----|-------------------------|
| PCI1 | Total hysterectomy for CIN3 | CIN3 patients who are over age 50 years | Patients who had total hysterectomy | 562/1,188 | 47.3% (44.4–50.2) |
| PCI2 | Post-operative CCRT for pN1 | pN1 patients who had surgery without preoperative chemotherapy | Patients who had post-operative CCRT | 163/368 | 44.3% (39.1–49.5) |
| PCI3 | Post-operative therapy for pN1 | pN1 patients who had surgery without preoperative chemotherapy | Patients who had adjuvant chemotherapy without CCRT as post-operative therapy | 162/349 | 46.4% (41.1–51.8) |
| PCI4 | Post-operative therapy for pN0 or pT1 | pN0 or pT1 patients who had surgery without preoperative chemotherapy | Patients who had adjuvant chemotherapy without CCRT as post-operative therapy | 248/469 | 52.9% (48.2–57.5) |

CI, confidence interval; CIN3, cervical intraepithelial neoplasia 3; CCRT, concurrent chemotherapy and radiation therapy; JSGO, Japan Society of Gynaecologic Oncology; PCI, pattern-of-care item.

Table 4. Reasons for non-adherence to specified care* (47 hospitals)

| QI | QI descriptor | No. of patients | QI score (%) | Sufficient reasons (%) | Insufficient reasons (%) |
|----|---------------|----------------|--------------|------------------------|------------------------|
| QI3 | Radical hysterectomy for stage II adenocarcinoma | 12 | 67.7 | 41.2 | 8.3 | 8.3 | 16.7 | 25.0 |
| QI4 | CCRT as the first-line treatment for stage III or IVA | 66 | 55.1 | 63.6 | 6.1 | 12.1 | 3 | 6.1 | 9.1 |
| QI5 | CCRT using cisplatin for stage III or IVA | 15 | 79.9 | 66.7 | - | 6.7 | - | - | 26.6 |
| QI8 | Cystoscope or proctoscope for stage IVA | 14 | 50.0 | 7.1 | 14.3 | 7.1 | 7.1 | 71 | 57.1 |
| QI9 | Curative radiation therapy using brachytherapy | 59 | 78.8 | 30.5 | 18.6 | 6.8 | 1.7 | 30.5 | 11.9 |

CCRT, concurrent chemotherapy and radiation therapy; QI, quality indicator.

*Reasons cited for less than 10 patients were excluded from the list.
Recommended was generally high. However, other QIs had markedly variable adherence rates, implying non-uniform practice patterns among facilities. Additional data collection relating to reasons for non-adherence helped in elucidation of the causes of the variations.

Trimble et al. studied the change in patterns of care through a period in which a series of new evidences was published and distributed by the National Cancer Institute as part of a clinical announcement for cervical cancer patients in the United States [15]. As per this study, surgery for stage I, radiation therapy — either with or without chemotherapy — for stage II to IVA, and chemotherapy for stage IVB disease, appeared to be the dominant treatment regimens in clinical practice. Overall, our results correlated well with the trend of clinical practice revealed through this study, and suggest that efforts to adhere to optimal care guidelines are the norm. However, the use of CCRT as per our study remained disturbingly low, in contrast to the sharp increase of this treatment modality in the United States as reported by the aforementioned study [16-18].

Comparative analysis of similar studies conducted globally highlights one of the unique traits of Japanese practice patterns — conservative use of radiation therapy, especially CCRT. Currently, in the United States, radiation therapy (including CCRT) is gaining popularity, with a concomitant decrease in surgical resection for gynecological cancers [19]. The guideline published by the National Comprehensive Cancer Network recommends CCRT as an effective treatment modality comparable to any surgical method, in stage IB and IIA patients [20]. Moreover, for those with stage IIB disease and above, CCRT is now regarded as a primary choice of treatment after several randomized clinical trials (RCTs) revealed an improved survival rate [17,21,22]. Although CCRT is the recommended treatment option, almost 50% of stage IIB patients still receive surgery in Japan [23]. Moreover, our study shows that the adherence rate for QIs and PCIs pertaining to the use of CCRT, such as ‘CCRT as the first-line treatment for stage III or IV A’ (QI4) or ‘post-operative CCRT for pN1’ (PCI2), remained relatively low.

The trend was also evident in the choice of adjuvant therapy. Although CCRT is now the standard for adjuvant therapy for high recurrence risk patients [23], as adherence data for ‘post-operative therapy for pN1’ (PCI3) shows, chemotherapy was selected in a substantial number of cases as post-operative therapy across the board in Japan. As a study by Ikeda et al. [24] showed, disagreements regarding the optimal adjuvant therapy remain unresolved. To resolve this issue, a nation-wide retrospective study comparing the effect of adjuvant chemotherapy with that of radiation-based therapy was conducted. The results revealed similar overall recurrence as well as mortality for high-risk patients [25]. To further confirm the findings, a new prospective trial conducted by the Japanese Gynecologic Oncology Group is currently ongoing.

The lack of widespread use of radiation therapy is partially explained by the history of gynecological medicine in Japan. With the delayed availability of radiation therapy, surgical resection had long been chosen as a primary source of treatment [5]. Surgical expertise is believed to be the reason for the limited use of radiation therapy and CCRT [11,23]. In addition, side effects such as postsurgical ileus and severe lymphedema have prevented this procedure from gaining popularity. Finally, with regard to curative radiation therapy, a study has shown that the median age in RCTs conducted in the United States from which the conclusion was drawn was 40, while median age of those receiving such care in Japan is 70 [26]. The presented age gap could prevent direct application of the RCT findings to the
Japanese population, making further studies necessary for solidifying the optimal choice of treatment for this population.

Although the trend was most clearly elucidated for the QI referring to radiation therapy, reasons for non-adherence implicated comorbidities as the major reason for choosing alternatives for most of the QIs. Although the comorbidities were varied, a substantial number of patients were treated with alternative treatment due to age-related issues such as impairment of the liver and/or the kidney. Overall, except for QI8, which showed heavy use of CT and MRI as diagnostic tools, ‘insufficient reasons’ for non-adherence were observed in as low as 10% to 20% of the cases. We conclude from our results that though there is room for improvement, efforts were made by the participating hospitals to provide care in accordance with the guidelines.

Our study has several limitations. The primary limitation is the inability to capture details of care provided at hospitals other than those at which the relevant cases were registered, though such cases are infrequent, as revealed by our survey of reasons for non-adherence. In addition, lack of sub-stage information in the HBCR prevented QIs and PCIs requiring sub-stage information from defining target patients effectively. This was unavoidable, since the mandate to record disease sub-stage data was implemented only in the year 2016. Likewise, the scarce information available on operative procedure in claims data, especially the extent of lymph node dissection, limited the range of measurable QIs. Augmenting data sources by linkage, and refining the procedure codes, could expand the application of QIs to broader aspects of care in the future.

Finally, although we recognize the importance of validity test, the validity of the QIs in terms of the process-outcome link is yet to be proven. Although many standards of care are derived from well-designed RCTs, effectiveness of those standards may not apply in real world settings in which many patients have comorbidities or even multiple primary cancers. Bristow et al. in a study conducted in the United States, revealed a positive correlation between QI adherence and survival rate in ovarian cancer [27], and a similar study performed in a Japanese population in the field of cervical cancer would be valuable. Future studies are needed to confirm the association of QIs with survival, and broaden its potential as a measure of quality care.

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