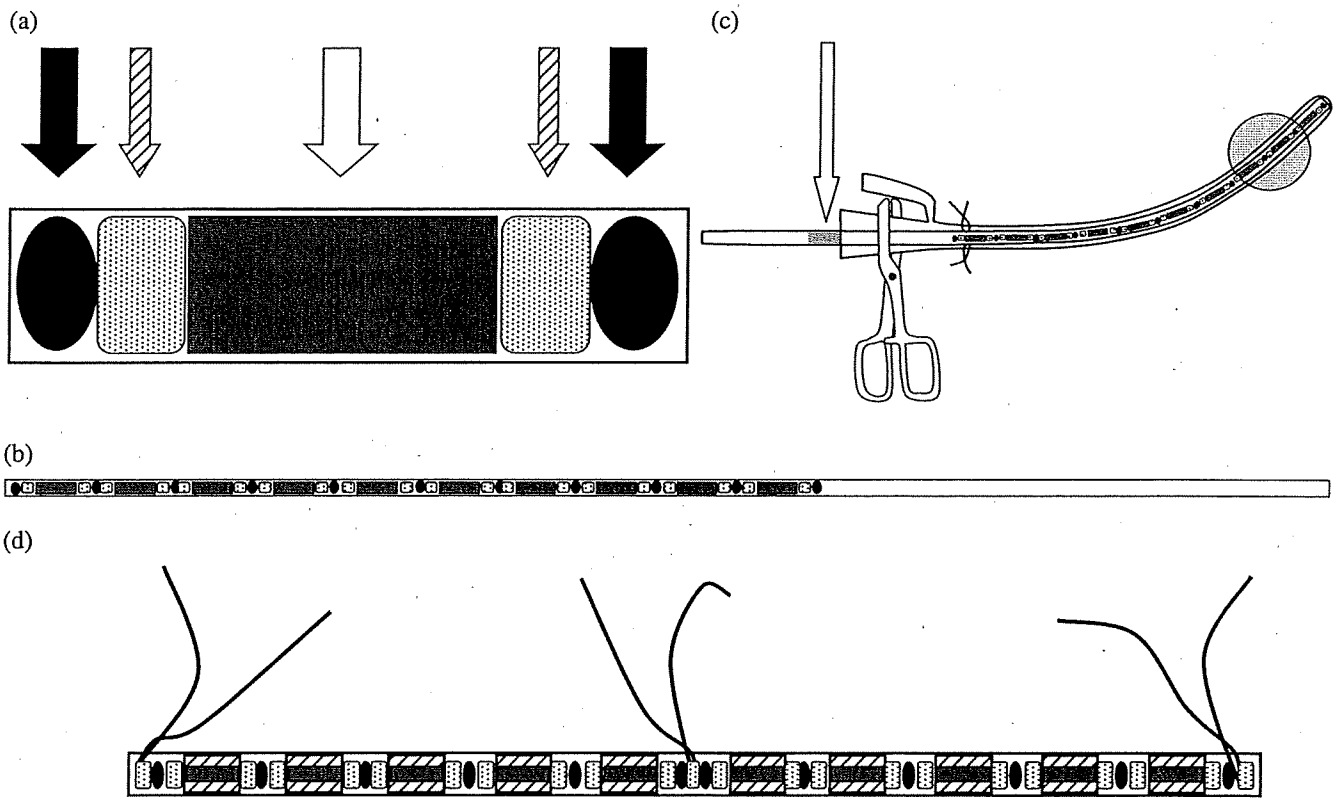


Fig. 1. (a) The Type 1 vector consists of a 1.5–mm-deep slot, carved on a vaginal cylinder or on a template; this houses an radiophotoluminescence glass dosimeter (RPLGD) complex, which consists of an RPLGD (white arrow) located centrally, a ø1 mm lead ball (black arrows) placed at each end, and 1-mm spacers (striped arrows) between the RPLGD and the lead balls. (b) The Type 2 vector, dedicated to the urethra; the ø2 mm Teflon tube contains 10 RPLGD complexes. (c) The Type 2 vector is inserted into the balloon catheter until the vector top touches the proximal catheter end at simulation and at each irradiation session. The vector and the catheter are clamped together with forceps near the distal catheter end. The point where the vector surface crosses the distal end of the catheter is marked using a felt-tip pen (arrow). (d) The Type 3 vector, dedicated to the rectum, is shown; the ø4-mm Teflon tube contains 10 encapsulated RPLGD complexes, with each RPLGD housed in a plastic capsule. The three nylon threads sutured to each end and the midportion of the vector enable fixation of the vector to the rectum.

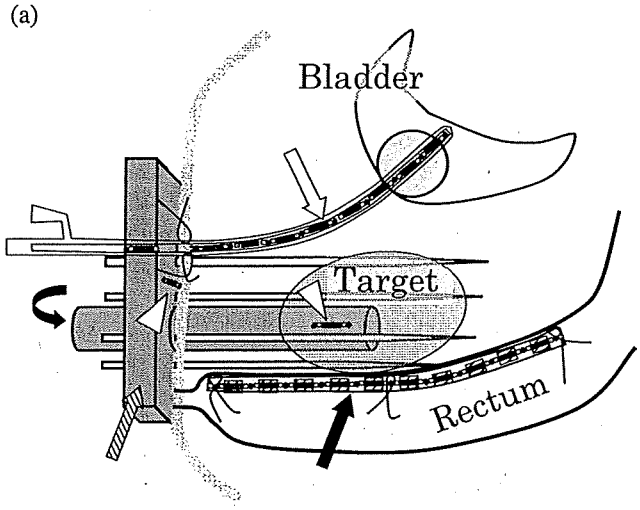
synchronously. For most female patients, tumor extent involved the vaginal wall such that vaginal wall dosimetry represented tumor dose. The template was sutured to the perineum such that the Type 1 RPLGD was in contact with the skin (Figs. 2a and 2b). Template dosimetry represented perineal skin dose. A balloon catheter was sutured to the urethral orifice after early experiences with the prostate implant and anterior vaginal implant in particular; the needle tips had collapsed the balloon and caused migration of the catheter from the original position. A total of 1142 points were measured by RPLGDs in the following locations: anterior wall of the rectum, $n = 599$; urethra, $n = 482$; vaginal cylinder, $n = 28$; perineal template, $n = 33$. Doses were measured by RPLGDs and were also calculated on a planning computer (CadplanBT 1.1, Varian TEM, Crawley, United Kingdom). Of the 1142 points, 58 points (5.1%) were not identified by X-ray films, and dose calculation was not obtainable; therefore, both measured and calculated doses were available for 1084 points.

Simulation, planning, and irradiation

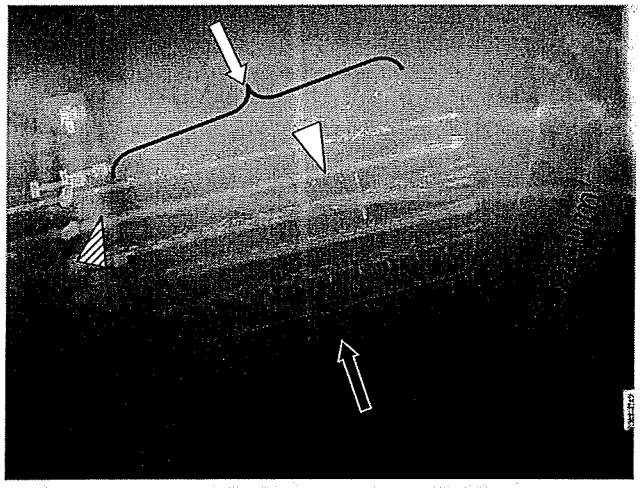
At simulation, the Type 2 vector was inserted into the balloon catheter until the vector top touched the proximal end of the catheter (Fig. 1c). Both the vector and the catheter were clamped together with forceps near the distal end of the catheter. The point where the vector surface crossed the distal end of the catheter was marked with a felt-tip pen to enable reproducible loading at each session. A dummy source was loaded into each applicator. A pair of radiographs was taken; the couch was then rotated 90°, and CT was performed at 5-mm intervals; all measured doses were therefore contaminated by simulation radiation. CadplanBT 1.1 was used for treatment planning. The geometry of the applicators was reconstructed from the radiographs before the superimposition of CT data. The central plane and basal dose points were determined according to the extrapolated Paris System (17, 18). An arbitrary isodose surface (median, 82% BDIS; range, 70%–98% BDIS) that covered the CTV was chosen for dose prescription. HDRIB schedules are described in Table 2; rectal and urethral doses represent constraints for dose prescription. For patients not previously irradiated, calculated rectal and urethral doses were set to a below-ceiling dose that was determined on the basis of clinical experiences of HDRIB at Osaka University and related hospitals (Table 2). For the 12 reirradiated patients, the previous radiotherapy consisted of 30-Gy whole pelvis (range, 0–50 Gy) and 10-Gy central-shielded field (range, 0–28 Gy) combined with 30-Gy HDR intracavitary brachytherapy ($n = 6$, range, 15–30 Gy) or 36 Gy HDRIB ($n = 1$). It was impractical to set a ceiling dose for these patients, and doses for

the rectum/urethra were modified to as low as possible. The maximum diameter of double the prescription isodose surface (hyperdose sleeve) was another concern related to morbidity. The Paris System recommends keeping this diameter ≤8–10 mm (18). If the diameter exceeded 8 mm, the dose distribution was modified by manually changing dwell times. When these three conditions (CTV coverage, rectal/urethral dose, hyperdose sleeve ≤8 mm) could not be achieved simultaneously, the plan was compromised at the cost of rectal/urethral dose, hyperdose sleeve, or both. For each RPLGD, three points (the midpoint and both ends of the readout part) were reconstructed. Doses were calculated for the three points, and the averaged value was regarded as the calculated dose for the particular RPLGD. The anatomic location of the RPLGD was classified as "anterior wall of the rectum"; "urethra (male/female)"; "vaginal wall," measured at the vaginal cylinder surface; and "perineal skin," measured at the template surface facing the perineum. Irradiation was performed using Varisource (Varian TEM). Source strength was determined following each purchase using a well-type chamber. The mean deviation from the supplier's value was only 0.08 ± 0.83% (range, –1.04 to 1.60%). HDRIB was delivered twice a day with an interval of at least 6 h. Before each session, the Type 2 vector was inserted into the balloon catheter to the depth of the felt-tip pen marker crossing the catheter (Fig. 1c).

(a)



(b)



(c)

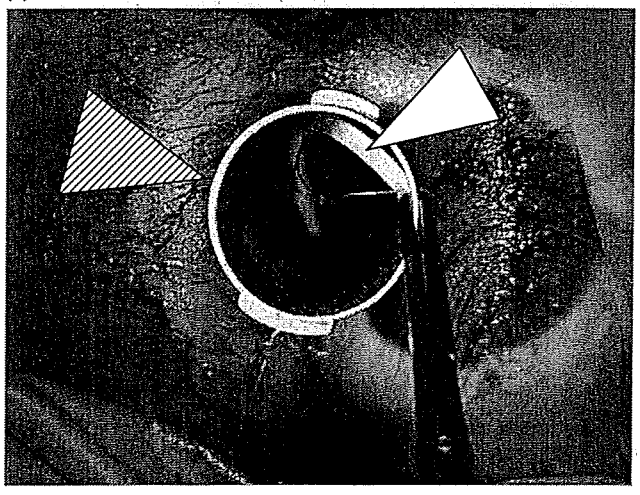


Fig. 2. (a) Schema of the current study. Application of two Type 1 radiophotoluminescence glass dosimeter (RPLGD) complexes: one on the template, the other on the vaginal cylinder (arrowheads); one Type 2 vector in a balloon catheter (white arrow); and one Type 3 vector on the anterior rectal wall (black arrow) for a female patient. The striped arrow indicates the perineal template and vaginal cylinder (curved arrow). (b) A radiograph from the study shows the application positions of the following vectors: Type 1 vectors on the template (striped arrowhead) and on the vaginal cylinder (white arrowhead); Type 2 vector in a balloon catheter (white arrow); and Type 3 vector on the anterior rectal wall (black arrow) of a female patient. (c) A Type 3 vector (white arrowhead) is sutured to the anterior rectal wall through a rigid rectoscope (striped arrowhead).

Absorbed simulation X-ray

Absorbed dose from the simulation was assessed in one prostate cancer patient using a Type 2 vector in the urethra. During a routine simulation, 10 RPLGDs in the urethra were exposed to 120 KV X-rays (mean effective energy ≈ 40 KeV) for a pair of radiographs and a 20-cm CT at 5-mm intervals. The readout value was corrected by both calibration factors for each RPLGD, as obtained for 4-MV photons, and by a relative correction factor of 3.8 for 40 KeV (Fig. A, 9.4 in ref. 16).

Statistics

Statistical analyses were performed using SPSS 8.0 software (Chicago, IL). The Mann-Whitney *U* test was used for nonparametric comparisons (19). Kaplan-Meier methods were used for analyses of local control (20).

RESULTS

Clinical results

There were no unexpected events attributable to the use of RPLGDs. Moreover, the location of anterior rectal wall that is not visible on CT was easily found, and the corresponding dose was calculated. In all patients, the use of RPLGD was well tolerated. The local control ratio was 87% with a median follow-up of 30 months. Late sequelae were graded as G0 in 38 patients, G1 in 6 patients, G2 in 5 patients, G3 in 7 patients, and not specified in 10 patients.

Table 2. HDRIB schedule

	HDRIB	EXRT	Ceiling dose for rectum	Ceiling dose for urethra
HDRIB alone (n = 45)				
Previously nonirradiated (n = 33)	54 Gy/9 fr/5 d	-	42 Gy/9 fr/5 d	76 Gy/9 fr/5 d
Previously irradiated (n = 12)	48 Gy/8 fr/4 d	-	Not specified	Not specified
HDRIB+EXRT (n = 21)				
Previously nonirradiated (n = 21)	30 Gy/5 fr/3 d	WP 30 Gy + CS 20 Gy	24 Gy/5fr/3 d	58 Gy/5 fr/3 d

Abbreviations: HDRIB = high-dose-rate interstitial brachytherapy; EXRT = external radiotherapy; fr = fraction; WP = whole pelvis field; CS = central-shielded field.

Absorbed simulation X-ray by RPLGDs

The median measured dose of all 1084 points was 17.19 Gy (range, 0.41–88.73 Gy). The median absorbed simulation dose for the 10 RPLGDs was 0.048 Gy (range, 0.043–0.054 Gy), corresponding to 1.06% (0.048 Gy × 3.8 / 17.19 Gy; range, 0.21% [0.048 Gy × 3.8 / 88.73 Gy] to 44.49% [0.048 Gy × 3.8 / 0.41 Gy]) of the median absorbed dose. Setting the threshold for the simulation dose at 5% of the total absorbed dose, 3.65 Gy (0.048 Gy × 3.8 / 5%) was the minimum total measured dose required. Doses for 80 points (rectum, n = 30; urethra, n = 41; vagina, n = 1; perineum, n = 8) were <3.65 Gy; these values were eliminated from further analyses.

Results of 1004 RPLGDs

The remaining 1004 points (≥3.65 Gy), comprised of rectum, n = 549; urethra, n = 415; vaginal wall, n = 25; and perineal skin, n = 15 were used for further analyses. For the 1004 dosimeters, the median measured and calculated doses were 18.59 Gy (range, 3.65–88.73 Gy) and 19.94 Gy (range, 2.42–94.68 Gy), respectively. The compatibility ratio of the measured and calculated doses was 0.98 ± 0.23. Measured doses, calculated doses, and compatibility according to location are displayed in Table 3. The frequencies of compatibility according to location are displayed in Figs. 5a–5e.

Dose for the rectum

For the 549 dosimeters, the median measured and calculated doses were 17.64 Gy (range, 3.68–64.64 Gy) and 18.32 Gy (range, 3.19–75.70 Gy), respectively. The compatibility ratio of the measured and calculated doses was 0.99 ± 0.20 (Fig. 3a).

Dose for the urethra (female and male)

For the 415 dosimeters, the median measured and calculated doses were 20.47 Gy (range, 3.72–88.73 Gy) and 21.65 Gy (range, 2.58–78.84 Gy), respectively. The compatibility ratio of the measured and calculated doses was 0.96 ± 0.26.

Dose for the male urethra

For the 181 dosimeters, the median measured and calculated doses were 28.31 Gy (range, 4.07–88.73 Gy) and 36.73 Gy (range, 3.35–78.84 Gy), respectively. The compatibility ratio of the measured and calculated doses was 0.90 ± 0.30 (Fig. 3b). The ratio for the male urethra was significantly different from that for the female urethra (p <0.01). Even with stitches to the urethral orifice in males, if the balloon was ruptured by the needle tips, the balloon catheter could migrate, depending on penis direction and length. A 10% negative shifted distribution suggests slipping of the original position.

Dose for the female urethra

For the 234 dosimeters, the median measured and calculated doses were 17.51 Gy (range, 3.72–71.69 Gy) and 18.16 Gy (range, 2.58–73.03 Gy), respectively. The compatibility ratio of the measured and calculated doses was 1.01 ± 0.20 (Fig. 3c).

Dose for the vaginal wall

For the 25 dosimeters, the median measured and calculated doses were 38.79 Gy (range, 9.51–82.42 Gy) and 42.98 Gy (range, 9.04–94.68 Gy), respectively. The compatibility ratio of the measured and calculated doses was 0.91 ± 0.08 (Fig. 3d).

Table 3. Measured dose, calculated dose, and compatibility according to locations for the 1004 points

Region	Measured dose	Calculated dose	Compatibility ratio*
Anterior wall of the rectum (n = 549)	17.6 Gy (3.7–64.6 Gy)	18.3 Gy (3.2–75.7 Gy)	0.99 ± 0.20
Urethra (n = 415)	20.5 Gy (3.7 Gy-88.7 Gy)	21.7 Gy (2.6 Gy-78.8 Gy)	0.96 ± 0.26
Male urethra (n = 181)	28.3 Gy (4.1 Gy-88.7 Gy)	36.7 Gy (3.4 Gy-78.8 Gy)	0.90 ± 0.30
Female urethra (n = 234)	17.5 Gy (3.7 Gy-71.7 Gy)	18.2 Gy (2.6–73.0 Gy)	1.01 ± 0.20
Vaginal wall (n = 25)	38.8 Gy (9.5 Gy-82.4 Gy)	43.0 Gy (9.0–94.7 Gy)	0.91 ± 0.08
Perineal skin (n = 15)	6.9 Gy (3.7 Gy-59.6 Gy)	6.3 Gy (2.4–61.6 Gy)	1.25 ± 0.32
Total (n = 1004)	18.6 Gy (3.7 Gy-88.7Gy)	19.9 Gy (2.4–94.7 Gy)	0.98 ± 0.23

* Compatibility ratio = measured dose/calculated dose.

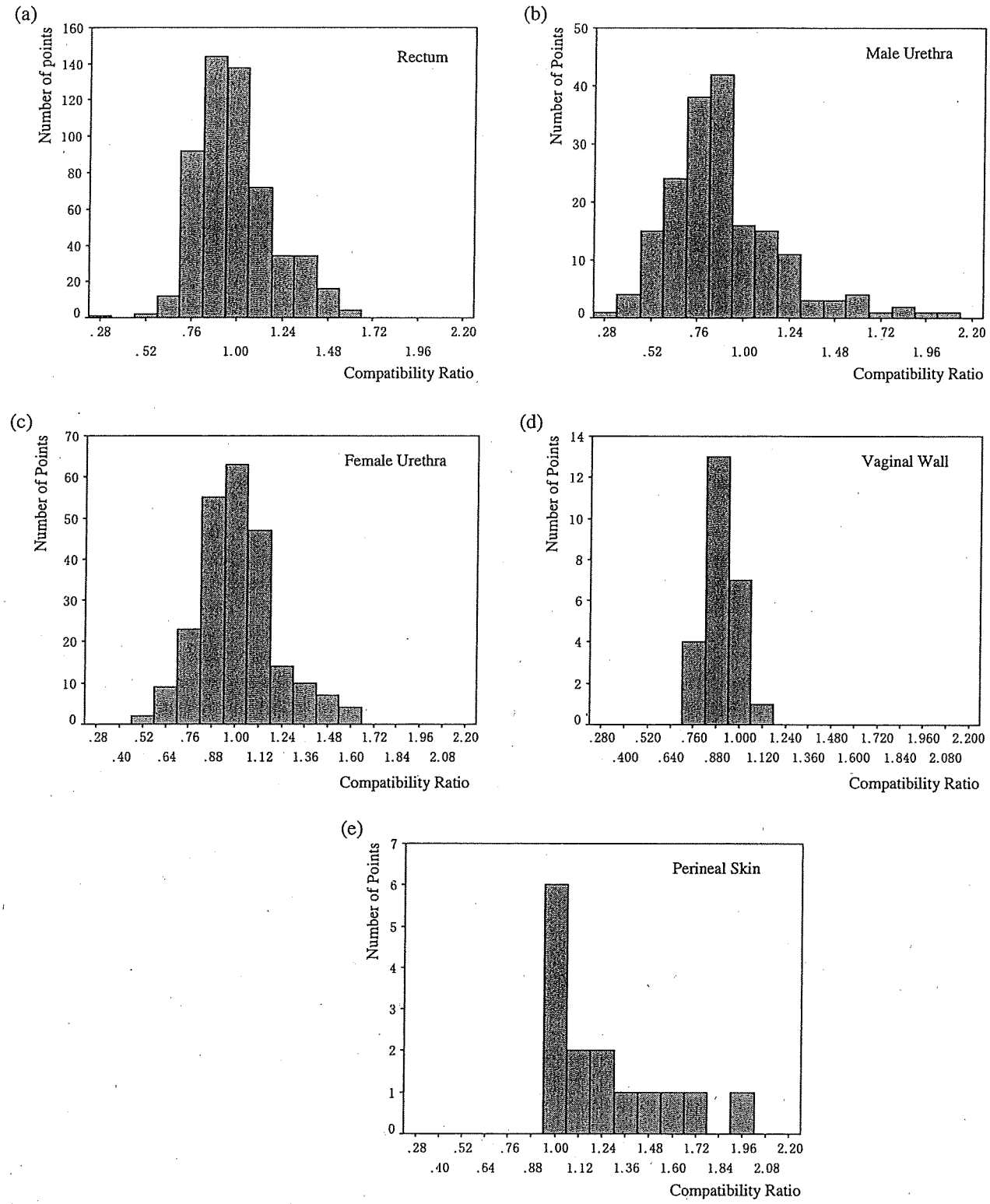


Fig. 3. (a) Frequency of compatibility ratio for radiophotoluminescence glass dosimeter (RPLGD) for the rectum. Abscissa: ratio of measured dose/calculated dose. Ordinate: number of points for RPLGDs. Distribution approximates Gaussian, with mean compatibility of 0.99 ± 0.20. (b) Frequency of compatibility ratio for RPLGD for the male urethra. Abscissa: ratio of measured dose/calculated dose. Ordinate: number of RPLGDs. Distribution is positive-skewed and negatively shifted, with mean compatibility of 0.90 ± 0.30. (c) Frequency of compatibility ratio for RPLGD for the female urethra. Abscissa: ratio of measured dose/calculated dose. Ordinate: number of RPLGDs. Distribution approximates Gaussian, with mean compatibility of 1.01 ± 0.20. (d) Frequency of compatibility ratio for RPLGD for the vaginal wall. Abscissa: ratio of measured dose/calculated dose. Ordinate: number of points for RPLGDs. Distribution is negatively shifted steep Gaussian, with mean compatibility of 0.91 ± 0.08. (e) Frequency of compatibility ratio for RPLGD for the perineum. Abscissa: ratio of measured dose/calculated dose. Ordinate: number of RPLGDs. Distribution is positive-skewed and with mean compatibility of 1.25 ± 0.32.

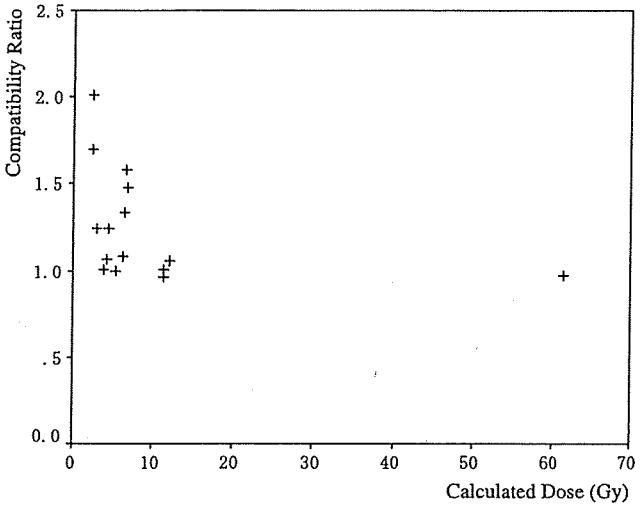


Fig. 4. Correlation between compatibility ratio (ordinate; measured dose/calculated dose) and the calculated dose (abscissa) for perineal skin.

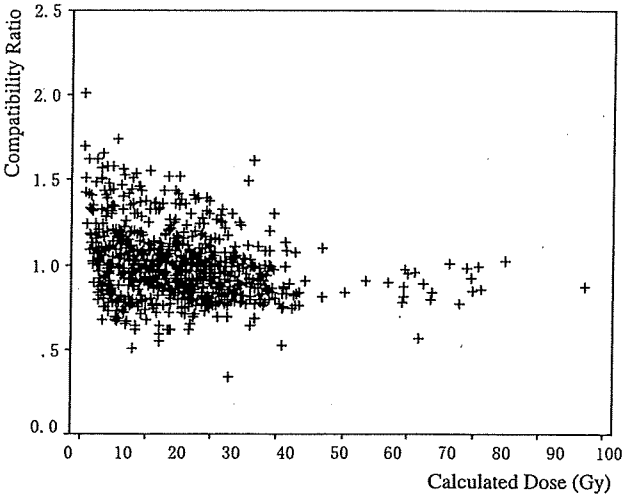


Fig. 5. Correlation between compatibility ratio (ordinate; measured dose/calculated dose) and the calculated dose (abscissa) for 823 points (male urethra excluded).

Dose for the perineal skin

For the 15 dosimeters, the median measured and calculated doses were 6.85 Gy (range, 3.65–59.62 Gy) and 6.33 Gy (range, 2.42–61.64 Gy), respectively. The compatibility ratio of the measured and calculated doses was 1.25 ± 0.32 (Fig. 3e). Transit dose plays an important role in positive discrepancy of the measured dose and its impact is known to depend on the calculated dose (21). Compatibility ratio according to calculated dose is displayed in Fig. 4.

DISCUSSION

In vivo dosimetry studies for interstitial brachytherapy have previously dealt only with small numbers of patients, except for pioneering work using RPLGDs at the Veterans Administration Hospital in New York in the 1950s and 1960s (5–9, 13). To the best of our knowledge, this is the largest *in vivo* dosimetry study conducted for interstitial brachytherapy. The simple handling of RPLGDs facilitates their routine use in clinical situations; in addition, their linearity and reproducibility are better than those of the TLDs used previously (5–9). Measured doses in this study were contaminated by simulation X-rays; data with excessive contamination were excluded by setting a threshold for measured doses.

For male urethral measurements, suturing of the catheter to the urethral orifice did not eliminate the migration of dosimeters that prevents precise data from being obtained. For female urethral measurements, this technique eliminated migration. The frequency for compatibility of measured and calculated doses displayed a wide Gaussian distribution, with mean 1.01 ± 0.20. For the rectum, compatibility displayed a similar Gaussian distribution (0.99 ± 0.20). These deviations (±20%) are attributable to the movements for these organs independent of movement for the target, and hence for the applicators. In our previous *in vivo* dosimetry study for 61 head and neck brachytherapy patients, the compatibility for nontarget organs (the submandibular skin and the mandible) displayed a wider Gaussian distribution, with mean 1.06 ± 0.32 (12). The movement of nontarget organs relative to the applicators is less in the pelvic region (where target organs and applicators do not move voluntarily) than in the head and neck region (where target organs move under the control of voluntary muscles). For nontarget organs in the pelvic region, actual absorbed doses can be 20% greater than calculated doses, compared with 32% in the head and neck region. Lead shielding is an effective protection that halves the absorbed dose to the nontarget organs in the region of the head and neck (4); however, shielding is impractical for the rectum and urethra during interstitial brachytherapy. Actual dose monitoring for organs at risk is feasible by employing an alternative real-time dosimeter such as MOSFET (22). If excessive dose is detected, the initial planning can be adapted for subsequent sessions.

For the target (vaginal wall), compatibility displayed a narrow Gaussian distribution (0.91 ± 0.08). This 8% deviation is the smallest among all the locations and is similar to the 10% deviation (0.95 ± 0.10) observed for the head and neck target in our previous study (12). Movement of the target is synchronized with the applicators, provided that the applicators are implanted in the target, irrespective of the target type and movement pattern (pelvis, nonvoluntary movement by surrounding organ volumes; head and neck, voluntary movement). The 9% negative shift is attributable to the lack of inhomogeneity correction in the software for the vaginal cylinder, which has a density of 1.24. The acceptable criteria for brachytherapy, as stated by the Radiological Physics Center, is 15% (23), which is achievable using inhomogeneity correction. Use of a real-time dosimeter is desirable to achieve more precise delivery of the planned dose.

The transit dose affects all the measured doses to some degree. The importance of the transit dose depends on calculated dose (21). As shown in Fig. 4, the calculated dose seems to affect the compatibility ratio for the perineal skin.

The compatibility ratio approaches unity as the calculated dose increases, especially for >10 Gy. For 823 points (excluding male urethral points), 294 points were to receive calculated dose <10 Gy, and the compatibility ratio was 1.09 ± 0.25, whereas 529 points were to receive calculated dose ≥10 Gy, and the compatibility ratio was 0.97 ± 0.18 (p <0.001) (Fig. 5). Transit dose should be incorporated in points with calculated dose <10 Gy, although the clinical impact of these low doses remains unclear.

In conclusion, the compatibility ratio of the measured and calculated doses for the target displayed a small deviation (8%) caused by synchronized movement with the applicators, and a 9% negative shift attributable to the cylinder material. The addition of inhomogeneity correction to the planning software would enable the acceptable criteria for the target of brachytherapy (15%) to be easily achieved. The transit dose should be incorporated into points with a calculated dose of <10 Gy. Measured doses for organs at risk displayed as much as 20% deviation from the planned doses because of involuntary movements. The next step to using these findings will be to establish an adaptive dose delivery system using a real-time dosimeter.

REFERENCES

1. Lachance B, Béliveau-Nadeau D, Lessard É, *et al.* Early clinical experience with anatomy-based inverse planning dose optimization for high-dose-rate boost of the prostate. *Int J Radiat Oncol Biol Phys* 2002;54:86–100.
2. Sumida I, Shiomi H, Yoshioka Y, *et al.* Optimization of dose distribution for HDR brachytherapy of the prostate using attraction-repulsion model. *Int J Radiat Oncol Biol Phys* 2006;64: 643–649.
3. Nose T, Peiffert D, Lapeyre M, *et al.* Clinical target volume-based dose specification for interstitial brachytherapy: Minimum target dose comparison with classical implant system. *J Brachyther Int* 2001;17:345–353.
4. Nose T, Koizumi M, Nishiyama K. High-dose-rate interstitial brachytherapy for oropharyngeal carcinoma: Results of 83 lesions in 82 patients. *Int J Radiat Oncol Biol Phys* 2004;59: 983–991.
5. Mangold CA, Rijnders A, Georg D, *et al.* Quality control in interstitial brachytherapy of the breast using pulsed dose rate: Treatment planning and dose delivery with an Ir-192 afterloading system. *Radiother Oncol* 2001;58:43–51.
6. Brezovich IA, Duan J, Pareek PN, *et al.* In vivo urethral dose measurements: A method to verify high dose rate prostate treatments. *Med Phys* 2000;27:2297–2301.
7. Hamers HP, Johansson KA, Venselaar JLM, *et al.* In vivo dosimetry with TLD in conservative treatment of breast cancer patients treated with the EORTC protocol 22881. *Acta Oncol* 1993;32:435–443.
8. Anagnostopoulos G, Baltas D, Geretschlaeger A, *et al.* In vivo thermoluminescence dosimetry dose verification of transperineal ^{192}Ir high-dose-rate brachytherapy using CT-based planning for the treatment of prostate cancer. *Int J Radiat Oncol Biol Phys* 2003;57:1183–1191.
9. Kälkner KM, Bengtsson E, Eriksson S, *et al.* Dosimetry of anal radiation in high-dose-rate brachytherapy for prostate cancer. *Brachytherapy* 2007;6:49–52.
10. Tsuda M. A few remarks on photoluminescence dosimetry with high energy X-rays. *Jpn J Med Phys* 2000;20:131–139.
11. Araki F, Ikegami T, Ishidoya T, *et al.* Measurements of Gamma-Knife helmet output factors using a radiophotoluminescent glass rod dosimeter and a diode detector. *Med Phys* 2003;30: 1976–1981.
12. Nose T, Koizumi M, Yoshida K, *et al. In vivo* dosimetry of high-dose-rate brachytherapy: Study on 61 head-and-neck cancer patients using radiophotoluminescence glass dosimeter. *Int J Radiat Oncol Biol Phys* 2005;61:945–953.
13. Roswit B, Malsky SJ, Reid CB, *et al.* In vivo radiation dosimetry. Review of a 12-year experience. *Radiology* 1970;97:413–424.
14. Perry JA. Luminescence phenomena. In: Perry JA, editor. RPL dosimetry. Radiophotoluminescence in health physics. Bristol, United Kingdom: IOP; 1987. p. 1–7.
15. Perry JA. Instrumentation and technique. In: Perry JA, editor. RPL dosimetry. Radiophotoluminescence in health physics. Bristol, United Kingdom: IOP; 1987. p. 141–160.
16. Japan Society of Medical Physics, editor. Standard dosimetry of absorbed dose in external beam radiotherapy (Standard Dosimetry 01). Tokyo: Tsuusyou Sangyou Kenkyu; 2002 [in Japanese].
17. Leung S. Perineal template techniques for interstitial implantation of gynecological cancers using the Paris System of dosimetry. *Int J Radiat Oncol Biol Phys* 1990;19:769–774.
18. Dutreix A, Marinello G, Wambersie A. Dosimétrie du système de Paris. In: Dutreix A, Marinello G, Wambersie A, editors. Dosimétrie en curiethérapie. Paris: Masson; 1982. p. 109–138.
19. Siegel S. In: Nonparametric statistics for the behavioral sciences. New York: McGraw-Hill; 1956.
20. Kaplan EL, Meier P. Nonparametric estimation for incomplete observation. *J Am Stat Assoc* 1958;53:457–511.
21. Thomadsen BR, Houdek PV, van der Laarse R, *et al.* Treatment planning and optimization. In: Nag S, editor. High dose rate brachytherapy: A text book. Armonk, NY: Futura; 1994. p. 79–145.
22. Cygler JE, Saoudi A, Perry G, *et al.* Feasibility study of using MOSFET detectors for in vivo dosimetry during permanent low-dose-rate prostate implants. *Radiother Oncol* 2006;80: 296–301.
23. Hanson WF, Shalek RJ, kennedy P. Dosimetry quality assurance in the U.S. from the experience of the Radiological Physics Center. In: Starkschall G, Horton J, editors. Quality assurance in radiotherapy physics. Madison, WI: Medical Physics; 1991. p. 255–282.

DISEASES OF THE COLON & RECTUM

ORIGINAL CONTRIBUTION

Preoperative Radiation Response Evaluated by 18-Fluorodeoxyglucose Positron Emission Tomography Predicts Survival in Locally Advanced Rectal Cancer

Keiichi Nakagawa, M.D.[1] • Hideomi Yamashita, M.D.[1] • Naoki Nakamura, M.D.[1] • Hiroshi Igaki, M.D.[1] • Masao Tago, M.D.[1] • Yoshio Hosoi, M.D.[2] • Toshimitsu Momose, M.D.[1] • Kuni Ohtomo, M.D.[1] • Tetsuichiro Muto, M.D.[3] • Hirokazu Nagawa, M.D.[2]

1 Department of Radiology, University of Tokyo Hospital, Tokyo, Japan
2 Department of Surgical Oncology, University of Tokyo Hospital, Tokyo, Japan
3 Department of Surgical Oncology, The Cancer Institute Hospital, Tokyo, Japan

PURPOSE: This study focuses on the prognostic survival value of postirradiation metabolic activity in primary rectal cancer as measured with 18-fluorodeoxyglucose positron emission tomography.

METHODS: From July 1995 to March 2002, all 59 patients underwent two series of fluorodeoxyglucose positron emission tomography: one before preoperative radiation (standardized uptake values-1), and the other two to three weeks after radiation (standardized uptake values-2). Standardized uptake values-1 and standardized uptake values-2 correspond to before and after radiation, respectively.

RESULTS: In univariate analysis, the following emerged as significant prognostic variables: with or without residual tumor, pathologic differentiation, with or without recurrence, standardized uptake values-2, and with or without lymph node metastases. In multivariate analysis, residual tumor and standardized uptake values-2 were significant prognostic factors for survival. The median survival and the five-year overall survival rate comparing standardized uptake values-2 values <5 *vs.* >5 were 95 *vs.* 42 months and 70 *vs.* 44 percent, respectively ($P=0.042$).

CONCLUSION: A significant survival benefit was observed in patients with low fluorodeoxyglucose uptake after preoperative radiotherapy in primary tumors of rectal cancer.

KEY WORDS: Positron emission tomography; Radiotherapy; Prognostic value; Standardized uptake values; Rectal cancer; Preoperative radiation.

A number of studies have reported that preoperative radiotherapy (RT) reduces the recurrence rate for locally advanced rectal cancer.[1–6]

Several studies have suggested that in selected patients with low rectal tumors, high-dose preoperative RT might permit the resection of the primary tumor with a high rate of preservation of sphincter function.[7–11] Such treatment results could have survival rates similar to those observed with more radical surgery without increasing the risk of pelvic or perineal recurrences.

However, except for a single European trial, definitive improvement in overall survival has not generally been demonstrated with preoperative RT alone.[3,12]

The prognosis of rectal cancer is generally related to the degree of penetration of the tumor through the bowel wall and the presence or absence of nodal involvement.[13–16] However, diagnostic accuracy of tumor penetration and nodal status is not sufficient.[17]

Many other prognostic markers have been evaluated retrospectively in determining the prognosis of patients with rectal cancer, although most, including allelic loss of chromosome 18q or thymidylate synthase expression, have not been prospectively validated.[18–20]

In those cases of rectal cancer in which preoperative RT was administered, nodal involvement and penetration of the tumor seemed to be significant for prognosis as well.[21–25] Besides nodal involvement and penetration status, no definitive prognostic markers have been reported in the preoperative radiation setting for this malignancy.

Prognostic information available before surgery is useful to select the candidates for a more aggressive surgical approach, such as extended lymphadenectomy, as well as intensive postoperative adjuvant therapy.[26–30] Also, the identification before the start of the entire treatment course of subsets of patients who are at low or high risk for recurrence can help to optimize treatment. For high-risk subsets, a more aggressive preoperative approach,

Address of correspondence: Keiichi Nakagawa, M.D., Ph.D., Department of Radiology, University of Tokyo Hospital, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. E-mail: nakagawa-rad@umin.ac.jp

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such as combined modality preoperative treatment should be considered. Few predictors have been reported for this use.

Several studies have now been reported claiming the potential of fluorodeoxyglucose–positron emission tomography (FDG-PET) in predicting treatment outcome after preoperative RT for malignant neoplasms, including rectal cancer.[31,32] However, no consensus has been established on the usefulness of FDG-PET in predicting survival outcomes.

This study was designed to clarify the role of FDG-PET as a prognostic tool for patients with rectal cancer treated with preoperative RT.

PATIENTS AND METHODS

Study Design

From July 1995 to March 2002, the authors prospectively enrolled 59 patients with primary rectal cancer deemed eligible for preoperative RT, on the basis of a clinically bulky or tethered tumor or on imaging-based evidence of T3–4 or N1 disease by use of transrectal ultrasound. The distance from the anal edge of the tumor to the anal verge was <3 cm in 11 cases, 3 to 5 cm in 42 cases, and >5 cm in 6 cases. All patients received 50 Gy to the pelvis and were subjected to two series of FDG-PET: one before preoperative RT, and the other two to three weeks after the treatment (days after radiotherapy ranged from 11–50; mean, 17; median 16). Surgery was performed 20 to 77 (mean, 43.3; median, 41) days after the completion of preoperative RT and 3 to 63 (mean, 26.2; median, 25) days after the second FDG-PET study.

The study was a prospective trial and had institutional review board approval. Informed consent was obtained from all patients.

Treatments

For RT, a 6-MV x-ray accelerator delivered 50 Gy in 25 fractions, 5 fractions per week during five weeks. Two AP/PA opposed fields were used as a Japanese conventional radiation technique for pelvic tumors. The clinical target volume included the entire pelvic cavity, anal canal, primary tumor, mesorectal and presacral lymph nodes, nodes along the internal iliac artery, lumbar nodes up to the level of the lower border of the fifth lumbar vertebra, and nodes at the obturator foramen. No chemotherapy was added to the RT in a preoperative setting. All surgeries were performed by colorectal specialists. Abdominoperineal resection with permanent colostomy was performed mainly for low rectal cancers located <5 cm from the anal verge, and for other rectal cancers mainly intersphincteric resection with coloanal anastomosis, according to surgeons' judgment. When residual tumor cells were found in the surgical resection margin, postoperative adjuvant 5-fluorouracil–based chemotherapy was performed.

Positron Emission Tomography, Standardized Uptake Values

All patients received two series of FDG-PET: one before preoperative RT, and the other two to three weeks after the treatment (days after RT ranged from 11–50; mean days after RT, 17±7.6).[33] 18-fluorodeoxyglucose (18F) was synthesized using the Cypris Model 370 Cyclotron® (Sumitomo Heavy Industries, Shinagawa-ku, Tokyo, Japan), and FDG with an automated FDG synthesizer based on the method reported by Harms and Starling[11] radiochemical purity was >95 percent. The physical characteristics of this machine have been described in detail in a previous study.[31] Patients fasted for at least 4–1/2 hours before PET scanning so that serum glucose levels were between 80 and 110 mg/ml. All studies were performed using a Headtome IV dedicated PET scanner® (Shimadzu Corporation, Kyoto-city, Kyoto, Japan) with seven imaging planes at 13-mm intervals, each 10-mm thick. The inplane resolution was 4.5-mm full width at half maximum (FWHM). The axial resolution was 9.5-mm FWHM and the sensitivities were 14 and 24 kcps/(micro Ci/ml), respectively, for direct and cross planes. Each transmission scan was performed for eight minutes. For injections, 333 to 444 MBq of FDG were introduced via the cubital vein. A series of static acquisitions for 6 minutes each were initiated 60 minutes after the injection, and the mean time for the main tumor lesion was fixed at a constant setting of 63 minutes.

PET Data Analysis

Cross-sectional sinogram data were corrected for dead time, decay, random coincidences, and attenuation. Image reconstruction was performed by using a filtered back-projection algorithm with a Hanning filter using a cutoff frequency of 0.3 and a 128×128 matrix. Several regions of interest (ROIs) were drawn manually on the hot spots of tumors. To minimize the partial volume effect associated with decreasing tumor sizes resulting from radiotherapy, the ROIs were set to have a number of pixels between 40 and 99. FDG accumulation was measured by using standardized uptake values (SUV) obtained by the following equation:

$$\text{SUV} = (\text{decay corrected PET value})/[(\text{injected dose})/(\text{body weight})].$$ [33,34]

We defined SUVs in FDG-PET before preoperative RT as SUV_1 and two to three weeks after the treatment as SUV_2.

Pathologic Analysis

Analysis of the surgical specimen included a determination of the following parameters: 1) histologic type of the tumor; 2) degree of extension of the tumor through the rectal wall; 3) nodal involvement; and 4) status of proximal and distal margins. Pathologic response criteria were

Table 1. Univariate analysis

Factor	N	Relative risk	95% confidence interval	P value
Residual tumor				
+	8	1		
−	51	0.147	0.056–0.384	<0.0001
Differentiation				
Well	41	1		0.0011
Moderate	11	3.923	1.229–12.518	0.0210
Mucinous	4	6.14	1.57–24.012	0.0091
Poorly	2	23.093	4.09–130.371	0.0004
Unknown	1			
Recurrence				
+	31	1		
−	28	0.113	0.026–0.494	0.0038
Post-SUV	59	1.306	1.073–1.591	0.0079
SUV ratio				
>100%	4	1		
<100%	55	0.239	0.067–0.854	0.0276
LN				
+	30	1		
−	29	0.341	0.121–0.958	0.0411
Astler-Coller				
B1	10	0.21	0.027–1.63	0.1354
B2	18	0.315	0.088–1.132	0.0767
C1	4	1.123	0.247–5.097	0.8808
C2	26	1		0.1643
SUV ratio	59	1.014	0.994–1.033	0.1648
Pre-SUV	59	1.088	0.962–1.232	0.1788
Pathologic effect				
Grade 0	2	0.235	0.014–4.059	0.3193
Grade 1	44	0.102	0.012–0.868	0.0366
Grade 2	12	0.121	0.012–1.182	0.0693
Grade 3	1	1		0.1877
Sex				
Male	37	1		
Female	22	0.603	0.215–1.692	0.3363
Age (yr)	59	0.986	0.941–1.032	0.5392

SUV=standardized uptake values, LN=lymph node metastases.

defined as proposed by the Japanese Society for Esophageal Disease: Grade 0, no treatment effect; Grade 1, more than one-third viable tumor cells; Grade 2, less than one-third viable tumor cells; and Grade 3, no viable tumor cells.[35]

Statistical Analysis

Statistical analyses were performed by using StatView Dataset File version 5.0 J for Windows computers. Survival periods were calculated from the start of irradiation. The survival functions were estimated with the Kaplan-Meier method estimator, and log-rank tests were used to compare the survival distributions. Both univariate and multivariate analyses for survival were performed.

RESULTS

Pathologic effect and SUV ratio (SUV_2/SUV_1) were related statistically ($P=0.047$). Pathologic effect, however, showed no significant correlation with recurrence and survival. Histologic tumor type and SUV ratio were correlated and the ratio was >100 percent when the tumor type was poorly differentiated adenocarcinoma. Although recurrence rate tended to be higher with an elevated value of SUV_2, there was no significant association between them.

SUV ratio showed a tendency to be related with recurrence, and recurrence rate was of marginally higher significance when SUV ratio was >100 percent. Survival period was significantly short when SUV ratio was >100 percent ($P=0.0121$) and/or when SUV_2 was >5 ($P=0.0378$).

In univariate analysis, residual tumor, pathologic differentiation, recurrence, SUV_2 value, and lymph node metastasis were significant prognostic factors (Table 1). In multivariate analysis, no residual tumor and SUV_2 were significant prognostic factors for survival (Table 2). The survival curves comparing patients with *vs.* without residual tumor are shown in Fig. 1. Notably, when SUV_2 value was >5, overall survival was significantly poorer (Fig. 2). The median survival time and five-year overall survival rate comparing <5 *vs.* >5 SUV_2 value was 95.4 *vs.* 41.9 months and 70.4 *vs.* 43.6 percent, respectively ($P=0.042$).

DISCUSSION

SUV before RT and Prognosis

In this study, recurrence or poor prognosis was not related to high SUV before RT, which is in agreement with previously published reports. For head and neck cancers, Greven *et al.*[36] claimed that SUV before RT did not have any correlation with local control when examined for the entire group, primary site, or T stage (n=45). Others, however, have reported studies that differed from our results. Both Allal *et al.*[37] and Rege *et al.*[38] concluded that FDG uptake followed by RT, as measured by the SUV, had potential value in predicting local control and survival in head and neck carcinomas (n=63 and n=12, respectively).

SUV after RT and Prognosis

Recurrence or poor prognosis was related to high SUV after RT in our study. This result also concurs with earlier

Table 2. Multivariate analysis

Factor	Relative risk	95% confidence interval	P value
Residual tumor	0.302	0.094–0.973	0.0449
Differentiation			
Well			0.1552
Moderate	2.774	0.734–10.482	0.1326
Mucinous	2.875	0.574–14.406	0.1990
Poorly	10.486	0.988–111.283	0.0511
Recurrence	0.155	0.019–1.297	0.0854
Post-SUV	1.502	1.128–2	0.0054
SUV ratio <100%	0.675	0.107–4.268	0.6759
LN	0.362	0.080–1.637	0.1867

SUV=standardized uptake values; LN=lymph node metastases.

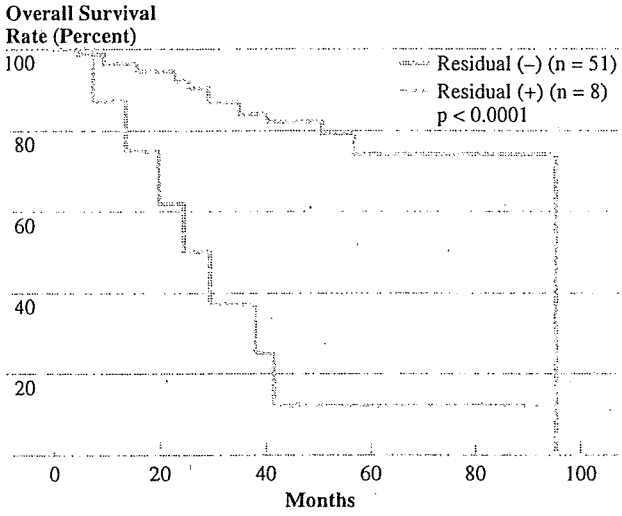


FIGURE 1. Overall survival curves comparing patients with *vs.* without residual tumor.

reports.[39,40] Higher SUV after preoperative RT predicts poor prognosis. Kunkel *et al.*[39] concluded that postirradiation FDG-uptake significantly predicted survival ($P=0.046$) and local tumor control ($P=0.0017$) in advanced oral squamous-cell carcinoma (n=35). Brun *et al.*[40] concluded that when a high initial tumor SUV was found, the reduction of SUV in the second PET examination might predict local tumor response in head and neck cancer (n=17). Swisher *et al.*[41] concluded that FDG-PET was predictive of survival in patients with esophageal carcinoma who had received preoperative chemoradiation ($P=0.01$; n=83). In our previous report,[32] only SUV_2 correlated with recurrence, although no significant correlation was observed in this study. It might be explained by the increased number of the patients involved to the study.

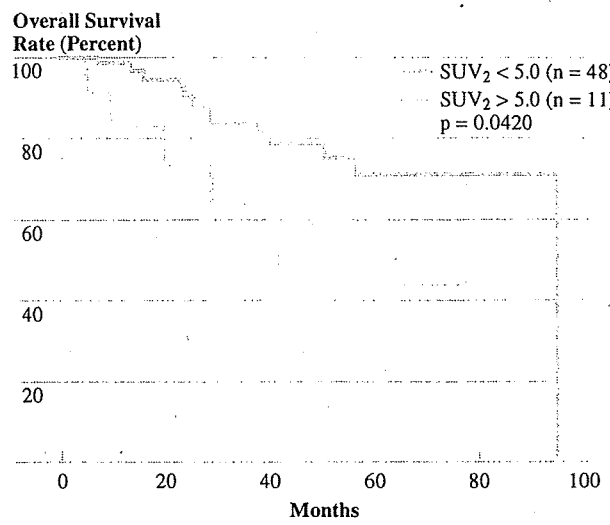
SUV before or after RT and Histologic Effects

SUV before or after RT was marginally correlated with histological effects. This finding is in agreement with previous reports. Kunkel *et al.*[42] reported a significant correlation ($P=0.045$) between post-RT FDG-uptake and histologic tumor regression was observed for mouth carcinoma (n=30). In their report, SUV>2.75 as a practical clinical threshold value for the identification of residual tumor resulted in a specificity of 88 percent, sensitivity of 68 percent, a positive predictive value of 94 percent, and a negative predictive value of 50 percent (in their report]).[41,42] In our actual follow-up data, a significant correlation could not be confirmed between post-RT SUV and patients' survivals. Brücher *et al.*[43] claimed an association for histology and survival in esophageal squamous-cell carcinoma (n=24). In responders, FDG uptake decreased by 72±11 percent; in nonresponders, it decreased by only 42±22 percent. Nonresponders to PET scanning (n=11) had a significantly poorer survival after resection than responders. Flamen *et al.*[44] also reported a correlation with histology and survival in locally advanced esophageal cancer (n=36). Response to chemoradiation as assessed by serial FDG-PET was strongly correlated with pathologic response ($P=0.002$) and survival ($P=0.087$).[44] In our study, SUV value after preoperative RT (SUV2) was significant in overall survival. In addition, the SUV ratio (SUV2/SUV1) showed an association with histopathologic effects and recurrence. These values are only available after the completion of preoperative radiation. In this respect, they may influence the surgical approach and postoperative adjuvant therapy. For example, if SUV1 was a prognostic marker, decisions could be made regarding preoperative treatment. SUV1 can control the entire treatment strategy, whereas SUV2 defines the surgical procedure and postoperative adjuvant therapy.

FDG-PET for Prediction of Survival in Rectal Cancer

The important implication of this study is that FDG-PET may be useful in assessing cytotoxic or ablative therapy. de Geus-Oei *et al.*[45] reported that a significant benefit ($P=0.017$) was observed in patients with low FDG uptake (SUV<4.26) with metastases of rectal cancer (of 152 patients, 67 were treated with resection of metastases and 85 with chemotherapy). A recent study from the Memorial Sloan-Kettering Cancer Center reported on monitoring the response to therapy with FDG-PET and the biologic basis of the change in FDG uptake of tumors in patients treated with neoadjuvant chemotherapy for hepatic colorectal metastases (13/42 evaluated patients underwent preoperative chemotherapy).[46] Fernandez *et al.*[47] concluded that post-resection screening by FDG-PET was associated with excellent five-year overall survival for patients undergoing resection of hepatic metastases from colorectal cancer (19 studies; 6,070 patients). Guillem *et al.*[48] from Memorial

FIGURE 2. Overall survival according to standardized uptake values-2 (SUV_2).



Sloan-Kettering Cancer Center suggested that FDG-PET might be useful in assessing the response of primary rectal cancer to chemoradiotherapy (n=15).

Denecke *et al.*[49] compared CT, MRI, and FDG-PET in the prediction of outcome of neoadjuvant radiochemotherapy in 23 patients with locally advanced primary T3/4 rectal cancer. The mean SUV reduction in responders (60±14 percent) was significantly higher than in nonresponders (37±31 percent; $P=0.03$). The sensitivity and specificity of FDG-PET in identifying response was 100 percent (CT 54 percent, MRI 71 percent) and 60 percent (CT 80 percent, MRT 67 percent). Positive and negative predictive values were 77 percent (CT 78 percent, MRI 83 percent) and 100 percent (CT 57 percent, MRI 50 percent) (PET $P=0.002$, CT $P=0.197$, MRI $P=0.5$). Additionally, Kalff *et al.*[50] evaluated the prognostic information obtained from the degree of change in tumor FDG-PET uptake induced by chemoradiation before radical curative surgery in 34 patients with T3/T4 rectal cancer. PET response was highly significantly associated with overall survival duration ($P<0.0001$) and time to progression ($P<0.0001$). Complete pathologic response was the only other statistically significant prognostic factor ($P<0.03$). The percentage of maximum SUV change after chemoradiation was not predictive of survival in partial metabolic response patients. Guillem *et al.*[31] tried to determine the prognostic significance of FDG-PET assessment of rectal cancer response to preoperative chemoradiation. The mean percentage decrease in SUV_{max} (ΔSUV_{max}) was 69 percent for patients free from recurrence and 37 percent for patients with recurrence ($P=0.004$). $\Delta SUV_{max} \geq 62.5$ was the best predictors of no-evidence-of-disease status and freedom from recurrence. Patients with $\Delta SUV_{max} \geq 62.5$ had significantly improved disease-specific and recurrence-free survival ($P=0.08$ and $P=0.03$, respectively).

The continued accumulation of clinical data on SUV for preoperative RT will contribute to establishing its usefulness. Studies in other malignancies, such as maxillary sinus carcinoma, are under consideration, for which preoperative RT is frequently performed.

CONCLUSION

A significant survival benefit was observed in patients with low FDG uptake (SUV<5) after preoperative radiotherapy in primary tumors of rectal cancer.

REFERENCES

1. Gerard A, Buyse M, Nordlinger B, *et al.* Preoperative radiotherapy as adjuvant treatment in rectal cancer: final results of randomized study (EORTC). Ann Surg 1988;208:606–14.
2. Anonymous. Preoperative short-term radiotherapy in operable rectal carcinoma: a prospective randomized trial. Stockholm Rectal Cancer Study Group. Cancer 1990;66:49–55.
3. Anonymous. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med 1997;336:980–7.
4. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. Lancet 2001;358:1291–304.
5. Mendenhall WM, Millon RR, Bland KI, Pfaff WW, Copeland EM. Preoperative radiotherapy for clinically resectable adenocarcinoma of the rectum. Ann Surg 1985; 202:215–22.
6. Mohiuddin M, Marks G. Patterns of recurrence following high-dose preoperative radiation and sphincter-preserving surgery for cancer of the rectum. Dis Colon Rectum 1993; 36:117–26.
7. Mohiuddin M, Marks G. High dose preoperative irradiation for cancer of the rectum, 1976–1988. Int J Radiat Oncol Biol Phys 1991;20:37–43.
8. Ng AK, Recht A, Busse PM. Sphincter preservation therapy for distal rectal carcinoma: a review. Cancer 1997;79:671–83.
9. Mohiuddin M, Marks G, Bannon J. High-dose preoperative radiation and full thickness local excision: a new option for selected T3 distal rectal cancers. Int J Radiat Oncol Biol Phys 1994;30:845–9.
10. Willett CG. Organ preservation in anal and rectal cancers. Curr Opin Oncol 1996;8:329–33.
11. Harms BA, Starling JR. Current status of sphincter preservation in rectal cancer. Oncology (Williston Park) 1990;4:53–60.
12. Martling A, Holm T, Johansson H, Rutqvist LE, Cedermark B; Stockholm Colorectal Cancer Study Group. The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. Cancer 2001;92:896–902.
13. Herrera L, Brown MT. Prognostic profile in rectal cancer. Dis Colon Rectum 1994;37:S1–5.
14. Tang R, Wang JY, Chen JS, *et al.* Survival impact of lymph node metastasis in TNM stage III carcinoma of the colon and rectum. J Am Coll Surg 1995;180:705–12.
15. Hojo K, Koyama Y, Moriya Y. Lymphatic spread and its prognostic value in patients with rectal cancer. Am J Surg 1982;144:350–4.
16. McLeod HL, Murray GI. Tumour markers of prognosis in colorectal cancer. Br J Cancer 1999;79:191–203.
17. Dershaw DD, Enker WE, Cohen AM, Sigurdson ER. Transrectal ultrasonography of rectal carcinoma. Cancer 1990;66:2336–40.
18. Wang WS, Lin JK, Chiou TJ, *et al.* Preoperative carcinoembryonic antigen level as an independent prognostic factor in colorectal cancer: Taiwan experience. Jpn J Clin Oncol 2000;30:12–6.
19. Jen J, Kim H, Piantadosi S, *et al.* Allelic loss of chromosome 18q and prognosis in colorectal cancer. N Engl J Med 1994;331:213–21.
20. Lanza G, Matteuzzi M, Gafa R, *et al.* Chromosome 18q allelic loss and prognosis in stage II and III colon cancer. Int J Cancer 1998;79:390–5.
21. Rinkus KM, Russell GB, Levine EA. Prognostic significance of nodal disease following preoperative radiation for rectal adenocarcinoma. Ann Surg 2002;68:482–7.

22. Myerson RJ, Michalski JM, King ML, *et al.* Adjuvant radiation therapy for rectal carcinoma: predictors of outcome. Int J Radiat Oncol Biol Phys 1995;32:547–8.
23. Onaitis MW, Noone RB, Hartwig M, *et al.* Neoadjuvant chemoradiation for rectal cancer: analysis of clinical outcomes from a 13-year institutional experience. Ann Surg 2001;233:778–85.
24. Theodoropoulos G, Wise WE, Padmanabhan A, *et al.* T-level downstaging and complete pathologic response after preoperative chemoradiation for advanced rectal cancer result in decreased recurrence and improved disease-free survival. Dis Colon Rectum 2002;45:895–903.
25. Mohiuddin M, Hayne M, Regine WF, *et al.* Prognostic significance of postchemoradiation stage following preoperative chemotherapy and radiation for advanced/recurrent rectal cancers. Int J Radiat Oncol Biol Phys 2000;48:1075–80.
26. Moriya Y, Sugihara K, Akasu T, Fujita S. Importance of extended lymphadenectomy with lateral node dissection for advanced lower rectal cancer. World J Surg 1997;21:728–32.
27. Moriya Y, Hojo K, Sawada T, Koyama Y. Significance of lateral node dissection for advanced rectal carcinoma at or below the peritoneal reflection. Dis Colon Rectum 1989;32:307–15.
28. Minsky BD. Adjuvant therapy for rectal cancer: the transatlantic view. Colorectal Dis 2003;5:416–22.
29. Rodel C, Sauer R. Perioperative radiotherapy and concurrent radiochemotherapy in rectal cancer. Semin Surg Oncol 2001;20:3–12.
30. Wils J, O'Dwyer P, Labianca R. Adjuvant treatment of colorectal cancer at the turn of the century: European and US perspectives. Ann Oncol 2001;12:13–22.
31. Guillem JG, Moore HG, Akhurst T, *et al.* Sequential preoperative fluorodeoxyglucose-positron emission tomography assessment of response to preoperative chemoradiation: a means for determining long term outcomes of rectal cancer. J Am Coll Surg 2004;199:1–7.
32. Oku S, Nakagawa K, Momose T, *et al.* FDG-PET after radiotherapy is a good prognosis indicator of rectal cancer. Ann Nucl Med 2002;16:409–16.
33. Kanno I, Iida H, Miura S, *et al.* Design concepts and preliminary performances of stationary-sampling whole-body high-resolution positron emission tomography: HEADTOME IV [in Japanese]. Kaku Igaku 1989;26:477–85.
34. Zasadny KR, Wahl RL. Standardized uptake values of normal tissues at PET with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose: variations with body weight and a method for correction. Radiology 1993;189:847–50.
35. The Japanese Society for Esophageal Disease. Histopathologic criteria for the effects of radiation or anticancer chemotherapy. In: Isono K, ed. Guidelines for clinical and pathologic studies on carcinoma of the esophagus. 9th ed. Tokyo: Kanehara Shuppan, 1999:55.
36. Greven KM, Williams DW III, McGuirt WF Sr, *et al.* Serial positron emission tomography scans following radiation therapy of patients with head and neck cancer. Head Neck 2001;23:942–6.
37. Allal AS, Dulguerov P, Allaoua M, *et al.* Standardized uptake value of 2-[(18)F] fluoro-2-deoxy-D-glucose in predicting outcome in head and neck carcinomas treated by radiotherapy with or without chemotherapy. J Clin Oncol 2002;20:1398–404.
38. Rege S, Safa AA, Chaiken L, Hoh C, Juillard G, Withers HR. Positron emission tomography: an independent indicator of radiocurability in head and neck carcinomas. Am J Clin Oncol 2000;23:164–9.
39. Kunkel M, Forster GJ, Reichert TE, *et al.* Radiation response non-invasively imaged by [18F]FDG-PET predicts local tumor control and survival in advanced oral squamous cell carcinoma. Oral Oncol 2003;39:170–7.
40. Brun E, Ohlsson T, Erlandsson K, *et al.* Early prediction of treatment outcome in head and neck cancer with 2–18FDG PET. Acta Oncol 1997;36:741–7.
41. Swisher SG, Erasmus J, Maish M, *et al.* 2-Fluoro-2-deoxy-D-glucose positron emission tomography imaging is predictive of pathologic response and survival after preoperative chemoradiation in patients with esophageal carcinoma. Cancer 2004;101:1776–85.
42. Kunkel M, Grotz KA, Forster GJ, *et al.* Therapy monitoring with 2-(18F)-FDG positron emission tomography after neoadjuvant radiation treatment of mouth carcinoma [in German]. Srahlenther Onkol 2001;177:145–52.
43. Brücher BL, Weber W, Bauer M, *et al.* Neoadjuvant therapy of esophageal squamous cell carcinoma: response evaluation by positron emission tomography. Ann Surg 2001;233:300–9.
44. Flamen P, Van Cutsem E, Lerut A, *et al.* Positron emission tomography for assessment of the response to induction radiochemotherapy in locally advanced oesophageal cancer. Ann Oncol 2002;13:361–8.
45. de Geus-Oei LF, Wiering B, Krabbe PF, Ruers TJ, Punt CJ, Oyen WJ. FDG-PET for prediction of survival of patients with metastatic colorectal carcinoma. Ann Oncol 2006;17:1650–5.
46. Akhurst T, Kates TJ, Mazumdar M, *et al.* Recent chemotherapy reduces the sensitivity of [18F]fluorodeoxyglucose positron emission tomography in the detection of colorectal metastases. J Clin Oncol 2005;23:8713–6.
47. Fernandez FG, Drebin JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg M. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). Ann Surg 2004;240:438–5.
48. Guillem JG, Puig-La Calle J Jr, Akhurst T, *et al.* Prospective assessment of primary rectal cancer response to preoperative radiation and chemotherapy using 18-fluorodeoxyglucose positron emission tomography. Dis Colon Rectum 2000;43:18–24.
49. Denecke T, Rau B, Hoffmann KT, *et al.* Comparison of CT, MRI and FDG-PET in response prediction of patients with locally advanced rectal cancer after multimodal preoperative therapy: is there a benefit in using functional imaging? Eur Radiol 2005;15:1658–66.
50. Kalff V, Duong C, Drummond EG, Matthews JP, Hicks RJ. Findings on 18F-FDG PET scans after neoadjuvant chemoradiation provides prognostic stratification in patients with locally advanced rectal carcinoma subsequently treated by radical surgery. J Nucl Med 2006;47:14–22.

特集にあたって

死生学とがん医療の接点を求めて

東京大学医学部附属病院緩和ケア診療部　中川　恵一

自然との触れ合いや宗教心がなくなり，急速に寿命が延びた結果，今の日本人の生活や意識のなかから死が忘れ去れているかのようである。すべての人間に唯一平等に訪れる死も，その95％を病院のなかに隔離してしまい，皮膚感覚で捉えることができなくなってしまった。そして，戦争も兵役もないわが国で，現在，死に直結するイメージをもつのは，がんである。まさに，がんこそが，現代の「メメント・モリ」なのである。

がんは，簡単にいえば，細胞の老化といえるため，世界一の長寿国であるわが国は，世界一のがん大国である。実際，日本人の２人に１人が，生涯にがんに罹患し，３人に１人が，がんで死亡する。しかし，死をみつめることを避けようとすれば，唯一死を想起させるがんという病気は，他人事にしか思えない。その結果，日本人のがんに対する知識や態度，医療体制は，先進国のなかでは，とりわけ後進的である。このことは，がんの治療とケアのアンバランスに，特に観察される。死を敗北，悪として忌避するムードを，医療者と患者が共有する結果，医療現場では，「治療＞＞ケア」の図式が成立してきた。しかし，治癒とは，「治し，癒す」ことを意味する。実際，すべての医療機関に医師とナースが勤務することは，「治」と「癒」の両立の必要性を示すものであろう。

治療とケアのアンバランスは，がん医療のみならず，日本の臨床医療全体にわたる最大の問題点であり，日本の緩和ケアの遅れの原因である。筆者も関わった毎日新聞社による世論調査でも，「緩和ケア」を知っているのは，わずか28％と，衝撃的な結果が出ている。

がんによる痛みを和らげることは，緩和ケアの最も重要な役割だが，モルヒネに代表される医療用麻薬（オピオイド）の使用が中心となる。しかし，このモルヒネの使用量が，日本はカナダ，オーストラリアの約７分の１，アメリカ，フランスの約４分の１程度と先進国のなかで最低レベルであり，さらに，オピオイド全体についていえば，日本は米国のなんと20分の１程度で，世界平均以下の使用量である。いい方を変えれば，わが国のがん患者は，それだけ激しい痛みを耐えているのであ

Introdution
Kenichi Nakagawa（部長，准教授）

る。しかし，現実には，モルヒネなどを適切に使って痛みのない患者のほうが長生きする傾向があるのだ。食事もとれ，睡眠も確保できるので，当然なのだが，「麻薬」の死のイメージを見いだす傾向はなかなか払拭できない。これも，やはり「死の忌避」が根底にあるからだろう。死を避け，生きている間を少しでも長くしようと思って，苦しい時間を増やしているどころか，命の時間そのものも短くなってしまっているのだ。日本人の死生観のあり方が，がんの医療においては，具体的な患者の損失として顕在化するのである。世界一のがん大国，日本の医療の盲点といえる部分である。

しかし，昨年に施行されたがん対策基本法は，この流れを大きく変える可能性がある。全体目標は「がんによる死亡者の減少」の他，「すべてのがん患者及びその家族の苦痛の軽減並びに療養生活の質の維持向上」であり，重点的に取り組むべき課題として，放射線療法，化学療法，がん登録の推進とともに，「治療の初期段階からの緩和ケアの実施」が定められた。本特集でも，厚生労働省健康局総務課がん対策推進室の加藤室長補佐が解説されている。

今回の特集では，緩和ケアと死生の問題との関連に最大の力点を置いている。臨床医学系の雑誌の体裁としては異例ともいえるが，実際，執筆を頂いたタイトルのなかにある，「死」の文字の数は５つに上る。また，東京大学大学院人文社会学系研究科を中心としたグローバルCOE(GCOE)研究「死生学の展開と組織化」の研究組織から，島薗進教授，清水哲郎特任教授に参加をいただいている点も特徴的である。

この死生学GCOEは，島薗教授が拠点リーダーとなり，筆者も事業推進担当者の１人として参加している。ここで，そのホームページから，島薗先生の研究への取り組みを要約する。多くの医療者にも，死生学研究に関心をもってもらいたいからである。

「死生学は新しい学問である。それはまず医療と人文・社会系の接点で求められている。現代の病院は死に往く人々のケアに多くの力をさかねばならないが，自然科学的アプローチによる近代医学の枠内ではその方法がわからない。1960年代から欧米ではホスピス運動が急速に広がり，死に直面した患者や家族のニーズに応えるための死生学の教育・研究が進められるようになった。生命倫理に関わる多くの問題が噴出してきたのも同時期である。臓器移植や体外受精や遺伝子診断が可能になり，これまではとても克服できなかった困難を超えて，人々の欲求を充たすことができる可能性が大幅に増大しつつある。だが，医療がその力を強めていく一方で，どこで医療の介入に限界線を引くのかという難しい問題に直面するようになってきた。このため医療臨床と医学研究の現場では日常的に死生観に基づく倫理的判断が問われるようになっている。」

筆者が，東京大学医学部附属病院で緩和ケアに取り組み始めたときに立てた目標の１つが，「東大全学での死の研究」であった。GCOE研究では，人文科学の現代的実践現場への関与にも重点を置いており，夢が叶ったことになる。人文科学と医学が相互に刺激しあうダイナミックな展開を期待したい。そして，本特集が，その足がかりの１つになれば幸いである。

Workflow Analysis of Medical staff in Surgical Wards Based on Time-Motion Study Data

Hodaka Numasaki

Hodaka NUMASAKI[1], Yuko OHNO[2], Atsue ISHII[2], Satoko KASAHARA[2], Harumi FUJIMOTO[3], Hajime HARAUCHI[4], Kiyonari INAMURA[5], Morito MONDEN[6], Masato SAKON[7]

1 Department of Medical Physics and Engineering, Osaka University Graduate School of Medicine
1-7, Yamadaoka, Suita, Osaka, 565-0871, JAPAN
2 Department of Health Promotion Science, Osaka University Graduate School of Medicine
3 Department of Nursing, Saiseikai Hyogo Hospital
4 Department of Radiological Technology, Kawasaki College of Allied Health Professions
5 Department of Business Management, Kansai University of International Studies
6 Department of Surgery and Clinical Oncology, Osaka University Graduate School of Medicine
7 Nishinomiya Municipal Center Hospital, Japan

Abstract

The aim of this study is to clarify the change over time in the elements of work (job elements) and their features, as well as the relationship between job elements and the type of job, job class, and the role of the hospital they are performed in. A time-motion study was conducted on the medical staff in the surgical wards of two hospitals. An analysis of roles bys by (a) type or class of job type, and (b) hospital function was conducted. The number of working hours was analyzed, as well as the ratio of working hours with respect to direct and indirect job elements. The job elements required for each medical staff member were proven to differ by type of job (doctors and nurses) and also by job class (nurse leaders and staff). When comparing between hospital the differences in job elements were proven not to be a result of differences in hospital function, but to result from the ward system (ward design and nursing system).

1. Introduction

It is well known that doctors and nurses are hard-working professionals. It is recognized worldwide that planning an efficient, effective, and safe job workflow is one of the most important problems in hospital administration [1], [2].

The number of medical staff, their abilities, and the function of the ward (hospital) must be accurately assessed, and the interrelation of these parameters should be clarified.

In this study, we surveyed the numbers of doctors and nurses working in hospitals with different roles. We aimed to clarify the change over time in job elements and their features, as well as the relationship between job elements and the type of job, job class, and the function of the hospital they are performed in.

2. Methods

2.1. Time-motion study

A time-motion study of the job workflow of medical staff (doctors and nurses) was conducted in a surgical ward at an advanced treatment hospital in Osaka, and at a regional general hospital in Hyogo. Both hospitals are in Japan. The study was conducted for 24 consecutive work hours in the advanced treatment hospital, and throughout a working day shift in the regional general hospital [3]-[6]. To maintain accuracy in job records, graduate certified nurses, radiological technologists, and clinical laboratory technicians were asked to record job elements and their durations in units per second. Each observer recorded job elements performed by the nurse or doctor involved in a free format, using the terms "where," "since when," "until when," "by whom," "for whom," and "which job

element". Classified codes or templates were not prepared beforehand to avoid observer bias.

The recorded job workflow was checked in parallel to maintain accuracy and oversight of the documentation.

2.2. Classification of job elements by coding

The coding format for the observed data was defined by the Osaka Time-Motion Study Group, consisting of academic researchers and experienced clinical staff. The format consisted of up to 91 items for nurses and 105 items for doctors. The documented records of job elements were entered into a time-Motion database using a specific format devised by trained coding specialists.

The classification had a three-level hierarchy for doctors and nurses. The top level hierarchy was "main category," followed by "sub category" and "specified category."

2.3. Data analysis

Firstly, jobs were analyzed by job type or job class. The number of working hours was analyzed, as well as the ratio of working hours spent on direct and indirect job elements. Secondly, jobs were analyzed by hospital function. The number of working hours was analyzed, as well as the ratio of working hours spent on direct and indirect job elements. The results of this analysis were used as data in 2000 and 2004. The respondent doctors were residents in the advanced treatment hospital, and full-time doctors in the regional general hospital. Job analysis by hospital function was not conducted for doctors.

For nurses, the advanced treatment hospital used a primary nursing care system and the regional general hospital used a team nursing care system. Both hospitals had three working shifts per day (eight working hours per shift). Job analysis by hospital function was conducted for nursing staff in the regional general hospital and all nurses in the advanced treatment hospital.

Two "flags" were prepared to distinguish between simultaneously or ambiguously recorded jobs. The "Serial job elements" flag was used if an observer could not record the end of a job element because the medical staff member performed many job elements quickly one by one in a short period of time. The "Parallel job elements" flag was used if a staff member performed two or more job elements in the same unit of time. For example, carrying out vital sign measurements (e.g., recording body temperature) while observing patient status and explaining the status to the patient.

Two more flags were classified: The "Direct job elements" flag was used if doctors or nurses contacted patients directly and the "Indirect job elements" flag was used for job elements other than direct job elements.

3. Results

3.1. Analysis of jobs by job type or job class (advanced treatment hospital)

3.1.1. Working hours

Table 1 shows the working hours of doctors and nurses. When the working hours were calculated for serial job elements, those of doctors were about 45 minutes longer than those of nurses. For parallel job elements, the working hours of doctors were about 30 minutes longer

■ Table 1: Working hours of doctors and nurses (advanced treatment hospital)

Job type	Job class	Working hours (Serial)	Working hours (Parallel)	Serial / Parallel
Doctor	Resident	10:15:25	11:01:24	1.07
Nurse	Staff	9:31:17	10:31:44	1.11

■ Table 2: Percentages of working hours spent on direct and indirect jobs by doctors and nurses (advanced treatment hospital)

	Doctors		Nurses	
	Working hours	Ratio (%)	Working hours	Ratio (%)
Direct job elements	5:01:46	58.1	2:20:56	27.3
Direct job elements (preparation or cleaning up)	0:34:42	6.7	1:07:56	13.1
Indirect job elements	2:54:45	33.7	4:56:38	57.4
Indirect job elements (preparation or cleaning up)	0:08:04	1.6	0:11:12	2.2
Total	8:39:16	100.0	8:36:42	100.0

than those of nurses. Nurses had a higher ratio of parallel time to serial time than doctors.

3.1.2. Working hours spent on direct and indirect jobs

Table 2 shows the working hours spent on direct and indirect jobs for doctors and nurses. The percentage of working hours spent on direct jobs by doctors was higher than that of nurses, which was the opposite case to the percentage of working hours spent on indirect jobs. The percentage of working hours spent by doctors on "preparation or cleaning up", for direct and indirect jobs, was lower than that of nurses.

3.2. Analysis of jobs by job type or job class (regional general hospital)

3.2.1. Working hours

Table 3 shows the working hours of doctors and nurses. When the working hours were calculated for serial job elements, those of doctors and nurses were almost identical. For parallel job elements, the working hours of nurses were about one hour longer than those of doctors. Nurses had a higher ratio of time spent on parallel tasks compared to time spent on serial tasks than doctors.

For nurses, the working hours of leaders and staff were almost identical when they were calculated for parallel job elements. For serial job elements, the working hours of nurse leaders were about 40 minutes longer than those of nursing staff. Nursing staff had a higher ratio of time spent on parallel tasks compared to time spent on serial tasks than nurse leaders.

3.2.2. Working hours of direct and indirect jobs

Table 4 shows the working hours spent on direct and indirect jobs for doctors and nurses. The percentage of working hours spent by doctors on direct jobs was higher than that of nurses, which was the opposite case to the percentage of working hours spent on indirect jobs. The percentage of working hours spent by doctors on "preparation or cleaning up" for direct and indirect jobs was much lower than that of nurses.

For nurses, the percentage of working hours spent on direct jobs by nurse leaders was lower than that of nursing staff, which was the opposite case to the percentage of working hours spent on indirect jobs. The percentage of working hours spent on direct jobs (preparation or cleaning up) was almost identical for nurse leaders and staff. The percentage of working hours spent on indirect

■ Table 3: Working hours of doctors and nurses (regional general hospital)

Job type	Job class	Working hours (Serial)	Working hours (Parallel)	Serial / Parallel
Doctor	-	9:18:32	9:39:31	1.04
Nurse	All	9:14:19	10:24:22	1.13
	Leader	9:40:41	10:27:49	1.08
	Staff	9:03:47	10:22:59	1.15

■ Table 4. Percentages of working hours spent on direct and indirect jobs by doctors and nurses (regional general hospital)

	Doctors		Nurses					
			All		Leaders		Staffs	
	Working hours	Ratio (%)	Working hours	Ratio (%)	Working hours	Ratio (%)	Working hours	Ratio (%)
Direct job elements	4:53:49	66.9	2:34:27	30.4	1:39:36	18.6	2:56:24	35.5
Direct job elements (preparation or cleaning up)	0:02:55	0.7	0:42:26	8.4	0:45:45	8.6	0:41:06	8.3
Indirect job elements	2:17:03	31.2	4:51:04	57.4	5:47:50	65.1	4:28:22	54.0
Indirect job elements (preparation or cleaning up)	0:05:34	1.3	0:19:24	3.8	0:40:55	7.7	0:10:47	2.2
Total	7:19:21	100.0	8:27:21	100.0	8:54:06	100.0	8:16:39	100.0

jobs (preparation or cleaning up) was higher for nurse leaders than nursing staff.

3.3. Analysis of Jobs by hospital function

3.3.1. Working hours

Table 1 and table 3 show the working hours of nurses in both hospitals. The working hours of nurses in the advanced treatment hospital were longer than those of nurses in the regional general hospital, for time spent on serial tasks as well as on parallel tasks. Nurses in the regional general hospital had a higher ratio of time spent on parallel tasks compared to time spent on serial tasks than those in the advanced treatment hospital.

Table 5 shows the detailed working hours of nurses in both hospitals. The percentage of working hours spent by nurses in the regional general hospital on jobs related to "patient assistance with activities of daily living" was higher than that for nurses in the advanced treatment hospital. This was the opposite case for the percentage of working hours spent on jobs related to "assisting with procedures" and "miscellaneous activities". Jobs classified as "meals," "domestic care," "emotional care," "postmortem care," "physical examination," "medication administration," "explanation/instructing/educating," "collecting patient information," "home care service," "teaching students," "ward secretary jobs," "hospital administrative activities," and "sending messages" took a higher percentage of time for nurses in the advanced treatment hospital than for nurses in the regional general hospital, though the opposite held for the percentage of time spent on jobs classified as "hygiene assistance," "elimination management," "arranging the patient's

■ Table 5. Detailed working hours and percentages for doctors and nurses (advanced treatment hospital and regional general hospital)

	Activity duration	Ratio (%)	Activity duration	Ratio (%)			Activity duration	Ratio (%)	Activity duration	Ratio (%)
Meal	0:00:48	0.1	0:00:35	0.1		Information exchange within healthcare professionals	1:08:23	12.0	1:10:42	13.0
Hygiene assistance	0:13:17	2.3	0:15:10	2.8		Patient Calls	0:01:00	0.2	0:01:45	0.3
Elimination management	0:08:12	1.4	0:17:02	3.1		Home care service	0:00:02	0.0	0:00:00	0.0
Arranging the patient's environment	0:07:27	1.3	0:11:29	2.1		Other	0:02:57	0.5	0:00:00	0.0
Domestic care	0:00:39	0.1	0:00:22	0.1		Subtotal	4:34:56	48.1	4:11:06	46.2
Transporting patients	0:09:11	1.6	0:12:02	2.2		Chartwork	1:24:11	14.7	1:22:38	15.2
Emotional care	0:00:34	0.1	0:00:23	0.1		Teaching students	0:04:25	0.8	0:00:34	0.1
Safety	0:00:00	0.0	0:00:13	0.0		Ward secretary jobs	0:29:26	5.2	0:10:25	1.9
Physical comfort promotion	0:05:06	0.9	0:05:34	1.0		Hospital administrative activities	0:07:22	1.3	0:00:02	0.0
Call for/see off patients	0:00:00	0.0	0:00:00	0.0		Sending message	0:07:29	1.3	0:00:58	0.2
Postmortem care	0:00:05	0.0	0:00:00	0.0		Infection protection	0:05:17	0.9	0:08:40	1.6
Other	0:00:10	0.0	0:00:00	0.0		Walking/waiting	0:58:20	10.2	1:17:27	14.2
Subtotal	0:45:29	8.0	1:02:51	11.6		Other	0:00:00	0.0	0:01:58	0.4
Physical examination	0:06:18	1.1	0:04:10	0.8		Subtotal	3:16:30	34.4	3:02:43	33.6
Treatments	0:11:29	2.0	0:11:08	2.0		Research/study	0:00:39	0.1	0:00:00	0.0
Medication administration	1:10:17	12.3	0:42:32	7.8		Break	0:51:03	8.9	0:47:00	8.6
Physical assessment	0:40:30	7.1	1:10:56	13.0		Other	0:02:07	0.4	0:00:00	0.0
Explanation/instructing/educating	0:34:58	6.1	0:25:53	4.8		Subtotal	0:53:49	9.4	0:47:00	8.6
Collecting patient information	0:39:03	6.8	0:24:01	4.4	Error	Error	0:00:33	0.1	0:00:08	0.0

environment," "transporting patients," "Safety," "improving physical comfort," "treatments," "physical assessment," "exchanging information between healthcare professionals," "patient calls," "chartwork," "infection protection" and "walking/waiting".

3.3.2. Time series distribution of working hours

Figure 1 shows the time series distribution of working hours for nurses in both hospitals. The percentage of working hours spent on "patient assistance with activities of daily living" jobs decreased during the time periods immediately after work started and before the end of work in both hospitals. For both hospitals the percentage of working hours spent on jobs classed as "assisting with procedures" was higher than in the afternoon; the opposite of the percentage of working hours spent on "miscellaneous activities" jobs.

3.3.3. Working hours for direct and indirect jobs

Table 2 and table 4 shows the working hours spent on direct and indirect jobs for nurses in both hospitals. The percentage of working hours spent on direct jobs by nurses in the regional general hospital was higher than that for nurses in the advanced treatment hospital. The percentage of working hours spent on direct (preparation or cleaning up) and indirect jobs by nurses in the advanced treatment hospital was higher than that for nurses in the regional general hospital. The percentage of working hours spent on indirect jobs (preparation or cleaning up) was identical for nurses of both hospitals.

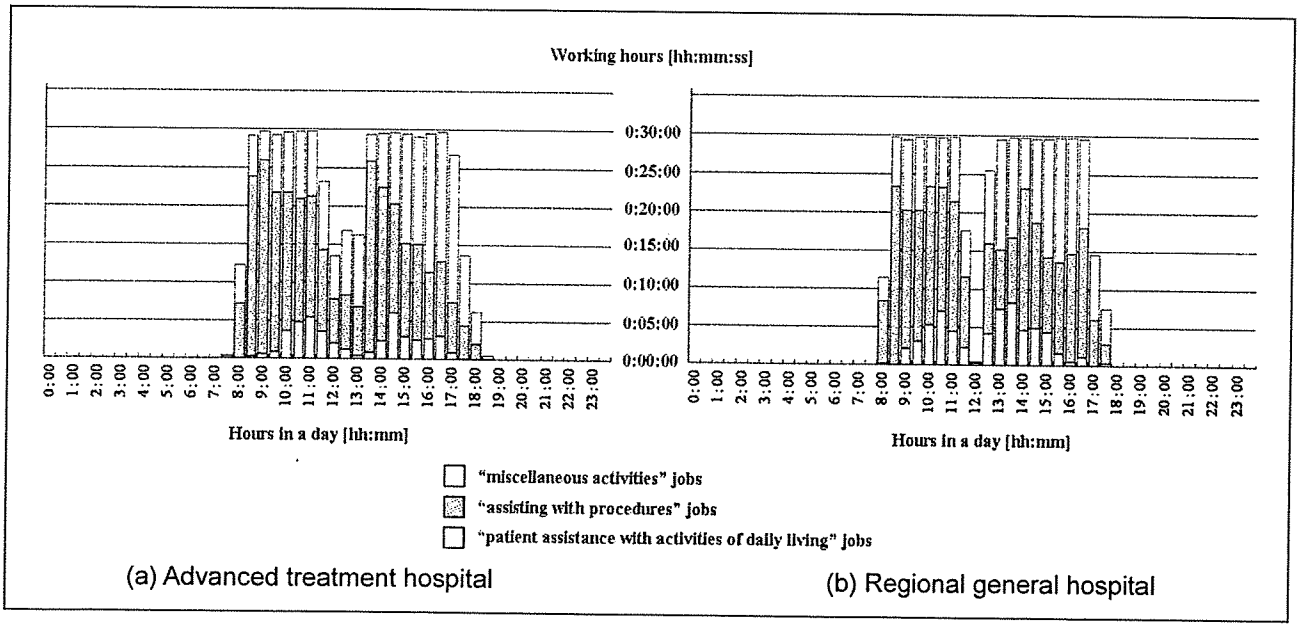
4. Discussion

It is thought that the number of operations when the nurses are not involved, and the length of these operations, contribute to the difference in the ratio of direct and indirect jobs when comparing job types (doctors and nurses). We need to survey the ward of another department and analyze their working hours by job type.

Nurse leaders did not manage patients. According to the analysis results in 3.2 they assisted the doctor's examination of the patient, aided nursing staff, or exchanged information with doctors and nursing staff. Nursing staff primarily cared for the patient.

It is thought that the differences in the nurse's job elements obtained from the analysis result 3.3 are not related to hospital function, but are related to the differences in nursing systems. The percentage of working hours spent on "ward secretary jobs," "hospital administrative activities" and "sending messages" by the nurses in the advanced treatment hospital was higher than for the regional general hospital. In the regional general hospital, with the team nursing care system in place, these three job elements are performed chiefly by the nurse leaders. The percentage of working hours spent on "patient assistance with activities of daily living" jobs by nurses in the regional general hospital was higher than

■ Figure 1. Time series distribution of working hours.
The horizontal axis indicates hours in a day, and the vertical axis indicates working hours.



that in the advanced treatment hospital, similar to that of direct job elements. This is because the so-called nurse leader's job elements are not performed by nursing staff in the regional general hospital.

In this study, a constant relationship was observed between job type/class and job elements. This result may change considerably depending on any one factor because this survey was performed in limited settings, i.e., survey schedules were short and there were few respondents.

The relationship between hospital function and job elements was not ascertained because it was not possible to separate them from the other factors. To do this we would need to survey hospitals with different functions yet having similar ward conditions.

5. Conclusion

The job elements required to be performed by each medical staff member was proven to differ according to job type (doctors and nurses) and job class (nurse leaders and staff).

In the comparison between hospitals the difference in job elements was proven to be not due to different hospital functions, but due to the ward system (ward design and nursing system).

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References

[1] Murray, L. R., 2002. Labor analytics software can help control labor costs. Healthc. Financ. Manage, 56(7) 50-54.

[2] Robert, A. B., 1998. Managed Care Made Simple (2nd ed.). Blackwell Pub, Cambridge.

[3] Finkler, A. S., Knickman, J. R., Hendrickson, G., Lipkin, M., and Thompson, W. A., 1993. A Comparison of work-sampling and time-and-motion techniques for studies in health services research. Health. Serv. Res, 28(5) 577-597.

[4] Melissa, R. C. and Betty, L. C., 1998. COMPUTER USE AND NURSING RESEARCH Computerized Data Collection: Example of a Time-Motion Study. West. J. Nurs. Res, 20(2) 251-256.

[5] Thomas, A. B., Jerry, R. M., and Helen, C. W., 2000. A Comparison of Time-and-Motion and Self-Reporting Methods of Work Measurement. J. Nurs. Adm, 30(3), 31-38.

[6] Wirth, P., Kahn, L., and Perkoff, G. T., 1977. Comparability of two methods of time and motion study used in a clinical setting: Work sampling and continuous observation. Med. Care, 15(11) 953-960.