patients among 2,016 patients who received mastectomy and adjuvant systemic therapy without postoperative radiotherapy [31]. Among 254 patients without simultaneous distant metastasis, isolated chest wall recurrence was found in 131 patients (52%), and locoregional recurrence with or without chest wall recurrence was found in 123 patients (48%). One hundred and sixty-six patients had locoregional recurrence and distant metastases simultaneously.

Isolated chest wall recurrence after mastectomy

Maximum local control of isolated chest wall recurrence is achieved with a wide excision whenever feasible [32–37]. Schwaibold et al. [36] reviewed 128 patients with isolated locoregional recurrence and reported that the 5-year overall survival and relapse-free survival rates of patients with a long DFI, surgical resection, and locoregional control were 61 and 59%, respectively. However, this favorable subgroup accounted for fewer than 20% of patients with isolated locoregional recurrence. On the other hand, aggressive surgery including extensive excision and reconstruction using skin grafts leads to a reduced quality of life, and, therefore, optimum treatment is achieved by balancing the potential benefits of local treatment with its adverse effects [38, 39]. If there is no clinical finding of axillary lymph node involvement, a prophylactic axillary dissection is unnecessary for patients who have undergone prior complete axillary dissection. The identification of SLN after prior axillary dissection is unlikely to be as successful as prior SLN biopsy alone (38 vs. 74%, $p = 0.0002$), and so SLN biopsy is not recommended for patients who have undergone prior complete axillary dissection [21].

Dahlstrom et al. [32] reported that 45% of patients had a new local recurrence after wide excision plus a 3-cm margin for isolated chest wall recurrence. In the study by Mallinckrodt, the 5-year freedom from chest wall re-recurrence of patients who received entire chest wall and regional lymph node irradiation was 75%, and that of patients who received small-field irradiation alone was 36% ($p = 0.0001$) [7]. Toonkel et al. [40] demonstrated that postoperative radiotherapy including chest wall and regional lymph node irradiation enhanced 5-year overall survival rates compared with chest wall irradiation alone (54 vs. 27%). The three-field or four-field technique including tangential chest wall fields and an en face supraclavicular area field are usually applied, even if the recurrent disease involves an isolated chest wall recurrence [32, 34, 36, 40–42]. The optimum daily fraction size is 1.8–2.0 Gy, and should be delivered five times weekly. The total dose administered to the initial field ranges from 45 to 50 Gy, with a boost of 10 to 20 Gy administered to areas of residual gross disease and the tumor bed. The biopsy scar should be covered by the bolus in order to obtain the optimum dose distribution [25]. In the MD Anderson Cancer Center, all areas treated prophylactically receive 54 Gy in 27 fractions, and all areas to be boosted because of microscopic disease receive an additional 12 Gy in 6 fractions [43].

A higher dose of definitive radiation for macroscopically residual tumors is associated with less in-field failure [7, 25]. It is difficult to obtain long-term local control in patients with diffuse inflammatory disease or unresectable disease. Neoadjuvant chemotherapy is considered for patients with unresectable disease in order to render the disease resectable, and radiotherapy is delivered after surgery. There is little information about re-irradiation after postoperative chest wall irradiation. Limited field re-irradiation using tailored conformal therapy techniques and concurrent chemoradiotherapy and/or twice daily fractionation regimens have been tested for patients with inoperative recurrent disease who had previously received radiotherapy [44, 45]. Re-irradiation of limited volumes with limited radiation doses can result in meaningful palliation for some patients.

Regional lymph nodes recurrence after mastectomy

Willner et al. [34] analyzed 145 patients with first locoregional recurrences after mastectomy and reported that the 5-year survival rate was better for patients with recurrences confined to the axillary lymph nodes (50%) than for those with recurrence confined to the supraclavicular lymph nodes (28%) or combined chest wall and axillary recurrences (28%). The 5-year survival rate of patients with supraclavicular lymph nodes recurrence and chest wall and/or axillary lymph nodes recurrence was only 5%.

Axillary lymph node recurrence after mastectomy

Axillary lymph node recurrence is rare after complete axillary dissection. Regional lymph node control for patients who receive axillary dissection after axillary recurrence is better than that for patients who receive radiotherapy alone [42]. Whenever feasible, a complete axillary dissection (Level I and II) is indicated for patients who have undergone prior SLN biopsy alone, and gross tumor resection is considered for patients who have undergone prior complete axillary dissection. Although the role of postoperative radiotherapy after salvage surgery is unclear, postoperative radiotherapy is used for patients who have not undergone prior axillary irradiation in some institutes [33, 34, 42, 46]. Radiotherapy should be considered for patients with incompletely resected disease or inoperable disease. The risk of symptomatic arm edema

after axillary dissection or axillary irradiation alone ranged from 4 to 8%; that after complete axillary dissection followed by radiotherapy was 36%, however [47].

Supraclavicular lymph node recurrence after mastectomy

Chen et al. [48] reviewed 63 patients with isolated supraclavicular lymph node recurrence among 3,170 breast cancers and reported that their 5-year survival rate was 33.6% and that surgical removal of the supraclavicular lymph nodes was associated with good overall survival after recurrence ($p = 0.03$). Although a surgical approach for supraclavicular lymph node recurrence is feasible, the clinical benefit of a surgical approach is believed to be small, because of the high frequency of local and distant relapse [49].

The clinical complete response rate for radiotherapy with or without chemotherapy ranged from 85 to 94%, the median time to progression was 28 months, and the 5-year overall survival rate after recurrence ranged from 21 to 35% [34, 46, 50]. Pergolizzi [51] compared 18 patients who received six-cycle chemotherapy alone with 19 patients who received initial three-cycle chemotherapy followed by involved-field radiotherapy and demonstrated that the local control of the former patients was worse than that of the latter patients (13 patients vs. 18 patients) and that the 5-year disease-free survival rate of the former was worse than that of the latter (5.5 vs. 21%, $p = 0.01$). Although there are no data supporting the use of systemic therapy for patients with locoregional recurrence, there is a trend toward the application of systemic therapy especially for patients with supraclavicular recurrence [23, 24, 34, 46].

Tumor infiltration of the brachial plexus induces shoulder pain, sensory changes in the fingers, and weakness and atrophy of the upper limbs. Radiation therapy is an effective local therapy for obtaining local control and avoiding distressing symptoms. Doses of 30–50 Gy are applied in 10–25 fractions over 2–5 weeks, and pain relief and the eradication of other distressing symptoms were achieved in more than two-thirds of patients [46, 50, 52]. Doses of 40 Gy or more were better at improving the distressing symptoms caused by supraclavicular lymph node metastases than those of less than 40 Gy (92 vs. 55%) [52].

New challenge

The 5-year overall survival rates of patients with ipsilateral breast or chest wall recurrence with simultaneous regional lymph node recurrence range from 7 to 24% [6, 34, 46]. Although systemic therapy has been commonly applied for patients with locoregional recurrence, the clinical benefit of systemic therapy including anthracycline-based and methotrexate-based regimens is uncertain. The clinical data regarding taxane-based regimens and molecular-targeted therapies, for example trastuzumab and lapatinib, should be evaluated using prospective trials, and a pilot study using hyperfractionated accelerated radiotherapy with or without systemic therapy has been conducted [44]. Additionally, patients with diffuse inflammatory disease and unresectable disease have an unfavorable prognosis. The optimum treatment for unresectable diffuse inflammatory recurrent disease needs to be established.

Locoregional recurrences of breast cancer have heterogeneous biological characteristics, and it is difficult to choose an appropriate treatment for each patient. Prospective clinical trials integrating adequate prognostic indices should therefore be conducted to define standard salvage treatment for patients with locoregional recurrence [9].

Conclusion

The optimum treatment for patients with locoregional recurrence requires a combination of modalities, and a comprehensive multidisciplinary treatment approach is essential. A multidisciplinary tumor board for breast cancer should be organized at each institute in order to propose an appropriate treatment for each patient.

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A Simple Respiratory Indicator for Irradiation during Voluntary Breath Holding: A One-Touch Device without Electronic Materials[1]

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Purpose: To evaluate the use, structural principles, operation, and acquired reproducibility of a respiratory monitoring device to be used for voluntary patient breath holding.

Materials and Methods: Evaluation was performed of a respiratory monitoring device that enables determination of the respiratory level in a patient by measuring the movement of two contacts on the abdomen and chest wall. Neither metallic nor electronic materials are used in the mechanics for this device. The initial study group comprised 21 consecutive patients (15 men, six women; mean age, 75 years; range, 56–92 years) with lung or abdominal tumors who underwent examination with the device and computed tomography (CT) for three-dimensional reproducibility of lung base position during voluntary breath holding with or without use of the device.

Results: One patient with mild dementia was excluded; in most of the remaining 20 patients, high reproducibility of the breath-holding position was achieved in a short time with the device. In these 20 patients who were able to adapt to use of the device, three-dimensional mean maximum differences in lung base position during three random voluntary breath holds were 2.0 mm along the cranial-caudal axis, 1.5 mm along the anterior-posterior axis, and 1.2 mm along the right-left axis. The differences in all axes were significantly smaller with use of the respiratory monitoring device than without the device.

Conclusion: The device demonstrates satisfactory reproducibility of voluntary patient breath holding easily and inexpensively and may offer a convenient device for easy use during irradiation with voluntary breath-holding conditions that require a small internal margin.

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During radiation therapy to the abdominal and thoracic organs, minimizing the size of the radiation field while allowing for organ motion is important to reduce normal tissue toxicity and improve therapeutic effectiveness. Although image-guided radiation therapy systems are effective for reducing interfractional setup margins, intrafractional internal motion caused by patient respiration cannot be controlled. Interest in techniques designed to control respiratory movements has been growing since the mid-1990s, with the development of approaches including breath holding (1–3), respiratory gating (4,5), and beam tracking (6). Of all these techniques, we consider breath holding to be the most obvious and simplest solution to reduce uncertainties related to movements induced by breathing and to increase the reproducibility of treatment. Two approaches can be used for breath holding: active breathing control (1) and voluntary breath holding (2,3). Although these methods initially appear similar, the former is relatively invasive in nature for patients, since breathing is controlled forcibly by a valve in the spirometer. Voluntary breath holding thus appears preferable for patients with lung cancer in whom pulmonary function is apt to be poor. Though some teams have tried nonmonitored voluntary breath holding with a certain degree of success (7–10), these techniques have been considered uncertain, and various respiratory monitoring apparatuses have been introduced to improve the reproducibility of breath holding. However, as most existing apparatuses are complex, costly, or inaccurate (11), voluntary breath-holding techniques that use such devices are again unsuitable for small and intermediate-sized medical facilities with inexperienced staff.

We therefore aimed to develop a method of self–breath holding that can be performed as simply, nonelectronically, noninvasively, and inexpensively as possible. The purpose of our study was to evaluate the use, structural principles, operation, and acquired reproducibility of a newly developed simple respiratory monitoring device that has two contacts on the abdominal and chest wall of the patient.

Advances in Knowledge

- We developed a respiratory indicator that is simpler and less expensive than other conventional indicators.
- This device enables determination of the respiratory level in a patient by measuring movement of two contacts on the abdomen and chest wall without needing electronic materials.
- Our preliminary experiences show that this device is easily used during irradiation with voluntary breath-holding conditions that require a small internal margin.

Materials and Methods

All study protocols were approved by the institutional review board, and all patients provided written informed consent prior to participating in the study.

Technical aspects of the device including the structural principles, materials used, and the indicator rotation setting in relation to the contact movement were partially suggested by the coauthor (H.K.) who is an investigator at Apex Medical (Tokyo, Japan). The company provided no other material or financial support and had no control or other involvement in the study.

Implications for Patient Care

- The device uses a simple method to achieve good reproducibility for voluntary patient breath holding during irradiation.
- The device can minimize intrafractional respiratory organ motion nonelectronically, noninvasively, and inexpensively.
- The device may offer substantial benefits to facilities that lack highly trained staff and resources.

Structure and Operation of the Device

Figure 1 shows the main body of the device, which consists of thoracic and abdominal contacts, a stand, a mechanical unit, and a respiratory level indicator panel. The framework of the device is hollow and made of carbon. As a result, the effect of radiation absorption by the device on dose distribution of the irradiation field is negligible.

The device is normally used by placing the one contact each on the chest and abdomen of the patient, who lies in a supine position (Fig 2). The equipment used for the study in conjunction with the device included a whole-body computed tomography (CT) scanner (Hi-Speed DX/I; GE Yokogawa Medical Systems, Tokyo, Japan), and an x-ray simulator (SAT-20; Shimadzu, Kyoto, Japan).

Vertical motions of the chest and abdomen associated with breathing are detected by the thoracic and abdominal contacts, and movements of the contacts are added and converted to a rotational angle of a needle in the level meter. The contacts are designed such that a 1-cm movement on the body surface results in a rotation of 23° on the level meter. When both contacts move 1 cm in the same direction as a result of breathing by the patient, the indicator rotates by as much as 46°. The patient can thus control his or her breathing by watching the indicator.

The level indicator panel has two markers, red and yellow, that define the levels of full exhalation and full inhalation and one blue marker that defines

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See Materials and Methods for pertinent disclosures.

Figure 1

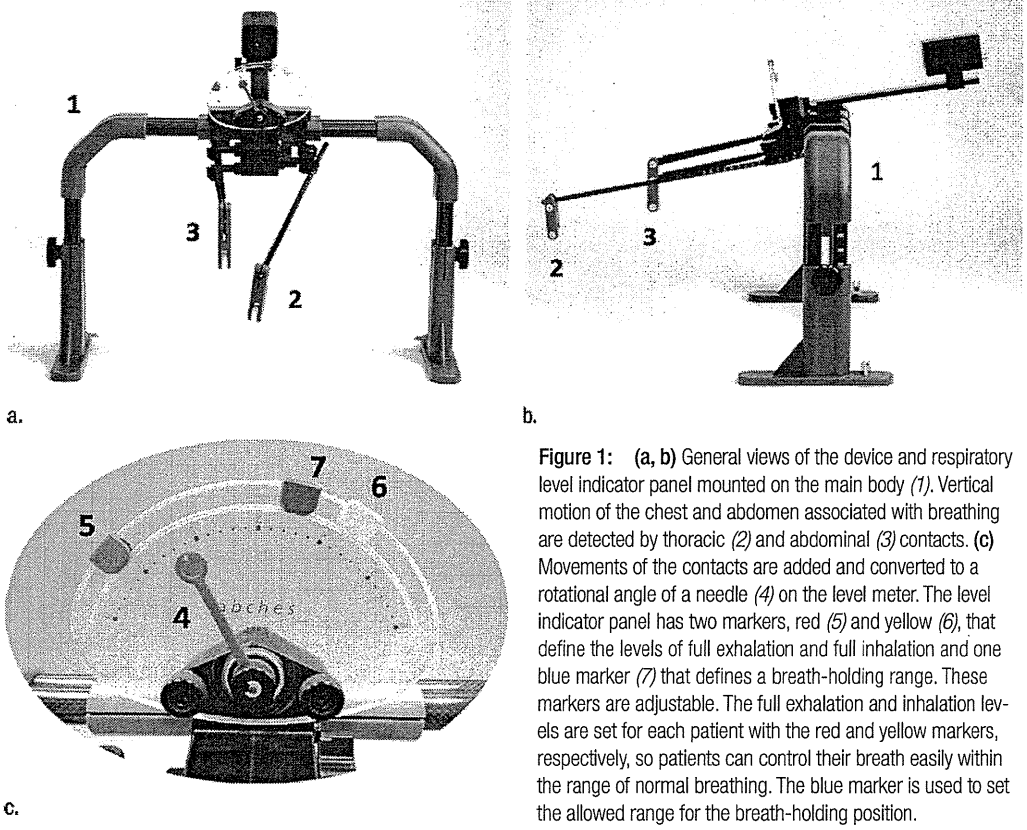


Figure 1: **(a, b)** General views of the device and respiratory level indicator panel mounted on the main body *(1)*. Vertical motion of the chest and abdomen associated with breathing are detected by thoracic *(2)* and abdominal *(3)* contacts. **(c)** Movements of the contacts are added and converted to a rotational angle of a needle *(4)* on the level meter. The level indicator panel has two markers, red *(5)* and yellow *(6)*, that define the levels of full exhalation and full inhalation and one blue marker *(7)* that defines a breath-holding range. These markers are adjustable. The full exhalation and inhalation levels are set for each patient with the red and yellow markers, respectively, so patients can control their breath easily within the range of normal breathing. The blue marker is used to set the allowed range for the breath-holding position.

a breath-holding range (Fig 1). The patient holds his or her breath to bring the indicator to the blue marker. In this way, CT scanning and irradiation can be performed accurately for the duration of patient-controlled breath holding.

The device has auxiliary components that include a mirror and a switch for the patient (Fig 2). The mirror allows the patient in the supine position to easily watch the level indicator. The switch is used by the patient to inform the radiotherapist of the breath-holding state, so that the radiotherapist can then perform treatment in collaboration with the patient.

The technician also can observe the device indicator needle remotely by means of a charge-coupled device monitor mounted on the patient table, and when the technician notices that the breath is not being held appropriately, the technician will assist the patient to improve control.

Setting of the Device and Instruction on Breath Holding

Initially, 21 patients who had been introduced consecutively to our department to undergo radiation therapy for lung or abdominal tumors were included as subjects, but one patient (92-year-old female) was excluded from the study because she was unable to understand the breath-hold technique owing to mild dementia. As a result, 20 patients were enrolled in the study. The background and clinical characteristics of the 20 patients are shown in Table 1. Nine patients had chronic pulmonary disease, and respiratory function parameters were below normal limits in seven of 20 patients.

The body of the patient was fixed with a vacuum pillow, and use of the device was explained to patients by showing them a fluoroscopic image of the diaphragm in respiratory motion. Using the device, subjects were taught to keep a regular respiratory rhythm within a uniform range on the indicator of the device. Signal waveforms of respiratory volume were acquired by using a spirometer (HI-801; Central Sports, Tokyo, Japan) during free respiration with and without use of the device. Subjects were then instructed to hold their breath during inspiration so as to maintain an identical position through voluntary breath holding.

Measurement of Reproducibility of Lung Base Position during Repeated Breath Holds

After patients fully understood and mastered voluntary breath holding with and without the use of the device, a set of three CT scans was obtained with the device and another set was obtained without the device (ie, six CT scans total), to obtain randomly timed images of 2 mm thickness in the vicinity of the lung base. The CT scanning interval

Figure 2

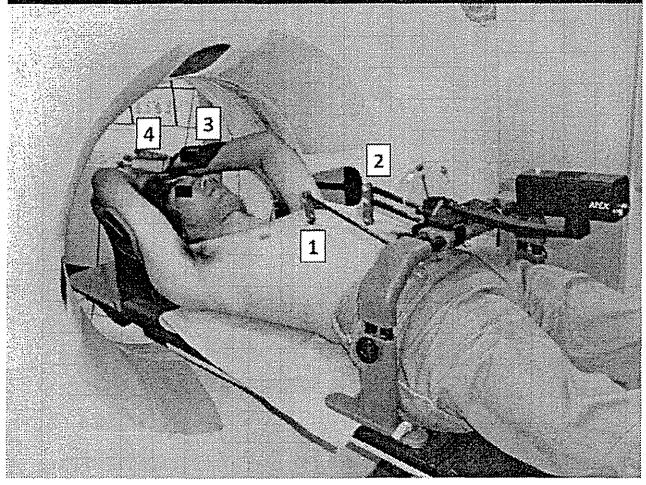


Figure 2: View of the main body of the device in use on a patient. Two contacts are placed on the chest *(1)* and abdomen *(2)* of a patient lying in a supine position. Auxiliary components on the device include a mirror *(3)* and a switch *(4)* for the patient. The height of the device is adjusted to the body size of each patient to ensure that the two contacts touch the abdomen and thorax.

Table 1

Patient Characteristics

Characteristic	Finding
Total no. of patients	20
Men	15
Women	5
Age (y)	56–86 (74)
Men	56–84 (72)
Women	72–86 (77)
Smoking index*†	
0–200	6
200–600	10
>600	4
Tumor site†	
Thoracic	16
Abdominal	4
ECOG performance status	0–2 (1)
$FEV_{1.0}$ (mL)	650–2350 (1520)
SaO_2 (mmHg)	65–90 (76)

Note.—Unless otherwise indicated, data are ranges, and numbers in parentheses are medians. ECOG = Eastern Cooperative Oncology Group, $FEV_{1.0}$ = forced expiratory volume in the first second, SaO_2 = arterial oxygen saturation.

*Average daily number of cigarettes multiplied by years.

† Data are numbers of patients.

was approximately 5 minutes. The first three scans were obtained during breath holding by using the device; the next three scans were obtained without the device. On the 2-mm-thick images in the vicinity of the lung base, an arbitrary point for measuring reproducibility of repeated breath holds was set on a clear peripheral vascular structure, and the maximum difference in measurement point for the three CT scans was calculated along three axes: cranial-caudal, anterior-posterior, and right-left. The detailed method for measuring reproducibility has been described previously (7).

Statistical Analysis

The statistical significance of disparities in maximum differences of lung base position in all patients with and without the device was determined by using a paired *t* test. All probabilities were two-tailed, with $P < .05$ considered to indicate a statistically significant difference. Statistical calculations were performed by using statistical software (StatView, version 5; SAS Institute, Cary, NC).

Results

Effect of the Device on Breathing

Figure 3 shows examples of respiratory volume curves measured with the spirometer obtained during free breathing without the device and under an instruction to breathe within a uniform range using the device. The respiratory volume curve obtained by using the device was more regular than that without the device.

Reproducibility of Breath Holding

All 20 patients practiced self-controlled breath holding by using the respiratory monitoring device. The mean time necessary for each of the 20 patients to be instructed on the use of the device and to master voluntary breath holding with and without the device was 20 minutes (range, 15–30 minutes). Mean duration of each breath hold was 18 seconds (range, 10–40 seconds).

Among the 20 patients who understood the breath-holding method, reproducibility of the measurement point during breath holds obtained by using the device was compared with that obtained without the device. The results are shown in Table 2. For the 20 patients, mean maximum differences in the measurement points obtained with and without the device, respectively, were 2.0 and 4.2 mm along the cranial-caudal axis, 1.5 and 2.8 mm along the anterior-posterior axis, and 1.2 and 2.0 mm along the right-left axis. Differences in all axes were significantly smaller ($P < .05$) with the device than without the device.

Case

An electronic portal imaging device was used to evaluate the reproducibility of tumor position during each radiation therapy session. Real-time electronic portal imaging was performed five to 10 times during each fraction. Examples of CT images and intrafractional electronic portal images in the vicinity of the tumor during voluntary breath holding with the device obtained before and during radiation therapy are shown in Figure 4 and 5, respectively.

Discussion

A widely used voluntary breath-holding technique is performed with a spirometer connected to a screen or video glasses

Figure 3

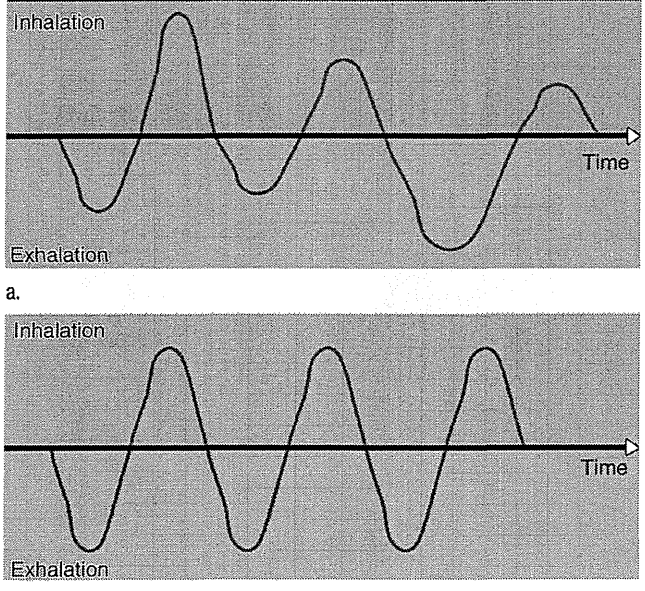


Figure 3: Examples of respiratory volume curves measured by using spirometry (HI-801; Central Sports, Tokyo, Japan) obtained during **(a)** free-breathing and **(b)** an instruction to breathe within a uniform range with the device.

Table 2

Reproducibility of Breath-holding Position of the Lung Base with and without the Device

Axis	With Device (mm)	Without Device (mm)
Craniocaudal direction		
Mean ± standard deviation*	2.0 ± 1.3	4.2 ± 2.2
Range	0–4	0–10
Anteroposterior direction		
Mean ± standard deviation*	1.5 ± 1.2	2.8 ± 1.8
Range	0–3.6	0.3–4.0
Left-right direction		
Mean ± standard deviation*	1.2 ± 1.1	2.0 ± 1.5
Range	0.0–3.0	0.3–3.8

*Differences in all axes were significantly smaller ($P < .05$) with this system than without it.

and indicates in real time, for the technicians and/or patient, the desired and actually achieved levels of breath hold (2,3). Hanley et al (2) used a voluntary deep-inspiration breath-hold system with a spirometer for patients with non–small cell lung cancer, and reported an intra–breath-hold reproducibility of 1.0 mm ± 0.9 and an inter–breath-hold reproducibility of 2.5 mm ± 1.6. In regard to intrafraction reproducibility of breath-holding positions, our technique using the device was not inferior to these other breath-hold techniques and devices.

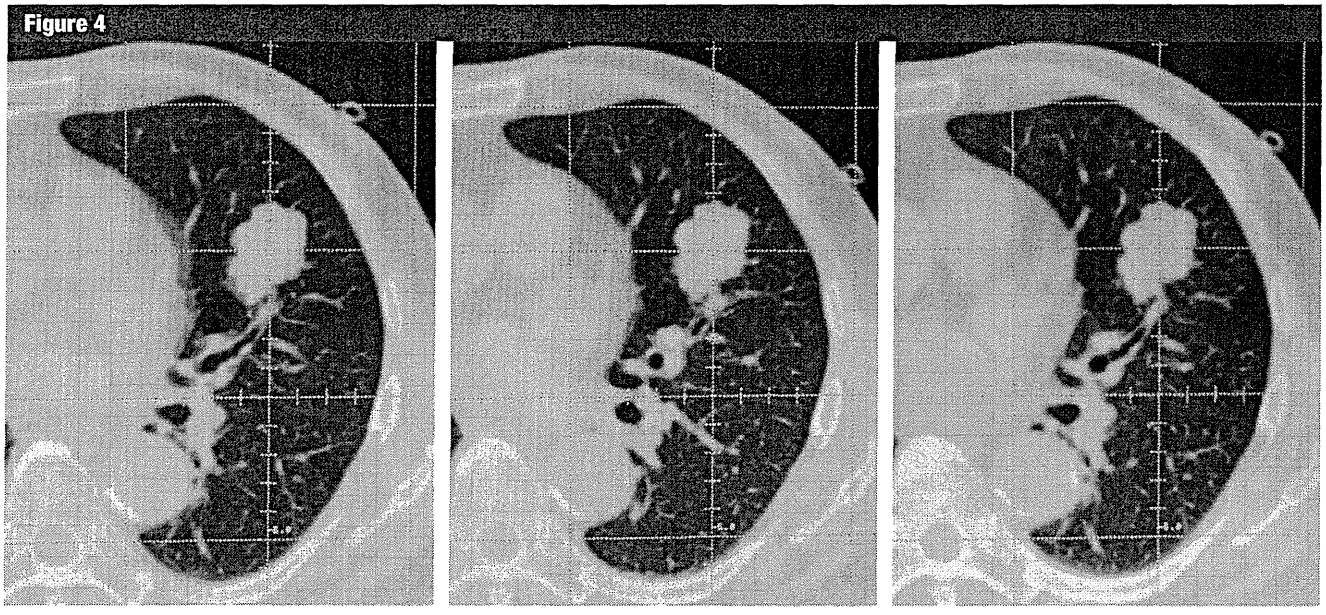
The method performed with the present device has some merits for voluntary breath-holding technique. The greatest merit of the device is the simplicity of the mechanism and structure and convenience for patients and radiation therapy staff. To our knowledge, no other devices have been described that do not use electronic materials. Setting of other existing systems is regarded to be relatively more complicated than that of the present device. This device is also easy to install and is inexpensive. While most small and intermediate-sized medical facilities do not have equipment to compensate for respiratory motion, because such facilities have insufficient time, manpower, and/or money to introduce complicated irradiation schemes, our device appears highly effective for solving the above-mentioned problems.

In addition, existing commercially available respiratory monitoring systems, such as the Real-time Position Management system (Varian, San Francisco, Calif) and the Anzai motion-monitoring system (AZ-773V; Anzai Medical, Tokyo, Japan), have only one detection point for respiratory monitoring and may not be able to capture precise breathing phases, which are affected in a complex fashion by the respiratory motions of the thorax and abdomen. While Mageras et al (12) and Vedam et al (13) reported a good phase relationship between abdominal and diaphragm motions, Nakamura et al (14) and Ahn et al (15) reported some differences between lung tumor and abdominal motions. A hysteresis curve was also observed. In contrast, with the present device, two detection points can be set arbitrarily on the chest and abdomen. This may allow synthesis of the movements measured at two sites, and we have been investigating whether the device can achieve more precise monitoring than other devices using one detection point.

Moreover, the device is versatile and enables a therapeutic procedure that normally requires high precision. The range of stabilized respiration was better with our device than without it (Fig 3). The device is also helpful for regulating breathing levels in a steady range and thus may be useful for gated or tracking radiation therapy.

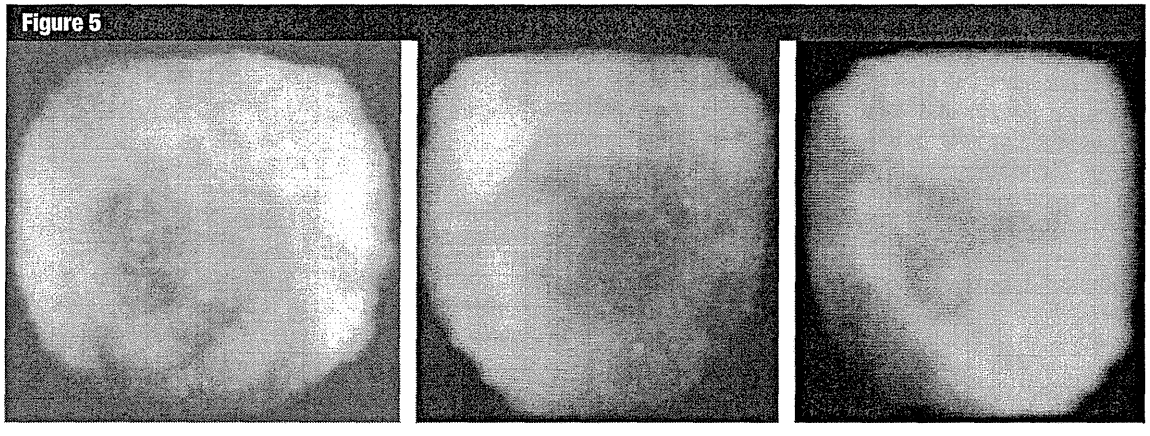
Finally, the device has the great merit of requiring active patient involvement in switching and voluntary breath holding. When using the device, it is most important that the patient understands the purpose and nature of the method. A report of Task Group 76 of the American Association of Physics in Medicine (16) stressed that breath control requires active participation of the patient. This device contributes to such participation in treatment.

Carlson et al (17) reported good breath-hold reproducibility by using a bellows-based breath-hold monitoring



a. b. c.

Figure 4: CT images obtained during voluntary breath holding with the device. Before every session of radiation therapy, a set of three CT scans is performed to obtain randomly timed images of 2 mm thickness in the vicinity of the tumor. **(a–c)** Images obtained with the first, second, and third scan, respectively. The scanning interval was approximately 5 minutes. Maximum differences in tumor position in craniocaudal, anteroposterior, and right-left directions on three CT studies were 1, 0.7, and 0.5 mm, respectively.



a. b. c.

Figure 5: Example of intrafractional electronic portal images obtained during radiation therapy during voluntary breath holding with the device. Radiation therapy was performed with 10 noncoplanar static ports. **(a–c)** Three of the 10 portal images show that the tumor shadow lay appropriately on the planned position in each port.

and feedback system for CT-guided biopsy of the lung and upper abdomen. The basic components of the system are a Velcro belt with expandable bellows, a light-emitting diode monitor for patient feedback, and a system control unit. Variation in the length of the bellows causes a pressure change within the tubing, which is measured with a pressure-sensitive transducer. Although no detailed reproducibility of breath hold using this system was described in the report, the patient feedback system resembles our own. The device used in our study may also contribute to such operations of interventional radiology requiring good breath-hold reproducibility.

Applicability of the device must be established for each patient during preliminary practice sessions. Moreover, some key points should be noticed when patients are instructed on how to hold their breath. We routinely instruct patients to maintain smooth and regular breathing before breath holding. It is also important to educate patients

not to use abdominal muscles to adjust the indicator. If a patient deviates from these instructions, a large error can be produced that exceeds the estimated error. Sufficient instruction and practice are essential to achieving good reproducibility with the device.

In summary, we developed a simple and accurate respiratory monitoring indicator for irradiation during self-controlled voluntary breath holding that will offer substantial benefits to all facilities even if they lack highly trained staff and resources.

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Strahlentherapie
und Onkologie

Original Article

Variability in Bladder Volumes of Full Bladders in Definitive Radiotherapy for Cases of Localized Prostate Cancer

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Background and Purpose: To evaluate variation in bladder volume of full bladders in definitive radiotherapy for localized prostate cancer and to investigate potential predictors of increased bladder volume variations.
Patients and Methods: In 40 patients, the bladder volume was measured with megavoltage computed tomography (MVCT) imaging performed just before irradiation during the administration of the 1st fraction (#1), the 10th fraction (#10), the 20th fraction (#20), and the 30th fraction (#30). Patients were instructed to avoid urinating for 60–90 minutes before the planning CT (pln-CT) scan and before daily irradiation. Patients were also encouraged to drink an unspecified volume of liquid that would result in a clear but tolerable urge to urinate.
Results: The population-mean bladder volume (±1SD) was 219 ml (±83 ml) at the planning CT scan (pln-CT), 186 ml (±96 ml) at #1, 149 ml (±73 ml) at #10, 137 ml (±59 ml) at #20, and 136 ml (±60 ml) at #30. The mean intrapatient variation in bladder volume (1 SD relative to the mean bladder volume of each patient) was 38% (range: 10–84%). The bladder volume at the pln-CT was correlated with the intrapatient variance in bladder volume with a correlation coefficient of 0.54 and $p<0.001$.
Conclusion: We observed a significant decline in bladder volumes during the course of radiotherapy. The bladder volume at the pln-CT was a significant predictor of increased bladder volume variations.

Key Words: Radiotherapy · Prostate cancer · IMRT · Bladder volume · Full bladder · MVCT

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Schwankungen des Volumens gefüllter Blasen in der definitiven Radiotherapie bei lokalisiertem Prostatakarzinom

Hintergrund und Zweck: Die Evaluierung der Schwankungen des Blasenvolumens gefüllter Blasen in der definitiven Radiotherapie bei lokalisiertem Prostatakrebs sowie die Untersuchung potenzieller Prädiktoren für erhöhte Schwankungen des Blasenvolumens.
Patienten und Methoden: Das Blasenvolumen von vierzig Patienten wurde mittels Megavoltage-Computertomographie (MVCT) bestimmt, die bei der Verabreichung der 1. Fraktion (#1), der 10. Fraktion (#10), der 20. Fraktion (#20) und der 30. Fraktion (#30) kurz vor der Bestrahlung durchgeführt wurde. Die Patienten wurden angewiesen, 60–90 Minuten vor dem Planungs-CT (pln-CT)-Scan und vor der täglichen Bestrahlung nicht zu urinieren. Die Patienten wurden zudem ermuntert, eine nicht näher bestimmte Menge an Flüssigkeit zu sich zu nehmen, um einen deutlichen aber tolerierbaren Harndrang herbeizuführen.
Ergebnisse: Der Mittelwert der Grundgesamtheit des Blasenvolumens (±1SA) lag beim Planungs-CT-Scan (pln-CT) bei 219 ml (±83 ml), 186 ml (±96 ml) bei #1, 149 ml (±73 ml) bei #10, 137 ml (±59 ml) bei #20 und 136 ml (±60 ml) bei #30. Der Mittelwert der Schwankung des Blasenvolumens innerhalb eines Patienten (1SA bezogen auf den Mittelwert des Blasenvolumens des einzelnen Patienten) lag bei 38 % (Spannweite: 10–84 %). Das Blasenvolumen zum Zeitpunkt des pln-CT wurde mit der Streuung des Blasenvolumens innerhalb eines Patienten korreliert, woraus sich ein Korrelationskoeffizient von 0,54 mit $p<0,001$ ergab.
Fazit: Im Laufe der Radiotherapie konnte eine deutliche Verringerung der Blasenvolumen festgestellt werden. Das Blasenvolumen zum Zeitpunkt des pln-CT-Scans erwies sich als signifikanter Prädiktor erhöhter Schwankungen im Blasenvolumen.

Schlüsselwörter: Radiotherapie · Prostatakarzinom · IMRT · Blasenvolumen · Gefüllte Harnblase · MVCT

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Introduction

The bladder is filled to various volumes during fractionated radiotherapy. Changes in the bladder volumes affect both bladder dose volume and the position of adjacent organs (the prostate, seminal vesicles, small intestine, sigmoid colon, and rectum). Furthermore, significant variations in bladder volume can confound the planned dose distributions for three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) [8, 9, 14, 20, 23]. Therefore, bladder volume must be kept consistent throughout planning and treatment to reduce positional uncertainties related to the prostate and the risk of increased toxicity in the normal surrounding tissue.

There is no current consensus regarding optimal bladder volumes. One possible advantage of maintaining a full bladder is that part of the bladder is moved away from the target volume, thus, reducing bladder toxicity [6, 11, 12]. Moreover, a full bladder moves the small intestine and the sigmoid colon out of the irradiation field, also reducing toxicity in these organs [3, 5, 10, 13]. For these reasons, we ask patients scheduled to undergo irradiation for prostate cancer to maintain a full bladder during irradiation. However, in patients with full bladders, large variations in bladder volume vs. time trends have been observed during the course of radiotherapy course [11, 16, 18].

The aim of this study was to quantify the variations and trends in full bladder volume during the course of radiotherapy in patients being treated for prostate cancer. The second aim was to investigate the potential predictors of increased bladder volume variations.

Methods and Materials

Patient Characteristics

Between December 2007 and March 2008, 40 patients with localized prostate cancer (cT1-3N0M0) were enrolled into this study (Table 1).

Table 1. Patient characteristics. cT: stage clinical tumor stage; PSA: prostate-specific antigen; IPSS: International Prostate Symptom Score.

Tabelle 1. Patientenmerkmale. cT-Stadium: klinisches Tumorstadium; PSA: prostataspezifisches Antigen; IPSS: International Prostate Symptom Score (Internationaler Prostata-Symptomscore).

	No. (%)
cT stage (TNM 6th ed.)	
1–2a	19 (48)
2b	4 (10)
2c–3	17 (43)
Gleason score	
2–6	15 (38)
7	9 (23)
8–10	16 (40)
Initial PSA	
0–10	25 (63)
10–20	10 (25)
>20	5 (13)
D'Amico's risk group	
Low	10 (25)
Intermediate	8 (20)
High	22 (55)
IPSS	
0–8	22 (55)
9-1-9	13 (33)
20–30	5 (13)
Neoadjuvant hormone therapy	
Yes	21 (53)
No	19 (48)
Age mean (range)	71 (53–83)

Radiotherapy

All patients received definitive radiotherapy with helical tomotherapy using the Hi-Art System (TomoTherapy, Inc., Madison, WI, USA) at Edogawa Hospital (Tokyo, Japan). Patients were classified according to D'Amico's risk-group definition [4]. The clinical target volume (CTV) was defined as prostate only for low-risk patients, and prostate with a 5 mm margin and a 2 cm wide section of the proximal seminal vesicle for the intermediate-risk and high-risk patients. The planning target volume (PTV) was defined as the CTV plus a 5 mm margin. The prescribed dose, which was defined as 95% of the PTV receiving 100% of the prescribed dose (D95), was 72 Gy in 36 fractions for the low-risk patients and 76 Gy in 38 fractions for the intermediate-risk and high-risk patients. Treatment planning optimization was performed to satisfy the dose constraints defined by the in-house protocols for both the PTV and the organs at risk (OAR). The dose constraints for the PTV are a mean dose <79.8 Gy (105% of the prescribed dose) and a maximum dose <83.6 Gy (110% of the prescribed dose). The dose constrains for OAR are (1) the rectum wall defined as 0.5 cm above and below the PTV of no more than 10% of the volume to receive a dose >78 Gy, no more than 25% of the volume to receive a dose >70 Gy, no more than 35% of the volume to receive a dose >60 Gy, and no more than 65% of the volume to receive a dose >40 Gy; (2) the bladder wall of no more than 35% of the volume to receive a dose >70 Gy, and no more than 65% of the volume to receive a dose >40 Gy; (3) the sigmoid colon of no more than 0.5 ml to receive a dose >65 Gy; and (4) the small bowel of no more than 0.5 ml to receive a dose >60 Gy. A total of 21 patients (53%) underwent hormone therapy sequentially and/or concurrently. The patients were irradiated in a supine position with a knee support. A megavoltage computed tomography (MVCT) scan was performed just before the daily irradiation. In addition, soft tissue-based 3D–3D matching of the MVCT images with the planning CT (pln-CT) images was performed with the couch shifted to the optimal position.

Patient preparations

The patients were instructed to refrain from urinating for 60–90 minutes before the planning CT scan (pln-CT) and before daily irradiation. The patients were also encouraged to drink an unspecified volume of liquids to ensure a clear but tolerable urge to urinate. The patients were instructed to take laxatives before the pln-CT, although no specific instructions regarding bowel movements before daily irradiation were issued.

Bladder volume measurement

Bladder volume at the pln-CT was measured by kilovoltage CT (kVCT) imaging with a thickness of 2.5 mm. Bladder volume was also measured by MVCT imaging with a thickness of 4 mm four times during the course of radiotherapy: at the 1st fraction (#1), at the 10th fraction (#10), at the 20th fraction (#20), and at the 30th fraction (#30). All bladder volumes were measured by the same radiation oncologist (N.N.) by delineating whole bladder outlines in Focal (CMS Inc., St. Louis, MO, USA) (Figure 1).

We assessed the variability in population bladder volumes throughout pln-CT and radiotherapy by calculating mean population bladder volumes and standard deviations (SD). The mean of five measurements for each patient is shown as V_{mean}. As a measure of variation in intrapatient bladder volumes, the SD of V_{mean} (denoted as σ_{bl}) is used, whereas, $\sigma_{bl\text{-}rel}$ was defined as σ_{bl} relative to V_{mean}.

Potential predictors

We also assessed the correlations between intrapatient bladder volume variations ($\sigma_{bl\text{-}rel}$) and potential univariate predictors. The following potential predictors were evaluated: age (continuous), T stage (T1–T2a, T2b, T2c–T3), Gleason score (2–6, 7, 8–10), pretreatment prostate-specific antigen (PSA) (continuous), risk group (low, intermediate, high), international prostate symptom score (IPSS) [2] (continuous), hormone therapy (with or without), bladder volume at the pln-CT (continuous), prostate volume (continuous), PTV volume (continuous), and acute cystitis (grade 0–1, grade 2, grade 3–5)

.

Statistical analysis

We used Prism version 5 (GraphPad Software Inc., La Jolla, CA, USA) for statistical analysis. Differences were considered significant if the relevant two-tailed p values were less than 0.05. The incidence of acute cystitis was described according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Results

All patients completed radiotherapy free of unscheduled interruptions exceeding 2 days. We successfully acquired all planned bladder volume measurements. The mean prostate volume was 27 ml (range: 9–77 ml), the mean PTV volume was 108 ml (range: 49–240 ml). The incidence of acute cystitis during radiotherapy was grade 2 in 7 patients (18%). No cases of grade 3–5 acute cystitis were observed.

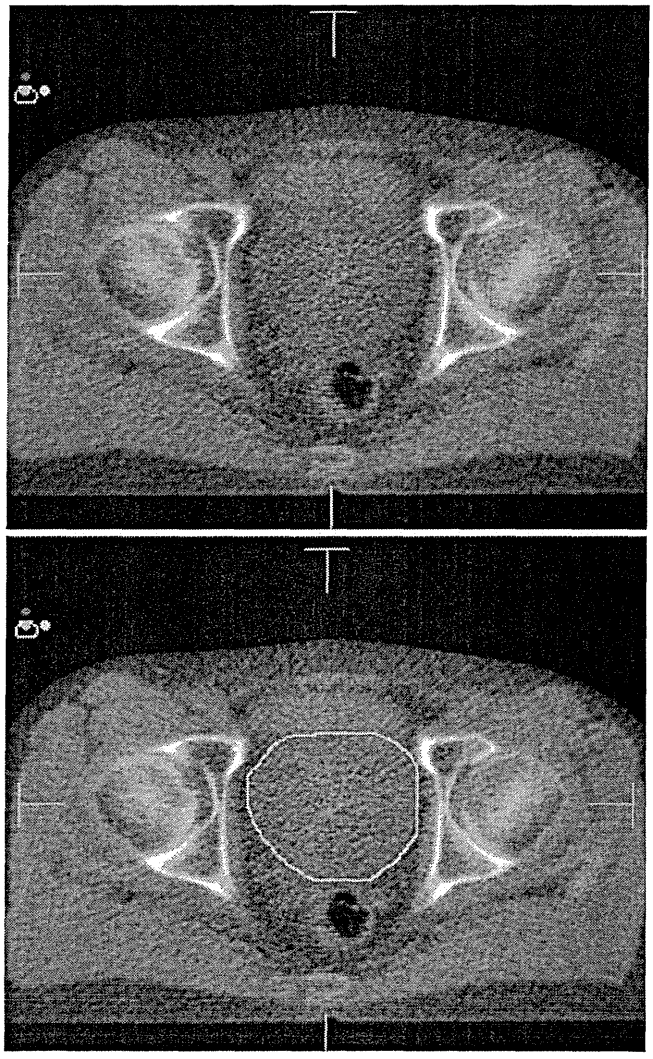

Figure 1. An example of mega voltage computed tomography (MVCT) imaging.

Abbildung 1. Beispiel einer Megavoltage-Computertomographie (MVCT).

Bladder volume trends

The mean population bladder volume (±1 SD) was 219 ml (±83 ml) at the pln-CT, 186 ml (±96 ml) at #1, 149 ml (±73 ml) at #10, 137 ml (±59 ml) at #20, and 136 ml (±60 ml) at #30 (Figure 2). A mean population bladder volume reduction of 38% was observed from the pln-CT to #30 ($p<0.001$ by Wilcoxon's matched pairs test). A significant mean population bladder volume reduction was also found from #1 to #30 ($p<0.001$ by Wilcoxon's matched pairs test). The meanσ_{bl} was 62 ml (range: 11–141ml), while the mean$\sigma_{bl\text{-}rel}$ was 38%

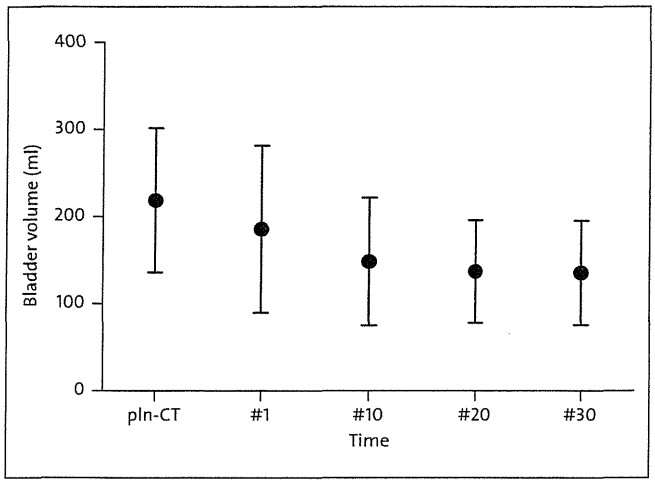

Figure 2. Population-mean bladder volume measured at the planning computed tomography scan (pln-CT) and during the course of radiotherapy. Error bars indicate one standard deviation. *#1, #10, #20, #30* = at the 1st fraction, at the 10th fraction, at the 20th fraction, and at the 30th fraction of radiotherapy, respectively.

Abbildung 2. Mittelwert der Grundgesamtheit des Blasenvolumens, der zum Zeitpunkt des Planungs-Computertomographie-Scans (pln-CT) und während des Verlaufs der Radiotherapie gemessen wurde. Die Fehlerbalken weisen auf eine Standardabweichung hin. *#1, #10, #20, #30* = bei der Verabreichung der 1. Fraktion, der 10. Fraktion, der 20. Fraktion bzw. der 30. Fraktion der Radiotherapie.

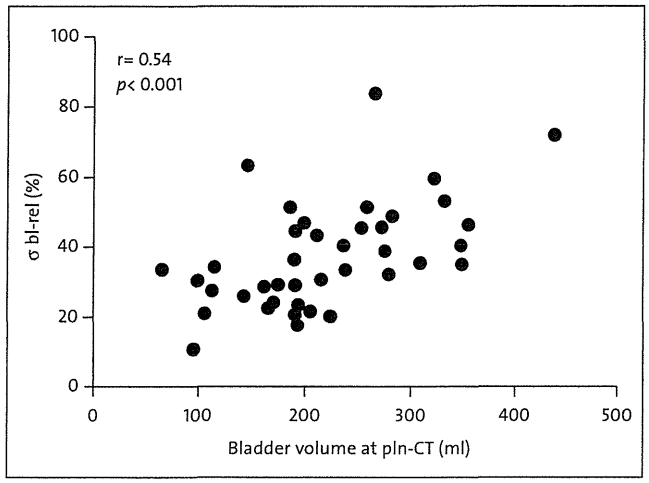

Figure 3. Correlation graph showing bladder volumes at the planning computed tomography scan (pln-CT) vs. intrapatient bladder volume variations ($\sigma_{bl\text{-}rel}$). $\sigma_{bl\text{-}rel}$ σ_{bl} relative to V_{mean}, σ_{bl} standard deviation of V_{mean}, V_{mean} the mean of five measurements of a patient.

Abbildung 3. Auf diesem Korrelationsdiagramm ist die Beziehung zwischen den Blasenvolumen zum Zeitpunkt des Planungs-Computertomographie-Scans (pln-CT) und den Schwankungen des Blasenvolumens innerhalb eines Patienten abgebildet ($\sigma_{bl\text{-}rel}$). $\sigma_{bl\text{-}rel}$ σ_{bl} relativ zu V_{mean}, σ_{bl} Standardabweichung von V_{mean}, V_{mean} der Mittelwert von fünf an einem Patienten vorgenommenen Messungen.

(range: 10–84%). We observed a statistically significant correlation between intrapatient variation in bladder volume ($\sigma_{bl\text{-}rel}$) and bladder volume at the pln-CT (Pearson r=0.54, $p<0.001$) (Figure 3). The intrapatient variation in bladder volume ($\sigma_{bl\text{-}rel}$) was not significantly associated with age ($p=0.68$), T stage ($p=0.88$), Gleason score ($p=0.78$), pretreatment PSA ($p=0.12$), risk group ($p=0.67$), IPSS ($p=0.66$), hormone therapy ($p=0.34$), prostate volume ($p=0.80$), PTV volume ($p=0.74$), or acute cystitis ($p=0.11$).

Discussion

In order to improve bladder volume consistency when the goal is to maintain a full bladder, many institutions specify the volume of liquids to be consumed and the times at which such liquids should be consumed (e.g., drink 500 ml of fluid an hour before the planning CT scan and treatment) [1, 5, 15, 19, 22]. However, large variations in bladder volume have been reported with such protocols [1]. O'Doherty et al. [16] report that a fixed drinking protocol did not eliminate all variations in the bladder volume, in part due to significant individual variations in velocity of bladder filling. They [16] also reported that patients are able to accurately judge their bladder filling state and suggested that subjective patient assessments should be taken into account during efforts to control bladder volume. Stam et al. [18] found a weak but significant correlation between subjective scores for urge to urinate and bladder volume. For these reasons, our institution applied a protocol that did not specify liquid volumes. Instead, the patients were told to adjust the amount of liquid ingested based on their urge to urinate. Nonetheless, our study showed large variations in bladder volume. In an alternative approach, Stam et al. [18] measured daily bladder volumes during daily treatment using a bladder ultrasound scanner and provided patients with feedback to achieve reproducible bladder volumes. The feedback consisted of informing the patients of their daily bladder volume coupled with drinking advice. However, the daily variations in bladder volume did not differ significantly between the control group and the feedback group ($p=0.20$). Table 2 summarizes the findings of previous reports on variations in intrapatient bladder volume, suggesting that no protocol can ensure consistent bladder volumes when the goal is to maintain a full bladder.

Our study showed a decline in bladder volumes during the treatment course. Several previous reports [11, 16, 18] on bladder volume variance in definitive radiotherapy for prostate cancer have found the same trend. This trend was also reported in postoperative radiotherapy for prostate cancer [7] and in radiotherapy for uterine cervical cancer [1]. Although various protocols intended to achieve reproducible bladder volumes were used in these studies, a decreasing trend in bladder volume was a common finding. The reason for the decline in bladder volume remains unclear and may be multifactorial. Although Pinkawa et al. [17] hypothesized that cystitis might lead to a decline in bladder volume, our study showed no sig-

Table 2. *Previous reports on bladder volume variation.*

*intrapatient one standard deviation (one standard deviation relative to mean bladder volume).

Tabelle 2. Frühere Berichte zur Variation des Blasenvolumens.

*eine Standardabweichung innerhalb eines Patienten (eine Standardabweichung gegenüber dem Mittelwert des Blasenvolumens).

Author	Diagnosis	Volume drunk	No. of patients	No. of measurements	Initial bladder volume	Bladder volume reduction	Bladder volume variation*
Lebesque et al. [9]	Prostate cancer	not fixed	11	3	255 ml	28%	89 ml (33%)
Stam et al. [14]	Prostate cancer	not fixed (control group)	18	Daily	348 ml	31%	149 ml (47%)
		gave patients drinking advice according to their daily bladder volume (feedback group)	16	Daily	367 ml	19%	156 ml (40%)
Ahmad et al. [19]	Uterine cervical	500 ml (1 hour before)	24	Twice weekly	378 ml	71%	168 ml
This study	Prostate cancer	not fixed	40	4	219 ml	38%	62 ml (38%)

* intrapatient one standard deviation (one standard deviation relative to mean bladder volume).

nificant correlation between intrapatient variations in bladder volume and the incidence of acute cystitis, and the mechanism underlying the decline in bladder volume can not be explained by cystitis alone, since our study and previous reports [1, 11, 16, 18] showed that reductions in bladder volume occurred immediately after treatment had been initiated. Bladder volume reductions during a treatment course may result in inadequate bladder dose–volume histograms (DVH) and may move the small intestine and sigmoid colon into the high dose irradiated field, increasing the potential toxicity for these organs. Based on the clear trend toward a decline in bladder volume during the course of radiotherapy, a more effective approach may be to perform planning CT scans in the middle of the fractionated radiotherapy course and perform replanning when large bladder volume variations are found.

In our study, larger bladder volumes at planning CT scans correlated with larger bladder volume variations, and previous studies reported similar findings [11, 16, 18, 21]. On the other hand, excessively small bladder volumes make it difficult to satisfy the planning dose constraints for adjacent organs (the bladder, small intestine, and sigmoid colon). For these reasons, several institutions target a half-full bladder or a comfortably full bladder [16, 18]. A half-full bladder appears to represent a reasonable target, offering the potential to improve bladder volume consistency in order to satisfy the dose constraints of the adjacent organs.

We used two different modalities to measure bladder volume: kVCT and MVCT. While the difference between these two modalities may have affected our results, the finding of bladder volume reductions during the treatment course was clear and definite. We also found significant population-mean bladder volume reductions from #1 to #30, which were both measured by MVCT imaging.

Conclusions

A significant decline in bladder volumes during the course of radiotherapy was observed. The bladder volume at the pln-CT was a significant predictor of increased bladder volume variations. It may be possible to harness this trend to reduce bladder volume variance in order to avoid over-full bladders.

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DISEASES OF THE ESOPHAGUS

Original article

Esophageal cancer: definitive chemoradiotherapy for elderly patients

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SUMMARY. **To investigate the efficacy and toxicity of definitive chemoradiotherapy (CRT) for elderly patients with locally advanced esophageal cancer. Twenty-two patients aged over 75 that performed definitive CRT were retrospectively reviewed. The regimen included concurrent CRT consisting of two cycles of chemotherapy (CTx) of platinum and 5-fluorouracil, and radiation therapy (RT) of 50–50.4 Gy (actual range: 45.4–71.4 Gy), and additional CTx where possible. Both CTx and RT were reduced in dose and field where necessary. The disease-free survival rate and the overall survival rate at 3 years were 33.3% ± 11.4% and 25.9% ± 10.8%. Grade 4 leukocytopenia and thrombocytopenia occurred in three (14%) and four (18%) patients. Treatment-related death was suspected in up to four (18%) patients at the most. Univariate analyses for disease-free survival showed that neither total radiation dose nor number of total cycles of CTx was significant. The pattern of relapse was predominantly more frequent in the intra-RT field than outside the RT field. For elderly patients, adverse events are frequent, and decreased organ reserve may cause treatment-related death. Reduction in CTx dose or RT field, appropriate only for two cycles of CTx, and careful monitoring may help to minimize toxicity. Physicians should not be too afraid of adverse events or be negative about CRT for elderly patients, as long as comorbidities and complications are managed carefully.**

KEY WORDS: **chemoradiotherapy, chemotherapy, elderly patient, esophageal cancer, radiotherapy.**

INTRODUCTION

Continual great advances in a broad range of fields, including medical care, social welfare, and elderly care, have resulted in an aging society in Japan. According to the 20th Life Tables in 2005 in Japan, the life expectancy was 78.56 and 85.52 for men and women, respectively, which has increased year after year.[1]

Esophageal cancer is one of the most aggressive cancers, with a 5-year survival rate of 25.0 ± 0.6%.[2] It occurs mainly in the middle aged and elderly. In 2004, the total incidence of esophageal cancer in the Japanese population was 17 815, of which the incidence in patients over the age of 75 was 4964 (28%).[3]

Up until now, surgery has been considered to be the mainstay treatment for locally advanced resectable esophageal cancer. However, it is clear that a combined modality therapy such as chemoradiotherapy (CRT) is also the key to successful treatment. Although elderly patients may often be unfit for surgery because of comorbidities or decreased organ reserve, recent improvements in surgical techniques and postoperative management provide safely esophagectomy, and now, it is not a contraindication for elderly patients. However, to gain a long-term definitive cure from radical surgical resection alone is difficult, and surgery-related reduction in quality of life is significant. Thus, definitive CRT, radiation therapy (RT) alone, or chemotherapy (CTx) alone must be considered for all patients. Today, it is most important to determine therapeutic strategy itself among various choices based on the concept of informed consent even in elderly patients. Nevertheless, in reality, many physicians are hesitant to deliver aggressive treatment to elderly patients because of severe toxicity. There have been a few reports on the use of definitive CRT for elderly patients with esophageal cancer,[4–9] and the appropriate dose intensity and method remain controversial.

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A previous study demonstrated that elderly patients have poor treatment compliance on CRT, resulting in a decreased survival rate as compared with non-elderly patients.[4] Meanwhile, Uno *et al.* revealed that old age by itself is not an adequate reason to exclude patients from aggressive treatment,[5] and some reports have also showed that definitive CRT in elderly patients was effective without a major increase in adverse events.[6–9] Nevertheless, it is not obvious how unfavorable or significant the effects of old age itself on treatment schedule and treatment course are.

Today, life expectancy keeps on increasing, and against such a background, it must be recognized that elderly patients do not necessarily have only a short time left to live. They could be given great and invaluable benefits if aggressive treatment could succeed in increasing their lifetime, which would be a just advantage from medical progress.

The aim of this study was to investigate retrospectively the efficacy and toxicity of definitive CRT for elderly patients aged 75 and older with locally advanced esophageal cancer.

MATERIALS AND METHODS

Patients

Between December 2003 and August 2008, 105 consecutive patients with newly diagnosed locally advanced esophageal cancer underwent definitive CRT at the University of Tokyo Hospital. Of these patients, 22 (21%) patients aged over 75 years were retrospectively reviewed. The main reasons for indication of CRT and/or contraindication of surgery were rejection of surgery ($n = 7$) or no indication of surgery because of advanced age ($n = 6$), lower performance status (PS) ($n = 3$), severe comorbidity ($n = 4$), or tumor location (cervical esophagus) ($n = 2$).

Selection for definitive CRT included the following criteria, which were met by all 22 patients: (i) histologically confirmed squamous cell carcinoma (SqCC) or adenocarcinoma; (ii) clinical stages I to IV disease according to the American Joint Committee on Cancer TNM classification on malignant tumors, 1983, except for stage IVb disease because of distant and hematogenous visceral metastasis (if a stage IVb was because of lymph node metastases that could be potentially covered in the same radiation fields, it was eligible); (iii) Karnofsky Performance Status (KPS) of at least 70%; (iv) no evidence of severe comorbidities or organ dysfunction; (v) adequate bone marrow, renal, hepatic, cardiac, and respiratory function (white blood cell >3000/μL, platelet >10 × 10^4/μL, serum creatinine <1.5 mg/dL); and (vi) no severe interstitial pneumonia (no interstitial pneumonia shadow on computed tomography [CT]). Prior therapy for esophageal cancer except for endoscopic mucosal resection and endoscopic submucosal dissection was ineligible. Although other severe malignant neoplasm was ineligible, that of controllable state was selected. There were two patients with other malignant neoplasms: one with hepatocellular carcinoma and another one with advanced stomach cancer (cT3N2M0) with partial response for CTx using paclitaxel and TS-1, tegafur, gimeracil, and oteracil potassium at the start of CRT for esophageal cancer.

Pretreatment evaluation

All patients were clinically evaluated for their pretreatment state by physical examination; biopsy of primary tumor; endoscopy of the upper gastrointestinal tract; CT of neck, chest, and abdomen; complete blood cell count; and biochemistry evaluation. Some optional examinations were carried out as follows: esophagography for 19 patients (86%) and [18F] fluoro-2-deoxy-D-glucose positron emission tomography for 18 patients (82%). Endoscopic ultrasonography and bronchoscopy were done only if considered necessary. All patients were assigned to a clinical stage on the basis of the American Joint Committee on Cancer TNM classification, 1983.

Treatment schedule

CTx was administered concurrently with RT, starting on day 1.

CTx

Platinum-based CTx, combined with 5-fluorouracil (5-FU), was given to all patients. Before 2006, cisplatin (CDDP) was used mainly as the platinum anticancer drug. After recommendation of its efficacy and safety, nedaplatin (NDP) instead of CDDP has been frequently used with 5-FU, and since 2006, it has become the standard CTx regimen at this institution regardless of renal dysfunction.[10–13] CDDP (75 mg/m^2) or NDP (80 mg/m^2) was administered intravenously on day 1 of each cycle, and 5-FU (1000 mg/m^2/day or 800 mg/m^2/day) was administered as a continuous intravenous infusion on days 1–4 of each cycle with standard premedication. This cycle of CTx was repeated with an interval of 4 weeks, and a total of three to four cycles were delivered where possible, which represented that this schedule was composed of concurrent CRT phase (first and second cycle of CTx) and adjuvant CTx phase. Several risks such as advanced age, lower PS, or renal dysfunction required a reduction in dose ($n = 11$ [50%] in this study). At the start of the second cycle, both white blood cell and platelet count had to be elevated at >2500/μL and >10 × 10^4/μL, respectively, and renal function had to be returned to normal. If these

criteria were not satisfied, CTx was suspended, discontinued, or given at a reduced dose.

RT

A linear accelerator of 6 MV or 10 MV was used. For all patients, the radiation field consisted of the four-portal approach: anterior and posterior opposed portals and two lateral oblique off-cord opposed portals positioned by three-dimensional CT planning in order to avoid a high dose to the spinal cord. In some cases, multiple (>4) portals were used in the field-in-field method to make the dose distribution within the planning target volume homogeneous (95–107% of the prescription dose). All fields were delivered every day, and the daily fractional dose was 1.8–2.0 Gy, administered 5 days a week, up to a total dose of 50–50.4 Gy. For patients aged less than 80 years, an extended field, consisting of gross tumor volume plus the thoracic and abdominal esophagus and M1a region, was irradiated where possible. This meant that cases in which the primary location was the cervical or upper thoracic esophagus could be treated by a so-called T-shape field, which included the bilateral supraclavicular lymph node areas. For patients with an advanced age of 80 years, an involved field including gross tumor volume plus a margin of 1.5 cm laterally and 3–5 cm cranio-caudally was used. Evaluation was performed by using a dose volume histogram as follows: The maximum dose to the spinal cord was limited to 50 Gy, the V_{20} of the lung was limited to <20%, and the mean dose to the lung was limited to 10 Gy.

Analysis of response and statistics

StatView Dataset File Version 5.0 J for Windows (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. Survival periods were calculated from the start of irradiation to either the date of death or the latest follow-up date. Disease-free survival (DFS) was calculated from the start of irradiation to the date of death, to the last follow-up date, or to the clearance of relapse by radiographic or endoscopic modality. Survival curves were estimated with the Kaplan–Meier method estimator, and log-rank tests were used to compare the survival distributions. Univariate analysis and further multivariate analysis were demonstrated by a log-rank test and Cox regression analysis. The World Health Organization response criteria for measurable lesions were used to determine the tumor response.[14] Toxicity was assessed and documented according to Common Terminology Criteria for Adverse Events version 3.0. Differences with values of $P < 0.05$ were considered statistically significant.

RESULTS

All 22 patients were followed until death or time of analysis. The last follow-up was performed on April 30, 2009. Six of the 22 patients (27%) were alive, consisting of five patients in a disease-free state and one patient with relapse. The median follow-up period for surviving patients was 23.8 months (range: 8.3–53.6 months).

Patient and tumor characteristics

Patient and tumor characteristics are shown in Table 1. Nineteen males and three females were included in the analysis. The median age was 79 years (range: 75–85 years). The middle thoracic esophagus was the most frequent primary location, occurring in 10 patients (46%). The most frequent tumor stage was T3, which was observed in 13 patients. N1 disease was observed in 14 patients. Only one patient had M1b (LYM) disease. All cases were SqCC. The most frequent number of total cycles of CTx was two ($n = 10$), and the most frequent total dose of RT was 50.4 Gy

Table 1 Patient and tumor characteristics

Factor	No.
Age	
Median (range)	79 (75–85)
Sex	
Male : female	19 : 3
Location	
Ce : Ut : Mt : Lt	2 : 4 : 10 : 6
Tumor stage	
T1 : T2 : T3 : T4	3 : 4 : 13 : 2
Nodal stage	
N0 : N1	8 : 14
Metastatic stage	
M0 : M1a : M1b	21 : 0 : 1
TNM stage	
I : II : III : IV	3 : 6 : 12 : 1
KPS	
≥90% : <90%	12 : 10
SUV max of primary	
<5 : ≥5	3 : 15
Tumor length	
<5 cm : 5–<10 cm : ≤10 cm	5 : 14 : 3
CTx regimen	
CDDP group : NDP group	5 : 17
Reduction in dose of CTx at the first cycle	
100% : 80% : 70% : 66%	11 : 7 : 3 : 1
Radiation dose	
50–50.4 Gy : the others	17 : 5
Serum SCC in pretreatment	
High : WNL	13 : 9
Serum CYFRA in pretreatment	
High : WNL	3 : 19
Serum CEA in pretreatment	
High : WNL	7 : 15

SUV max were available for 18 patients. CDDP, cisplatin; Ce, cervical; CEA, carcinoembryonic antigen; CTx, chemotherapy; CYFRA, cytokeratin 19 fragment marker; KPS, Karnofsky Performance Status; Lt, lower thoracic; Mt, middle thoracic; NDP, nedaplatin; SCC, squamous cell carcinoma antigen; SUV max, maximum standardized uptake value; Ut, upper thoracic; WNL, within normal limit.