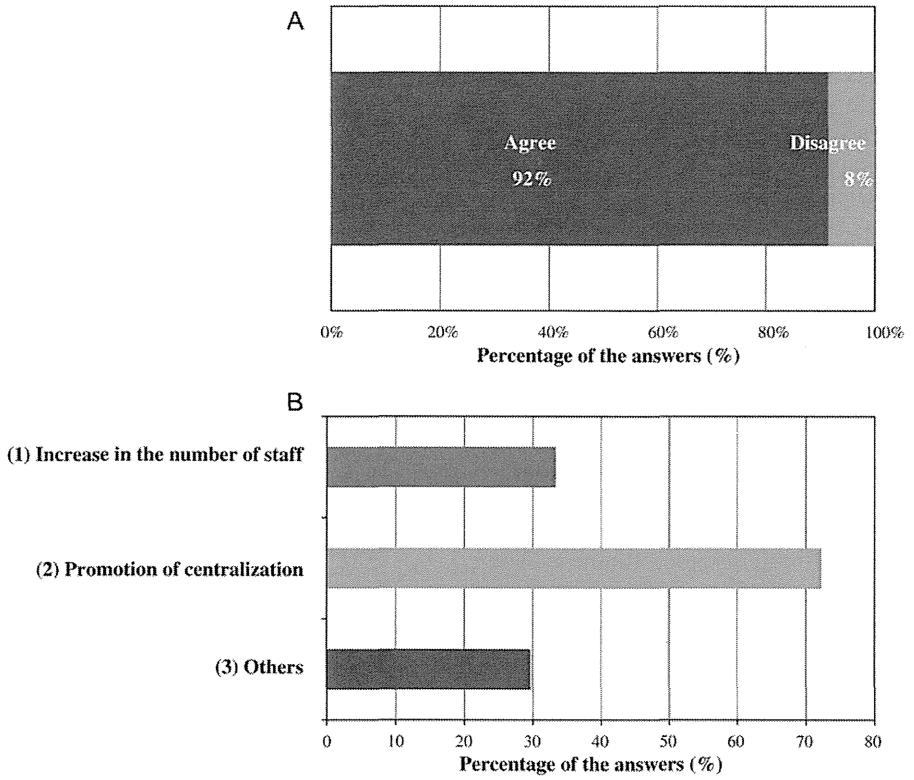

Figure 3. The influence of the consultation fee for outpatient radiotherapy on radiation oncology clinics in Japan. (A) The questionees were asked whether introduction of this consultation fee is expected to contribute to the future development of radiation oncology clinics in Japan. (B) Those who answered 'agree' in the above question were asked to select the reasons for their assumption from the following options: (1) compelling force to increase the number of staff in the radiation oncology department, (2) promotion of centralization of resources and staff in radiation oncology and (3) others. Multiple selections were allowed.

Of the remaining 59 questionees, 92% (54 out of 59) assumed that there was a positive influence of the consultation fee on radiation oncology clinics in Japan (Fig. 3A). The principal reason for this positive opinion was the compelling force to increase the numbers of staffs in the radiation oncology department (Fig. 3B).

DISCUSSION

In Japan, the consultation fee for outpatient radiotherapy was newly introduced in the national health insurance system in April 2012 (1). We assessed the effect of introduction of this consultation fee on radiation oncology clinics through a questionnaire survey. The results revealed that this consultation fee has prevailed in Japan, and most patients who receive radiotherapy in an outpatient setting in Japan are charged for this consultation fee (Fig. 1). The questionees of this survey were the councilors of JASTRO, whose affiliated hospitals were, in general, larger than those of average Japanese radiation oncology centers. Accordingly, the proportion of the patients who were charged a consultation fee might be overestimated in this survey.

Overall, an increased number of full-time radiation oncology nurses after introduction of the consultation fee for outpatient radiotherapy were reported by 15% of the questionees (Fig. 2A). A multidisciplinary medical care system was not common in Japan before the 1990s, but the Japanese MLHW introduced a multidisciplinary palliative care fee and a multidisciplinary nutrition support fee in 2002 and 2006, respectively, in the national health insurance system in Japan (3,4). These medical fees promoted multidisciplinary medical care teams for palliative care or nutrition support in Japan (4,5). A similar effect of promoting multidisciplinary radiation oncology teams is expected by introduction of the consultation fee for outpatient radiotherapy. In fact, more frequent observations of patients by medical staff were reported even from institutions where there was no increase in the number of medical staff for radiation oncology clinics.

JASTRO carries out national structure surveys in Japan every year, which include the number of personnel in each radiation oncology facility (6–8). The number of personnel is based on the answers from about 700 Japanese radiation oncology facilities (>90% of facilities at work in Japan), and these answers were provided by radiation oncologists at an administrative position of each facility. Compared with the JASTRO's national structure surveys, the targets for this questionnaire were a limited number of radiation oncologists, since there are about 1000 radiation oncologists in Japan (9). In addition, the data presented here were not based on the administrative data of the hospital, but on the reports from the questionees. This was a major limitation of the study. However, because it was a small survey for a specific topic, our questionnaire could promptly detect a change in the number of personnel engaged in radiation oncology clinics in relation to this new consultation fee, compared with the JASTRO's national structure survey.

In conclusion, our questionnaire survey revealed that one reason for the workforce shortage in radiation oncology clinics might be attributable to poor reimbursement from the health insurance system in Japan, where there have long been smaller numbers of medical staff engaged in radiation oncology clinics than in the USA and European countries (10,11). A large proportion of the questionees were also expecting positive results on the development of radiation oncology clinics in Japan due to introduction of the consultation fee (Fig. 3A). The authors also assume that this consultation fee compels the development of radiation oncology clinics in Japan through an increase in the number of full-time radiation oncologists and other medical staff, and the prevalence of multidisciplinary medical care teams in radiation oncology.

Supplementary data

Supplementary data are available at http://www.jjco.oxfordjournals.org.

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Conflict of interest statement

None declared.

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RADIATION ONCOLOGY

RESEARCH Open Access

Patterns of radiotherapy practice for biliary tract cancer in Japan: results of the Japanese radiation oncology study group (JROSG) survey

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Abstract

Background: The patterns of radiotherapy (RT) practice for biliary tract cancer (BTC) in Japan are not clearly established.

Methods: A questionnaire-based national survey of RT used for BTC treatment between 2000 and 2011 was conducted by the Japanese Radiation Oncology Study Group. Detailed information was collected for 555 patients from 31 radiation oncology institutions.

Results: The median age of the patients was 69 years old (range, 33–90) and 81% had a good performance status (0–1). Regarding RT treatment, 78% of the patients were treated with external beam RT (EBRT) alone, 17% received intraluminal brachytherapy, and 5% were treated with intraoperative RT. There was no significant difference in the choice of treatment modality among the BTC subsites. Many patients with EBRT were treated with a total dose of 50 or 50.4 Gy (~40%) and only 13% received a total dose ≥60 Gy, even though most institutions (90%) were using CT-based treatment planning. The treatment field consisted of the primary tumor (bed) only in 75% of the patients. Chemotherapy was used for 260 patients (47%) and was most often administered during RT (64%, 167/260), followed by after RT (63%, 163/260). Gemcitabine was the most frequently used drug for chemotherapy.

Conclusions: This study established the general patterns of RT practice for BTC in Japan. Further surveys and comparisons with results from other countries are needed for development and optimization of RT for patients with BTC in Japan.

Keywords: Biliary tract cancer, Radiotherapy, Chemotherapy, Adjuvant, Palliative

Background

Biliary tract cancer (BTC) is a rare disease that is curable by surgery in fewer than 10% of all cases. Prognosis depends in part on the anatomic location of the tumor, which affects its resectability. Total resection is possible for 25% to 30% of lesions originating in the distal bile duct, a rate that is clearly better than that for lesions in more proximal sites. However, the rate of relapse is as high as 60-75%, even if clear resection (R0 resection) is possible [1]. In many patients with a tumor that cannot be completely removed by surgery, other treatments such as radiotherapy (RT) or stenting procedures may maintain adequate biliary drainage and improve survival. Optimal management is therefore essential for both postoperative and unresectable BTC.

In Japan, there were an estimated 20,734 new cases of BTC in 2007, with more than a 3-fold increase over the last three decades [2], while RT has become much more common because new methods and technology for treatment planning are now available. For these reasons,

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optimal management of RT for BTC has become a major concern in Japan. For the study presented here, the Japanese Radiation Oncology Study Group (JROSG) conducted a nationwide questionnaire-based survey on BTC. The questionnaire elicited detailed information regarding patient characteristics, treatment characteristics, and outcomes of treatment. The primary goal of this study was to determine the patterns of RT practice for BTC in order to provide assistance with development of future randomized clinical trials. Therefore, factors influencing the treatment outcome are analyzed elsewhere (Yoshioka et al.: Factors influencing survival outcome in radiotherapy for biliary tract cancer, submitted). To the best of our knowledge, this is the first report to establish how RT is used nationally to treat BTC in Japan.

Methods

The JROSG conducted a nationwide survey of RT used for BTC treatment between 2000 and 2011 using a questionnaire requesting detailed information on patients and treatment characteristics. Patients were included if they met the following criteria: diagnosis of BTC without evidence of distant metastasis; treatment with RT between 2000 and 2011; no diagnosis of any other malignancy; and no previous RT. Diagnosis of BTC without pathologic verification was based on radiographic findings from contrast-enhanced computed tomography (CT), ultrasonography, endoscopic ultrasonography, and endoscopic retrograde/magnetic resonance cholangiopancreatography.

Of the 71 radiation oncology centers in Japan belonging to the JROSG, 31 (40%) agreed to participate in the survey. The other centers did not participate mostly because too few BTC patients had been treated with RT at the center in the study period. Each participating center provided a database of patients with BTC treated with RT between 2000 and 2011. The study was performed according to guidelines approved by the institutional review board of each institution whenever necessary.

The Mann–Whitney *U* test and Student's *t*-test were used to investigate relationships between variables. A p value of < .05 or a 95% confidence interval not including 1 was considered to be statistically significant. All statistical tests were 2-sided.

Results

Data collection

Detailed information was collected for 555 patients from 31 institutions with a median of 15 patients per institution (range: 1–56 patients). The distribution of the number of institutions based on the number of patients treated between 2000 and 2011 is shown in Figure 1. This indicates considerable variation among institutions in the number of patients treated during the 11-year period: ≤10 patients were treated at 13 institutions (42%), while over 30 patients were treated at only 6 institutions (19%).

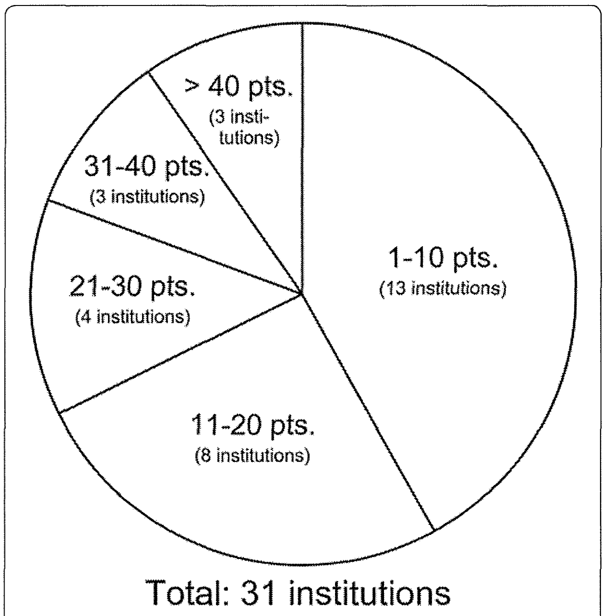

Figure 1 Distribution of institutions by number of patients treated during 2000–2011. The number of patients varied considerably among institutions.

Patient and disease characteristics

The background characteristics of all 555 patients are listed in Table 1. The median age was 69 years old (range, 33–90 years old) and 48% of the patients were ≥70 years old. Pre-therapeutic evaluations were performed by ultrasonography, CT, and magnetic resonance cholangiography in 81%, 93%, and 58% of the patients, respectively. Regarding the primary site, ~50% of BTC lesions arose in the perihilar regions of the extrahepatic bile duct, with distal regions of the extrahepatic bile duct being the second most common site (26%). Among all patients, >80% had an Eastern Cooperative Oncology Group performance status of 0–1, ~30% had a drinking or smoking habit, 52% had an unresectable tumor at diagnosis, and 53% had clinical stage T3-4 disease at diagnosis.

Characteristics of surgical procedures

Primary surgery before RT was performed in 242 patients (44%). Curative surgery was performed in 235 patients, but only 63 (26% of those who underwent surgery) had complete (R0) resection. R1 resection (microscopic positive margins) and R2 resection (macroscopic residual tumor) were performed in 142 (59%) and 37 (15%) patients, respectively. Note that surgeries included non-curative (R2) and curative-intent (R0 or R1) resections, because our cohort was based on a RT database. Lymph node dissection was performed on

Table 1 Patient and disease characteristics (n = 555)

Characteristic	Patients (%)
Age (median, 69 y)	
< 70 y	288 (51.9)
≥ 70 y	267 (48.1)
Gender	
Female	183 (33.0)
Male	372 (67.0)
Pathologic type, verified	
Yes, adenocarcinoma	417 (75.1)
Yes, other	5 (0.9)
No	133 (24.0)
Ultrasonography (before RT)	
Yes	451 (81.3)
No	21 (3.8)
Unknown	83 (14.9)
CT (before RT)	
Yes	515 (92.8)
No	5 (0.9)
Unknown	35 (6.3)
MRCP (before RT)	
Yes	324 (58.4)
No	152 (27.4)
Unknown	79 (14.2)
PTCD	
Yes	242 (43.6)
No	151 (27.2)
Unknown	162 (29.2)
Primary site	
Intrahepatic bile duct	71 (12.8)
Gallbladder	42 (7.6)
Extrahepatic bile duct	439 (79.1)
Perihilar	278 (50.0)
Distal	144 (25.9)
Unknown	17 (3.1)
Ampulla of Vater	3 (0.5)
Maximal tumor size (Median, 4.0 cm)	
< 4.0 cm	195 (35.1)
≥ 4.0 cm	198 (35.7)
Unknown	162 (29.2)
Tumor emboli	
Yes	32 (5.8)
No	292 (52.6)
Unknown	231 (41.6)
ECOG performance status	
0	223 (40.2)

Table 1 Patient and disease characteristics (n = 555) *(Continued)*

1	226 (40.7)
2	77 (13.8)
3	17 (3.1)
4	1 (0.2)
Unknown	11 (2.0)
Jaundice	
Yes	355 (64.0)
No or unknown	200 (36.0)
CA19-9 (U/mL)	
< 37	102 (18.4)
37-1,000	253 (45.6)
≥ 1,000	81 (14.6)
Unknown	119 (21.4)
CEA (ng/ml)	
< 5	300 (54.1)
5-10	63 (11.3)
≥ 10	49 (8.8)
Unknown	143 (25.8)
Alcohol consumption	
Yes	193 (34.8)
No	223 (40.2)
Unknown	139 (25.0)
Smoking	
Yes	175 (31.5)
No	239 (43.1)
Unknown	141 (25.4)
Diabetes mellitus	
Yes	75 (13.5)
No	383 (69.0)
Unknown	97 (17.5)
Clinical T stage	
TX	11 (2.0)
T1	41 (7.4)
T2	147 (26.4)
T3	183 (33.0)
T4	112 (20.2)
Unknown	61 (11.0)
Clinical N stage	
N0	310 (55.9)
N1	165 (29.7)
Unknown	80 (14.4)
Clinical stage	
I	96 (17.3)
II	202 (36.4)

Table 1 Patient and disease characteristics (n = 555) *(Continued)*

III	146 (26.3)
IV	25 (4.5)
Unknown	86 (15.5)
Resectable at diagnosis	
Yes	254 (45.8)
No	288 (51.9)
Unknown	13 (2.3)
Investigational protocol	
Yes	0 (0)
No	555 (100)

Abbreviations: *RT* Radiotherapy; *CT* Computed tomography; *MRCP* Magnetic retrograde cholangiopancreatography; *PTCD* Percutaneous transhepatic cholangiodrainage; *ECOG* Eastern cooperative oncology group; *CEA* Carcinoembryonic antigen; *CA19-9* Carbohydrate antigen 19–9.

173 patients (71%) and a positive node was identified pathologically in 85 patients (35%).

Radiation treatment characteristics

The most common treatment modality was external beam radiotherapy (EBRT) alone (78% of the patients), followed by intraluminal brachytherapy (ILBT) with or without EBRT (17%) and intraoperative RT (IORT) with or without EBRT (5%). Chemotherapy before, during, or after RT was used for 260 patients (47%).

The patterns of RT practice or choice of treatment modality according to the BTC subsites are shown in Figure 2. Because the subsites of 17 patients were unknown, the patterns for 538 patients were analyzed. The rate of primary surgery varied according to the tumor subsite: primary surgery was performed for only 30% of tumors that originated in proximal regions (intrahepatic and perihilar), but for 67% of those that originated in more distal lesions (distal and gallbladder) ($p < .05$). However, there was no significant difference in the choice of treatment modality among the BTC subsites.

Table 2 shows the treatment modality choices according to purpose of RT, which was divided into four groups: RT after curative resection (R0-1) (n = 183), RT after non-curative resection (R2) (n = 33), curative RT for inoperable cases (n = 235), and palliative RT for inoperable cases (n = 78). The purpose of RT for inoperative cases (curative or palliative) was chosen by radiotherapists who answered the questionnaire. Twenty-six patients with IORT were excluded from this analysis based on a comparison of doses among the variables because strong bias was suspected when a parameter such as IORT was used, which involved a very large dose at one time. Over 90% of the patients who underwent surgery received EBRT alone. For the patients who did not undergo surgery, there was a tendency for ILBT with EBRT to be used for a curative purpose more often than for a palliative purpose, but the difference was not statistically significant (25% vs. 15%, $p = .08$). To compare the combined dose of ILBT and EBRT with a single modality dose (ILBT alone or EBRT alone), the total dose (ILBT + EBRT) was calculated as the biologically equivalent dose in 2-Gy fractions (EQD_2) using the linear quadratic model. The value used for assessing effects on tumors was $\alpha/\beta = 10$ Gy. The median EQD_2 for EBRT alone, ILBT alone and EBRT with ILBT was 50 $Gy_{\alpha/\beta10}$, 36 $Gy_{\alpha/\beta10}$, and 60$Gy_{\alpha/\beta10}$, respectively, while that for ILBT with EBRT was significantly greater than EBRT alone or ILBT alone ($p = .001$). In terms of treatment purpose, however, there were no significant differences in the median EQD_2 among the groups (50$Gy_{\alpha/\beta10}$ for all variables).

EBRT characteristics

The characteristics of the 521 patients who received EBRT are shown in Table 3. The median duration from

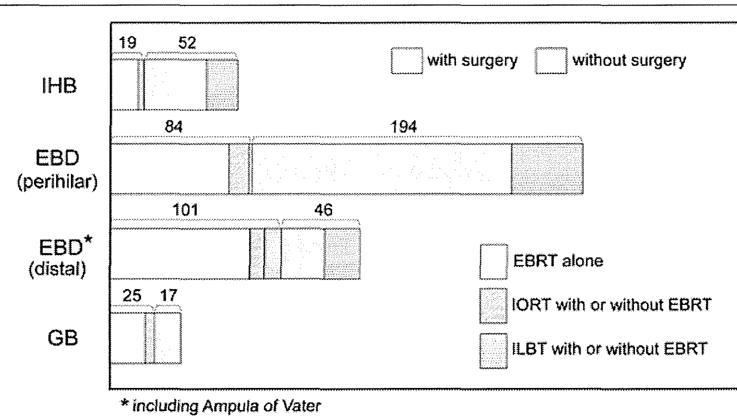

Figure 2 Patterns of radiation practice or choice of treatment modality by BTC subsites. There was no significant difference in the choice of treatment modality among the BTC subsites.

Table 2 Choices of treatment modality according to purpose of RT (n = 529)

Purpose of RT		Actual patients	Treatment modality (%)			median EQD_2 (range) $Gy_{\alpha/\beta 10}$
			EBRT alone	ILBT alone	ILBT + EBRT	
Surgery+	Curative intent (R0-1)	183	170 (92.9)	8 (4.4)	5 (2.7)	50 (6–90)
	Non-curative intent (R2)	33	31 (93.9)	1 (3.0)	1 (3.0)	50 (4–74)
Surgery-	Curative	235	177 (75.3)	0 (0)	58 (24.7)	50 (9–68)
	Palliative	78	55 (70.5)	11 (14.1)	12 (15.4)	50 (39–74)
	median EQD_2 (range) $Gy_{\alpha/\beta 10}$		50 (4–90)	36 (14–44)	60 (33–82)	

Abbreviations: *RT* Radiotherapy; *EBRT* External beam radiotherapy; *ILBT* Intraluminal brachytherapy; *EQD2* The biologically equivalent dose in 2-gray fractions.

Table 3 EBRT characteristics (n = 521)

Characteristic	Patients (%)
EBRT Radiation portals	
2 portals	162 (31.1)
≥ 3 portals	359 (68.9)
EBRT beam energy (MV)	
< 10	24 (4.6)
≥ 10	491 (94.2)
Unknown	6 (1.2)
EBRT dose/fraction (Gy)	
< 1.8	7 (1.3)
1.8	131 (25.1)
2	352 (67.6)
> 2.0	31 (6.0)
EBRT total radiation dose (Gy)	
< 40	69 (13.2)
40 - < 50	129 (24.8)
50/50.4	206 (39.5)
> 50.4 - < 60	52 (10.0)
≥ 60	65 (12.5)
Radiation field	
primary only	388 (74.5)
primary plus regional LN	119 (22.8)
LN only	5 (1.0)
Unknown	9 (1.7)
CT-based treatment planning	
Yes	468 (89.8)
No	53 (10.2)
Conformal therapy	
Yes	333 (63.9)
No	75 (14.4)
Unknown	113 (21.7)
IMRT	2 (0.38)

Abbreviations: *EBRT* External beam radiotherapy; *MV* Megavolt; *Gy* Gray; *LN* Lymph node; *CT* Computed tomography; *IMRT* Intensity-modulated radiotherapy.

surgery to EBRT was 34 days (range, 9–88 days). EBRT was administered with ≥3 portals to 69% of the patients, at ≥10-megavolt beam energy for >90%, and at 1.8 Gy or 2.0 Gy per fraction; and with a total dose of ≥40 Gy for ~90%. CT-based treatment planning and conformal RT were used for 90% and 64%, respectively, of patients treated with EBRT, but only two of these patients received intensity-modulated RT (IMRT).

A summary of the EBRT field based on performance of surgery and nodal status is shown in Table 4. The treatment field consisted of the primary tumor only in 388 (75%) of 521 patients and the primary tumor plus regional lymph nodes in 119 (23%). Patients who underwent surgery received RT for the primary tumor (bed) plus regional lymph nodes more frequently than patients who did not undergo surgery (29% vs. 19%, $p < .01$). Additionally, among the patients who underwent surgery, RT for the primary tumor (bed) plus regional

Table 4 EBRT field according to performance of surgery and N stage (n = 521)

Group	Patients (n)	Radiation field (%)		
		Primary	Primary plus LN	Others
Surgery +				
Total	219	151 (68.9)	63 (28.8)	5 (2.2)
pN0	75	54 (72.0)	20 (26.7)	1 (1.3)
pN1	78	49 (62.8)	29 (37.2)	0 (0)
Unknown	66	48 (72.7)	14 (21.2)	4 (6.1)
cN0	111	95 (85.6)	13 (11.7)	3 (2.7)
cN1	65	43 (66.2)	20 (30.8)	2 (3.0)
Unknown	43	13 (30.2)	30 (69.8)	0 (0)
Surgery -				
Total	302	237 (78.5)	56 (18.5)	9 (3.0)
cN0	189	171 (90.5)	11 (5.8)	7 (3.7)
cN1	79	34 (43.0)	44 (55.7)	1 (1.3)
Unknown	34	32 (94.2)	1 (2.9)	1 (2.9)
Total	521	388 (74.5)	119 (22.8)	14 (2.7)

Abbreviation: *EBRT* External beam radiotherapy; *LN* Lymph node.

lymph nodes of those with clinically positive nodes was more frequently performed than in patients with clinically negative nodes (31% vs. 12%, $p < .01$). However, patients with pathologically positive nodes tended to receive RT for the primary tumor (bed) plus regional lymph nodes more frequently than patients with pathologically negative nodes, but the difference was not statistically significant (37% vs. 27%, $p = .16$). Among patients who did not undergo surgery, RT for the primary tumor and regional lymph nodes of those with clinically positive nodes was more frequently performed compared to patients with clinically negative nodes (56% vs. 6%, $p < .01$). However, some patients with clinically positive nodes also underwent EBRT for the primary tumor only (43%).

Analyses of practice patterns of EBRT were performed according to caseload of institutions (Figure 3a-d) and patient age (Figure 3e-h). Caseloads were divided into three categories based on the number of patients treated within the study period at each institution (≤10, 11–29, and ≥30 patients). In institutions with ≥30 patients, the rates of postoperative RT (compared to inoperable cases) (Figure 3A), EBRT for the field of the tumor (bed) plus regional LN (compared to tumor only) (Figure 3B),

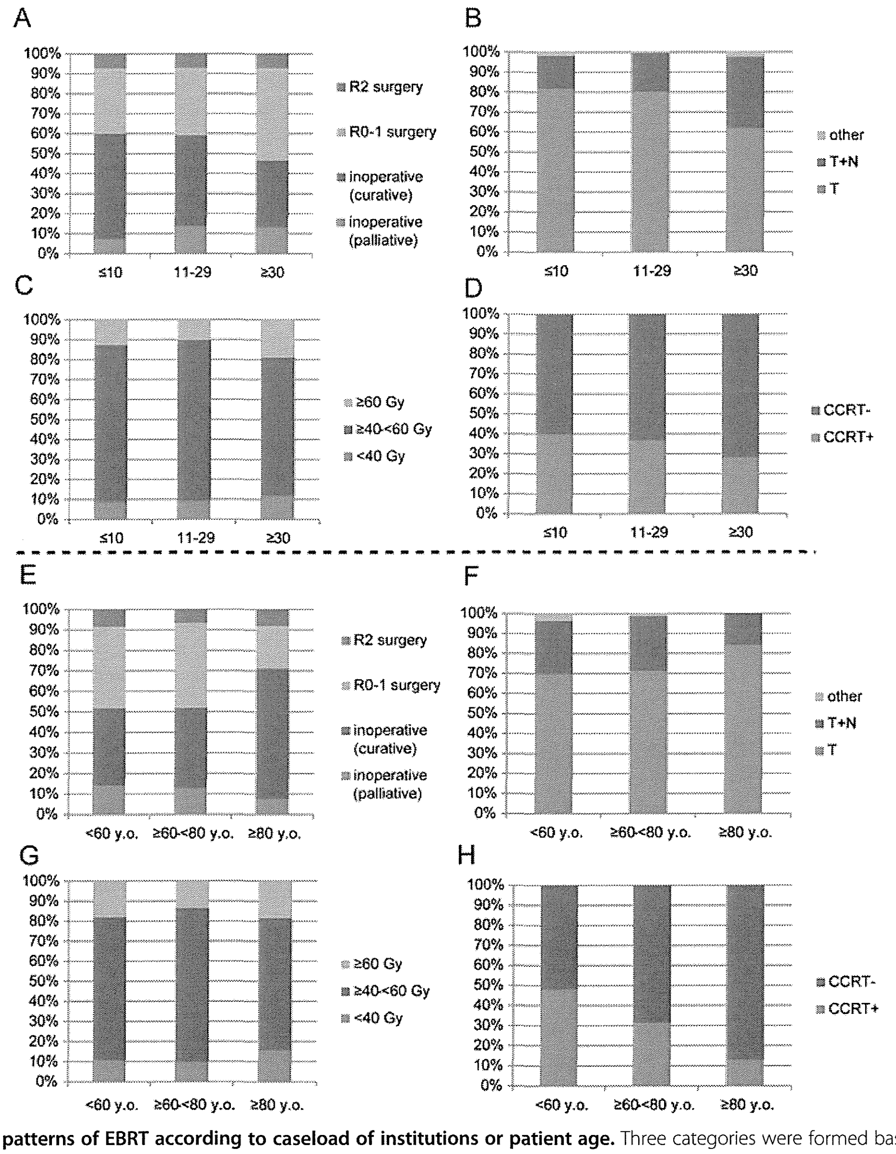

Figure 3 Practice patterns of EBRT according to caseload of institutions or patient age. Three categories were formed based on the number of patients treated at each institution (≤10, 11–29 and ≥30 patients) (**A-D**) or age (<60, ≥60- < 80, and ≥80 years old) (**E-H**) and evaluated based on treatment intent (**A, E**), EBRT field size (**B, F**), EBRT total dose (**C, G**), and concurrent chemotherapy (**D, H**).

and patients receiving ≥60 Gy (Figure 3C) were significantly higher than those in institutions with <30 patients. Age was also divided into three categories (<60, ≥60- < 80, and ≥80 years old). The use of CCRT was significantly higher in patients <60 years old compared to those ≥60- <80 years old, and in those ≥60- < 80 years old compared to those ≥80 years old (Figure 3H).

ILBT and IORT characteristics

A total of 96 patients (17%) received ILBT at 13 institutions (42%). The characteristics of these cases are listed in Table 5. All 96 patients were treated with ILBT using an iridium-192 source and at 5 or 6 Gy per fraction in 55% of cases and with a total dose of ≥15 Gy in 85%, 76 (79%) of whom received ILBT with EBRT at a median EBRT dose of 40 Gy (range, 20–60 Gy). The most common prescription point was 10 mm from the source (75%).

IORT was used for only 26 patients (5%) at four institutions (13%, 4/31), 12 (2%) of whom received IORT with EBRT and 14 (3%) received IORT alone. The median dose for IORT was 25 Gy (range, 20–30 Gy), with a median beam energy of 12 mega-electron volts (range, 4–25 mega-electron volts).

Chemotherapy

Chemotherapy was used for 260 patients (46%), including 167 concurrently with RT (78 concurrently alone; 7 pre-RT and concurrently; 67 concurrently and post-RT; and 15 pre-RT, concurrently, and post-RT), 4 pre- and post-RT, 12 pre-RT alone, and 77 post-RT alone. The drugs and timing of chemotherapy for these patients are listed in Table 6. Chemotherapy was most often given during RT (64%, 167/260) followed by after RT (63%, 163/260), while the most frequently used drug for chemotherapy was gemcitabine (47%) followed by 5-FU (37%). TS-1 and UFT were especially frequently used after RT.

The 167 patients who received chemotherapy during RT (concurrent chemoradiation (CCRT)) were analyzed further because this method has been shown to be efficacious for treatment of patients with BTC with or without surgery. The patients were divided into four groups according to performance of surgery and timing during the study period: Group A, surgery, 2000–2005 (n = 24); Group B, surgery, 2006–2011 (n = 30); Group C, no surgery, 2000–2005 (n = 65); and Group D, no surgery, 2006–2011 (n = 48). There was a significant difference in the use of gemcitabine-containing regimens between Groups A and B and between Groups C and D (Figure 4). This suggests a trend away from the use of 5-FU towards a more frequent use of gemcitabine concurrently with RT for patients with BTC treated with or without surgery.

Table 5 Intraluminal brachytherapy (n = 96)

Characteristic	Patients (n)
Source	
Ir-192	96 (100)
ILBT single dose/fraction (Gy)	
< 5	16 (16.7)
5	33 (34.4)
6	20 (20.8)
> 6	27 (28.1)
Total dose (Gy)	
< 15	14 (14.6)
15 - 25	41 (42.7)
≥ 25	41 (42.7)
Prescription point (from the source)	
5 mm	4 (4.2)
7 mm	4 (4.2)
10 mm	72 (75.0)
12 mm	14 (14.6)
Unknown	2 (2.1)
With EBRT (Median EQD_2, 60.4 Gy)	76 (79.2)
Without EBRT (Median EQD_2, 35.8 Gy)	20 (20.8)

Abbreviations: *Ir* Iridium; *Gy* Gray; *EBRT* External beam radiotherapy; *EQD_2* The biologically equivalent dose in 2-gray fractions.

Discussion

RT for BTC can be classified into adjuvant therapy after surgery or therapy for inoperable cases. While no randomized control trial has been conducted, a meta-analysis revealed that patients with extrahepatic cholangiocarcinoma treated with adjuvant RT show a significantly lower mortality rate than patients treated with surgery alone [3]. Data in the Surveillance Epidemiology and End Result database also suggest that palliative RT prolongs survival in patients with extrahepatic cholangiocarcinoma [4]. In these reports, the outcomes of the treatment were

Table 6 Drugs used and timing of chemotherapy (n = 260)

Variable	Actual patients (%)	Chemotherapy timing (%)		
		Before RT	During RT	After RT
Actual patients (n)	260	38	167	163
Drugs				
GEM	122 (46.9)	24 (63.2)	72 (43.1)	78 (47.9)
5-FU	97 (37.3)	9 (23.7)	74 (44.3)	43 (26.4)
Cisplatin	40 (15.4)	9 (23.7)	22 (13.2)	15 (9.2)
TS-1	45 (17.3)	6 (15.8)	5 (3.0)	42 (25.8)
UFT	34 (13.1)	3 (7.9)	12 (7.2)	24 (14.8)
Other	9(3.4)	3 (7.9)	4 (2.4)	2 (1.2)

Abbreviations: *RT* Radiotherapy; *GEM* Gemcitabine; *5-FU* 5-Fluorouracil; *TS-1* Tegafur-gimeracil-oteracil potassium; UFT Tegafur-uracil.

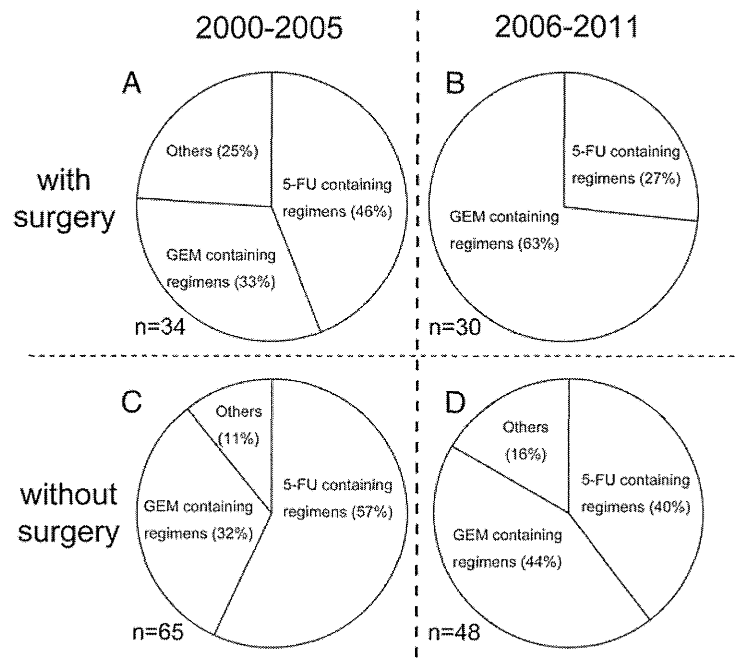

Figure 4 Changes in chemotherapy regime combined with radiotherapy during 2000–2011 based on prior therapy. The patients were divided into four groups according to performance of surgery and the timing during the study period. **A**: Surgery, 2000–2005 (n = 24); **B**: Surgery, 2006–2011 (n = 30); **C**: No surgery, 2000–2005 (n = 65); **D**: No surgery, 2006–2011 (n = 48).

reported in detail, but detailed information on RT use has not been provided and there are few reports on patterns of RT practice. We therefore decided to evaluate the practice of RT for BTC at Japanese radiation oncology centers, with the goal of assisting with development of randomized clinical trials. JROSG has conducted similar surveys and successfully determined the general patterns of RT practice for several other cancers in Japan [5,6]. Of the 31 responding institutions, 43% treated fewer than 10 patients over the period covered by the survey. Surprisingly, none of the patients were treated with an investigational protocol, clearly indicating a need for a prospective multicenter study to determine a standard therapeutic approach.

The results of the study showed that CT-based treatment planning was used for approximately 90% of the patients. Previous nationwide surveys of the structural characteristics of radiation oncology in Japan found that only 329 (45%) of 726 facilities in 2003 and 407 (57%) of 712 facilities in 2005 used CT-based treatment planning [7,8]. These results suggest that three-dimensional conformal RT planning became mainstream during the survey period or that patients with BTC received RT more frequently in facilities with advanced equipment.

We examined the variations in RT use (modality, total dose, or RT fields) according to the purpose of RT or BTC subsites. Some analyses have suggested that there is a dose–response relationship for treatment of BTC and have stressed the importance of dose escalation [9,10]. However, many patients with EBRT included in this survey were treated with a total dose of 50 or 50.4 Gy (~40%) and only 13% of the patients received a total dose ≥60 Gy. These data indicate that use of sufficient doses for EBRT for tumors in the hepatic hilum and liver regions was severely restricted by technical difficulties with the delivery of high doses to these regions while sparing surrounding organs, including the liver, duodenum, stomach, and spinal cord, even though most institutions used CT-based treatment planning. Recently, IMRT has emerged as a sophisticated technique for treatment of tumors, including BTC, in areas at risk of recurrence, while sparing adjacent normal tissue from high-dose irradiation [11]. However, only two patients were treated with IMRT for EBRT during the survey period.

ILBT can also be used for dose escalation in a region at risk [9,12] since it has the advantage of allowing delivery of a sufficient dosage to a target focus while reducing the effect of irradiation on surrounding tissues. Theoretically, a combination of ILBT and EBRT can enhance the beneficial effects of RT, with fewer adverse effects than those incurred with EBRT alone. In fact, ILBT with EBRT entailed a significantly higher EQD_2 dose than EBRT alone in our study cohort. While 42% of the institutions performed ILBT, only 14% of all patients received ILBT combined with EBRT, indicating that this treatment modality was used only in selected cases because the effect of ILBT is limited to the area surrounding the lumen of the biliary tract and improvement in local control can therefore be expected only for small tumors [9].

The optimal radiation field for BTC remains to be defined. The majority of relapses after resection with curative intent occur at the primary tumor site [13], which suggests that it may be reasonable to limit RT to the primary tumor (bed). Only 23% of the patients included in this survey received radiation to the tumor (bed) as well as the regional lymph nodes, regardless of the lymph node status. Although limiting the radiation field to the tumor (bed) has tended to become prevalent in Japan, the definition of clinical target volume included regional lymph nodes as well as the tumor (bed) in a recent meta-analysis of 14 selected papers with detailed information on adjuvant RT after surgery [3], as well as in many reports on unresectable BTC published since 2000 [14-17]. Collectively, these findings indicate that the radiation field for BTC is not yet standardized due to the lack of a large randomized control trial and that additional studies investigating the optimal radiation field should be conducted.

The study presented here showed that chemotherapy is frequently administered in combination with RT (47% of all patients). Chemotherapy was most often administered during RT, followed by after RT. Several trials have examined the efficacy of adjuvant chemoradiation after surgery [18] or of chemoradiation for unresectable cases [19]. The National Comprehensive Cancer Network (NCCN) reported that most CCRT for BTC involved the use of 5-FU, and that CCRT with gemcitabine is not recommended due to the limited experience with and potential toxicity of this treatment. However, the use of CCRT combined with gemcitabine-containing regimens increased in Japan during the period covered by the current survey, which suggests that additional studies should be undertaken to establish the optimal sequencing of RT and chemotherapy with drugs such as gemcitabine. For chemotherapy for advanced BTC, the recent randomized control phase III ABC-02 study showed that a combination of gemcitabine and cisplatin improved overall and progression-free survival by 30% over gemcitabine alone [20]. Based on these results, the combination of gemcitabine and cisplatin can now be considered to be the standard of care as first-line chemotherapy for patients with advanced or metastatic BTC. In Japan, however, oral anticancer drugs such as TS-1 or UFT also tend to be used as adjuvant chemotherapy after RT, and only two patients in the current study were treated with a combination of gemcitabine and cisplatin after RT.

Conclusions

Patients with BTC should continue to be enrolled in prospective studies of RT with radiosensitizing agents or of RT with dose escalation methods using techniques such as IMRT. Further surveys and comparisons with results from other countries are needed for development and optimization of RT for patients with BTC in Japan.

Consent

Written informed consent was obtained from the patient for publication of this report and any accompanying images.

Abbreviations

RT: Radiotherapy; BTC: Biliary tract cancer; EBRT: External beam radiotherapy; JROSG: The Japanese radiation oncology study group; CT: Computed tomography; ILBT: Intraluminal brachytherapy; IORT: Intraoperative radiotherapy; EQD_2: The biologically equivalent dose in 2-Gy fractions; IMRT: Intensity-modulated radiotherapy; CCRT: Concurrent chemoradiotherapy; NCCN: National comprehensive cancer network.

Competing interests

The authors made no disclosures and not receive specific funding.

Authors' contributions

KO coordinated the entire study. Patient data acquisition was done by FI, HO, HO, NU, TM, NK, TT, HA, TK, TU, YI, KK, MT, YM, HY, MT, KN, and YN. Data analysis was done by FI, KO, and YY. The manuscript was prepared by FI. Corrections and/or improvements were suggested by KO and YY. Revisions were done by HO, HO, NU, TM, NK, TT, HA, TK, TU, YI, KK, MT, YM, HY, MT, KN, and YN. All authors read and approved the final manuscript.

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子宮頸癌の画像誘導小線源治療

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はじめに

子宮頸癌に対し放射線治療は手術と並ぶ根治的治療法である。III期以上の進行例ではもちろんのこと、I、II期の手術可能の早期例においても、米国のガイドライン[1]のみならず本邦での治療ガイドライン[2]で根治的放射線治療は手術と並列する治療オプションの位置づけである。子宮頸癌の根治的放射線治療は、外部照射（全骨盤照射）と腔内照射の組み合わせからなる。他癌と同様に、子宮頸癌の放射線治療も2次元（2D）から3次元（3D）、さらに4次元（4D）へと進化しつつある。外部照射では臨床標的体積（clinical target volume：CTV）ベースの3D計画が普及し[3,4]、強度変調放射線治療（intensity modulated radiotherapy：IMRT）の臨床適用も進みつつある[5]。腔内照射では長らく2方向撮影されたX線画像をベースにした2D計画が行われてきたが、近年ようやくCT/MRIを用いた3D計画治療、画像誘導小線源治療（image-guided brachytherapy：IGBT）が注目されてきた[6]。

2D計画の限界

A点処方を基本としたマンチェスター法は、子宮頸癌腔内照射のスタンダードとして長らく治療の均てん化に貢献してきた。A点線量に基づく標準スケジュールが早くから確立し[7]、良好な治療成績をあげてきた[8]。直腸の晩期合併症の発生率／重症度が2D計画で規定した基準点（ICRU38）[9]での線量と関連することが報告されてきた[10]。しかし、A点線量と局所制御の線量効果関係を明確にできず[11]、膀胱合併症についてICRU38基準点での線量との相関を示せなかった[12]。特定点での線量評価を基本とし、腫瘍形状やリスク臓器全体の座標を考慮できない2D計画の限界は明らかであった。

IGBTの歴史

2D計画の限界を克服するため、CTなど3D画像を用いた腔内照射の試みが1980年代初めよりすでに開始されていた[13]。わが国でも1987年には中野らがMRIを用いた先駆的研究を報告している[14]。ウイーン大学のPotterらは1996年よりCTによるDVHベースの計画を開始した[15]。1998年よりMRIを用いた臨床応用が開始され、2000年よりGroupe Europeen de Curietherapie of the European Society for Therapeutic Radiology and Oncology（GEC-ESTRO）に3D計画を推進するWGが組織された。その後2004年にAmerican Brachytherapy Society（ABS）より[16]、2005年にGEC-ESTROより[17]ガイドラインが出版された。2005年7月にシカゴでワークショップが開催され、その後IGBTの標準化がGEC-ESTRO主導で進められることが合意された。

表1にIGBTの臨床的なメリットをまとめる。2D計画の弱点を克服し、より安全で効果的な治療を行うことが期待できる。

表1　子宮頸癌IGBTのメリット

・アプリケータと腫瘍・臓器との位置関係が把握できる
　タンデム：子宮内腔への留置確認、穿孔の有無確認
　オボイド：頸部、腟円蓋部との位置関係
・リスク臓器の正確な線量評価が可能（DVH）
　特にS状結腸、小腸の線量評価が可能（⇔2Dでは不可能）
・腫瘍（GTV, CTV）の正確な線量評価が可能（DVH）
　腫瘍に対するdose conformityの改善
　小腫瘍例に対するdose de-escalation
　大腫瘍例に対するdose escalation

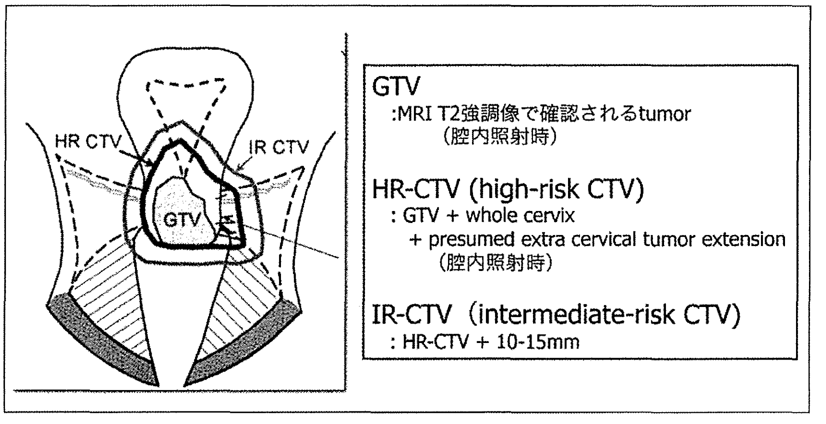

図1　子宮頸癌IGBTにおけるターゲットボリュームの定義[17)]

IGBTにおける治療計画パラメータ

1) Contouring

外部照射と同様に、IGBTにおいても、ターゲットとリスク臓器の適切なcontouringは最重要の作業プロセスである。contouringのばらつきは、IGBTの線量投与に不確実性を与える最も大きな要因と考えられている[18)]。

ターゲットに関しては、GEC-ESTROの定義が現在広く用いられている（**図1**）[17)]。しかし、MRIをベースに作成されているため、CTを用いた計画での運用は難しい。ViswanathanらはCTを使用する場合のHR-CTVの定義を提言した[19)]。彼女らは、MRIと比較してHR-CTVのD90が低めに算出されることを明らかにし、CTにて設定したHR-CTVがMRIよりも過大になることを示唆した[19)]。CTの組織分解能はMRIに劣るため、腫瘍はもちろんのこと周囲の血管や炎症等と子宮頸部との分離も困難なことは少なくない（**図2**）。

リスク臓器（organ at risk：OAR）に関しても、GEC-ESTROの方法[20)]を用いることが一般的である。Viswanathanらの検討では、HR-CTVの評価とは異なり、OARに関してCTはMRIと有意差がなかったことが示されている[19)]。従来の2D計画では、通常OARとして直腸と膀胱のみが評価されてきた。しかし実際にCT等の3D画像にて評価すると、S状結腸や小腸も高線量が投与さ

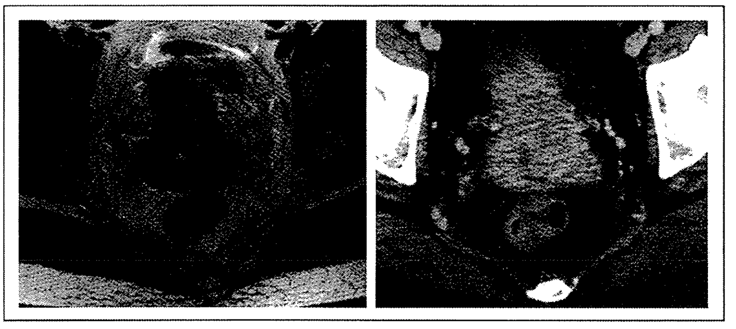

図2　同一症例におけるMRI（T2WI）とCT

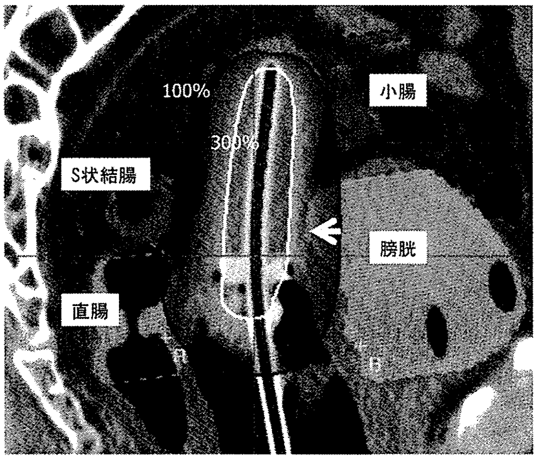

図3　R：ICRU38直腸線量評価点、B：ICRU38膀胱線量評価点
膀胱においてICRU基準点線量は許容値内であるが、矢印部で高線量が投与されている。また、S状結腸、小腸においても100%以上の線量が投与される部位があることがわかる。

れうるリスク臓器であることがわかる（**図3**）。したがって、これらの臓器もcontouringを行い評価することが推奨されている。

2）DVHパラメータ

GEC-ESTROのガイドラインではGTV、HR-CTV、IR-CTVのD100，D90を記録することを推奨している（**表2**）[20]。HR-CTVのD90が局所制御に相関したとの報告もある[21]。しかし、HR-CTVのD90に処方することに関するコンセンサスはなく、現時点ではA点で処方を行い、OARのDVHパラメータ等を確認しながら線量分布を調整し、結果としてのGTV、CTVのDVHパラメータを記録することが現実的であり推奨される。後述するように日本ではCTでの計画がほとんどであり、CTでのHR-CTVのcontouringが非常に難しいことを考えると、HR-CTVのD90処方はさらに慎重であるべきである。一方、OARに関しては、それぞれD0.1cc，D2ccを算出することが推奨されており（**表2**）[20]、晩期合併症の発生率との相関が示唆されている[22]。

3D計画の問題点と課題

表1にまとめたように、IGBTの臨床的なメリ

表2　子宮頸癌IGBTで記録されるべきパラメータ(Embrace protocol)

・A点線量(左、右、平均)
・D100: GTV, HR-CTV, IR-CTV
・D90: GTV, HR-CTV, IR-CTV
・D50: HR-CTV
・V100: HR-CTV
・D0.1cc, D2cc: bladder, rectum, sigmoid
・ICRU38評価点線量: rectum, bladder

表3　子宮頸癌IGBT実施状況

				計画用画像		
国	調査年	対象	回答率	単純X線	CT	MRI
米国(ABS)	2007	ABSメンバー	55%	*43%	*67%	*1%
カナダ	2009	放射線腫瘍医#	62%	50%	45%	5%
英国	2008	46施設	100%	73%	22%	4%
	2011	45施設	96%	26%	53%	21%
日本	2012	171施設	84%	79%	14%	1%

ABS: American Brachytherapy Society、 *US member、 #婦人科腫瘍を扱う

ットは明らかである。しかし普及と適切な適用に向けての課題は少なくない。**表3**に各国でのIGBT実施率を示す[23~26]。各国と比較し、日本ではまだまだ実施率は低い状況である。本邦を含めてIGBTの普及を阻む原因として、従来の2D計画と比較して時間と手間を要する治療であることが挙げられる。前述のアンケート調査でも、放射線治療部門でのマンパワー不足を理由にする回答が多くみられた。さらにCT/MRIへのアクセス、専用のアプリケータの普及や計画装置のスペックも大きな問題である。英国では2008年の調査で26%の実施率であったが、Royal College of Radiologists (RCR) を中心とした積極的な啓蒙活動により推進され、2011年の調査では71%と実施率が急速に増加したことが報告されている。臨床データの集積とともに、学会レベルでの推進、教育活動、さらにインフラの整備のために診療報酬の改善も重要と考えられる。

さらに、CTを用いたIGBTの標準化は重要な課題である。GEC-ESTROで推奨するMRIベースのIGBTは理想的であるが、日本で実施できる施設は非常に限られており、普及にはCTベースのIGBTを前提に考えるべきである。ウィーン大学が中心となり、MRIベースのIGBTの国際多施設臨床研究：EMBRACEが進行中である[27]。これまで26施設が参加し900例が登録されている(2013年6月)。今後CTベースのIGBTの標準化に向けたワーキンググループが国内にも組織され、活動が進められることが期待される。

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未来の放射線治療の方向性

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索引用語：放射線治療，高度化，多様化，センター化，個別化

1 はじめに

近年の放射線治療技術の進歩は著しく，定位放射線治療，強度変調放射線治療といった高精度エックス線照射技術は各領域の固形癌に対する放射線治療において治療効果の向上および副作用の低減に寄与しているのは間違いない．さらに，陽子線，炭素イオン線を用いた粒子線治療も研究段階から本格的な臨床応用，普及といった段階に入り，その特徴的な深部線量分布(飛程を持ち停止する直前で線量のピークを形成)を利用することにより線量集中性がさらに改善され，副作用のさらなる軽減および二次発癌リスクの低減が可能と期待されている．これらの放射線治療技術の進歩が肝胆膵領域の癌治療にも活かされていることは各項に述べられている通りである．高精度エックス線治療，陽子線治療，炭素イオン線治療は，それぞれ，従来型の放射線治療に比較して非常に有効な治療法であることは間違いないが，一方で，このように多様化した放射線治療技術をどのように使い分ければ良いのかという点では臨床現場にある意味で混乱を招いているのも事実である．また，内科領域では分子標的薬剤や免疫療法，外科領域ではロボット手術に代表される低侵襲外科治療，さらには，再生医療が癌治療の分野も注目されている時代であり，癌治療法はこれまでになく多様化の様相を呈している．

本稿では「未来の放射線治療の方向性」という非常に大きなテーマを頂き，どのように話をまとめれば良いのか苦慮するところではあるが，私が考えるあるべき将来の方向性について述べてみたい．

2 高精度エックス線治療と粒子線治療のベストミックスを探る時代へ

100年以上に及ぶ放射線治療の長い歴史を考えても，250kVエックス線からガンマ線，そして現在の主流である高エネルギーエックス線と癌治療に用いられる放射線は時代とともに癌治療により適したものへ変化してきた．この事実を考えた場合，将来的には陽子線や炭素イオン線といった粒子線治療が放射

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線治療の主役を担う時代が訪れてもおかしくないとも考えることができる．しかし，癌の病態はさまざまであり，腫瘍の性質や拡がりなどにより最適な治療法は異なり，ただ単に病巣への線量集中のみが求められるわけではなくエックス線やガンマ線治療の必要性は必ず残ると思われる．例をあげれば，咽頭癌などの頭頸部扁平上皮癌の放射線治療においては，頸部・鎖骨上領域といった広い範囲の系統的なリンパ節領域照射を合わせて行う必要があるため，エックス線を用いた強度変調放射線治療の方がむしろ適しているし，全骨盤照射＋小線源療法で根治可能な子宮頸癌をあえて粒子線で治療する必要もないであろう．その他にも全脳照射や乳癌術後照射，多くの緩和照射などさまざまな状況でエックス線治療はなくてはならない存在である．また，転移性脳腫瘍に対する定位照射もこれまで同様エックス線やガンマ線を用いた治療がその主役を担い続けるであろう．

一方，頭頸部の非扁平上皮癌，肺縦隔腫瘍，消化管原発を除く腹部骨盤部腫瘍などの多くの限局性の癌では，粒子線治療の線量分布の良さを活かしたさらなる低リスク放射線治療を目指すべきと思われる．もちろん，肺や肝臓の小さな腫瘍であれば定位照射で良好な成績が得られているが，粒子線治療を用いることにより副作用のさらなる低減に加え，これまで制御が困難であった比較的大きな腫瘍に対する局所制御も期待できる[1]．特に，肝胆膵の領域に目を向けると，肝細胞癌のようにベースに慢性肝機能障害を有する患者では，周囲正常肝の線量および照射容積を最小限に留められる粒子線治療は肝機能温存の点でメリットは大きく[2~4]，肝内再発例に対する複数回治療にも有利となる[5]．また，胆管癌や膵臓癌の治療においても比較的放射線感受性の高い正常肝，腎臓，腸管への線量を少なくできる点でエックス線治療に比較し明らかに有利である．また，膵癌や胆管癌治療においては，抗癌剤併用時の副作用低減にも役立つ．特に，炭素イオン線では生物学的効果が高く膵癌や胆管癌といった放射線低感受性腫瘍に対するさらなる効果も期待される[6]．

高精度エックス線治療 vs. 陽子線治療，陽子線治療 vs. 炭素イオン線治療といった構図で議論されることも多い昨今ではあるが，いずれも今後の放射線治療の発展には必要不可欠なものであり，より効果的かつ低リスクの放射線治療を確立するために，これらを如何に使い分け，また，いかに組み合わせるかを議論し検証していくことが重要な点である．粒子線治療は未来の放射線治療の可能性を大きく広げる治療法であることは間違いなく，その有効性を確認しながら，癌医療の中に着実に定着させていかなければならない．そのためには，粒子線治療施設の適正な配置と有効利用，臨床試験をベースとした質の高いエビデンスの蓄積，装置の小型化・低コスト化と普及がバランス良く行われていくことが極めて重要と思われる．

3 「均てん化」と「センター化」のベストバランスを探る時代へ

放射線治療は2004年から開始された第3次対癌10カ年総合戦略の重要な柱であり「癌医療水準の均てん化」のもと，放射線治療機器の整備や放射線治療医や医学物理士などの専門医療スタッフの育成が図られてきた．地域格差を是正し放射線治療の質を確保するという観点から一定の成果を上げてきたが，放射線治療機器の分散や増加する放射線治療のニーズに人材育成が追いついていないのが現状である．さらには，高精度X線治療，陽子

線治療，炭素イオン線治療といった放射線治療の高度化・多様化も加わり「均てん化」のみでは対応できないことも明らかとなってきている．事実，2012年6月に策定された厚生労働省の新たながん対策基本計画では，「一部の疾患や強度変調放射線治療などの治療技術の地域での集約化」という文言が盛り込まれている[7]．日本においても今後，強度変調放射線治療，陽子線治療，炭素イオン線治療といった高度な放射線治療技術に関しては「センター化」の方向性で整備が進められていく必要があろう．特に，粒子線治療においては「センター化」という観点での適正配置と有効活用が極めて重要な領域であり，そのためには，本当の意味での機能的な医療連携ネットワークの構築が必要である．また，センター化された数少ない施設を有効に活用するには，紹介側の医療機関との役割分担も大事であり，他の施設に入院中の患者が治療を受ける際でも保険制度上問題とならないような制度上の環境整備が同時に行われなければならない．粒子線治療分野は放射線治療におけるセンター化の良いモデルケースにならなければならない．

4 解剖学的画像ベースから機能・分子画像ベースの放射線治療の時代へ

従来の放射線治療計画は3次元治療計画が主体であったが，近年では腫瘍の呼吸性移動を考慮した4次元治療計画の時代となり，照射技術的にも呼吸同期照射や動体追尾照射や迎撃照射が可能となってきている．しかし，これまでの治療計画は主に形態画像(主にCT)を中心に行われ，腫瘍内の機能や組織環境，周囲正常臓器の内部の機能はあまり考慮されていなかった．一方，近年の分子・機能イメージング分野の進歩は著しく，一般的なものとしては，糖代謝を画像化したF-18 FDG-PETが癌の病期診断や予後予測，再発診断などに広く用いられており，放射線治療計画においても正確な標的体積の設定という点での有用性も高い．その他にも，アミノ酸代謝をみるC-11メチオニン，拡散代謝をみるF-18 FLT，低酸素細胞をみるF-18 MISO, Cu-62 ATSMなどの分子腫瘍イメージングの臨床研究・臨床応用も盛んに行われている．強度変調放射線治療や粒子線治療(特にペンシルビームによるスキャンニング照射)は，腫瘍内部を場所によって線量強度を変えて照射することができ，上記のような分子イメージングと治療計画上融合することにより，腫瘍内のviabilityの高い領域や低酸素領域(放射線低感受性)に線量高度を高めることも可能となり，さらなる局所制御・予後向上に役立つものと思われる[8]．

また，周囲正常臓器の機能画像を治療計画に用いて線量分布を最適化することによって，腫瘍発生臓器やその周囲正常臓器の機能低下を最小限に留めようとする試みも行われている．例をあげれば，肺癌に対する強度変調放射線治療の治療計画に肺血流シンチや4次元換気CT画像を用いて高い機能が残っている領域の照射線量・容積を減らし治療後の機能低下を最小限に留めるというアプローチである[9,10]．肝胆膵領域の治療においては，術後の肝予備能の予測における肝受容体シンチ(アシアロシンチ)の有用性が示唆されており，このような機能画像を用いることで，肝胆膵領域の放射線治療の最適化が今後可能となるかもしれない[11,12]．

いずれにしても，未来の放射線治療では分子腫瘍イメージングや正常臓器の機能イメージングを放射線治療の最適化に応用し，さらなる局所効果の向上と低リスク化を図るとい