Additional file 2: Figure S1. H4K20me3 staining in benign tumor tissue. Specimens of benign tumor tissue were stained using anti-H4K20me3 (left) and HE staining (right).

Additional file 3: Table S2. H4K20me3 staining score associates with subtype. H4K20me3 staining score was classified by the hormone receptor expression.

Additional file 4: Table S3. H4K20me3 staining and Luminal A/Luminal B distribution. H4K20me3 staining score was classified by the Luminal A and Luminal B. H4K20me3 staining score did not associate with Luminal A/Luminal B distribution.

Additional file 5: Figure S2. Kaplan-Meier analysis of estrogen receptor expression in breast cancer patients. The patient overall survival time and disease-free survival rate were compared between the estrogen receptor expression low- and high-staining groups by Kaplan-Meier analysis.

Abbreviations

BSA: bovine serum albumin; CK: cytokeratin; DCIS: ductal carcinoma *in situ*; DMEM: Dulbecco's modified Eagle's medium; EGFR: epidermal growth factor receptor; ELISA: enzyme-linked immunosorbent assay; ER: estrogen receptor; FBS: fetal bovine serum; HER2: human epidermal growth factor receptor; IDC: invasive ductal carcinoma; IgG: immunoglobulin G; mAbs: monoclonal antibodies; PgR: progesterone receptor; siRNA: small interfering RNA; SUV: suppressor of variegation EZH2 (enhancer of zeste homolog 2).

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YY, AM, YN, MHi, and NM designed the experiments. KY and MT performed immunohistochemical experiments and analysis of patient data. YY, AM, YS, EO, MHa, MHi, and HK performed immunochemical staining and all *in vitro* experiments. MH wrote the manuscript. All authors read and approved the manuscript.

Acknowledgements

We thank Kumiyo Hirai (Osaka University), Junko Imada (Osaka University), and Noriko Nagano for technical assistance. This work was supported by Leave a Nest (http://lne.st/, to YY); Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (to NM and MH); and a Grant-in-Aid for Scientific Research on Innovative Areas from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (to MH). A part of this study was performed as a joint research program with Wako Pure Chemical Industries, Ltd.

Author details

[1]Osaka University Graduate School of Medicine and Health Science, 1-7 Yamadaoka, Suita City, Osaka 565-0871, Japan. [2]Osaka University Graduate School of Frontier Science, 1-3 Yamadaoka, Suita City, Osaka 565-0871, Japan. [3]Department of Breast Surgery, Osaka Police Hospital, 10-31, Kitayamacho, Osaka City, Osaka 543-0035, Japan. [4]Department of Pathology, Osaka Police Hospital, 10-31, Kitayamacho, Osaka City, Osaka 545-0035, Japan.

Received: 24 July 2013 Accepted: 2 June 2014
Published: 22 June 2014

References

1. Campbell LL, Polya K: **Breast tumor heterogeneity, cancer stem cells or clonal evolution.** *Cell Cycle* 2007, **6**:2332–2338.
2. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, Deming SL, Geradts J, Cheang MC, Nielsen TO, Moorman PG, Earp HS, Millikan RC: **Breast cancer subtypes, and survival in the Carolina Breast Cancer Study.** *JAMA* 2006, **295**:2492–2502.
3. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey SS, Thorsen T, Quist H, Matese JC, Brown PO, Botstein D, Lønning PE, Børresen-Dale AL: **Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications.** *Proc Natl Acad Sci U S A* 2001, **98**:10869–10874.
4. Carey LA, Dees EC, Sawyer L, Gatti L, Moore DT, Collichio F, Ollila DW, Sartor CI, Graham ML, Perou CM: **The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes.** *Clin Cancer Res* 2007, **13**:2329–2334.
5. Prat A, Perou CM: **Deconstructing the molecular portraits of breast cancer.** *Mol Oncol* 2011, **5**:5–23.
6. Fullgrabe J, Kavanagh E, Joseph B: **Histone onco-modifications.** *Oncogene* 2011, **30**:3391–3403.
7. Piekarz RL, Bates SE: **Epigenetic modifiers: basic understanding and clinical development.** *Clin Cancer Res* 2009, **15**:3918–3926.
8. Rodriguez-Paredes M, Esteller M: **Cancer epigenetics reaches mainstream oncology.** *Nat Med* 2011, **17**:330–339.
9. Sharma S, Kelly TK, Jones PA: **Epigenetics in cancer.** *Carcinogenesis* 2010, **31**:27–36.
10. Fraga MF, Ballestar E, Villar-Garea A, Boix-Chornet M, Espada J, Schotta G, Bonaldi T, Haydon C, Ropero S, Petrie K, Iyer NG, Pérez-Rosado A, Calvo E, Lopez JA, Cano A, Calasanz MJ, Colomer D, Piris MA, Ahn N, Imhof A, Caldas C, Jenuwein T, Esteller M: **Loss of acetylation at Lys16 and trimethylation at Lys20 of histone H4 is a common hallmark of human cancer.** *Nat Genet* 2005, **37**:391–400.
11. Seligson DB, Horvath S, Shi T, Yu H, Tze S, Grunstein M, Kurdistani SK: **Global histone modification patterns predict risk of prostate cancer recurrence.** *Nature* 2005, **435**:1262–1266.
12. Seligson DB, Horvath S, McBrian MA, Mah V, Yu H, Tze S, Wang Q, Chia D, Goodglick L, Kurdistani SK: **Global levels of histone modifications predict prognosis in different cancers.** *Am J Pathol* 2009, **174**:1619–1628.
13. Behbahani TE, Kahl P, von der Gathen J, Heukamp LC, Baumann C, Gütgemann I, Walter B, Hofstädter F, Bastian PJ, von Ruecker A, Müller SC, Rogenhofer S, Ellinger J: **Alterations of global histone H4K20 methylation during prostate carcinogenesis.** *BMC Urol* 2012, **12**:5.
14. Balakrishnan L, Mikavetz B: **Decoding the histone H4 lysine 20 methylation mark.** *Crit Rev Biochem Mol Biol* 2010, **45**:440–452.
15. Van Den Broeck A, Brambilla E, Moro-Sibilot D, Lantuejoul S, Brambilla C, Eymin B, Khochbin S, Gazzeri S: **Loss of histone H4K20 Trimethylation occurs in preneoplasia and influences prognisis of non-small cell lung cancer.** *Clin Cancer Res* 2008, **14**:7237–7245.
16. Kovalchuk O, Tryndyak VP, Montgomery B, Boyko A, Kutanzi K, Zemp F, Warbritton AR, Latendresse JR, Kovalchuk I, Beland FA, Pogribny IP: **Estrogen-induced rat breast carcinogenesis is characterized by alterations in DNA methylation, histone modifications and aberrant microRNA expression.** *Cell Cycle* 2007, **6**:2010–2018.
17. Tryndyak VP, Kovalchuk O, Pogribny IP: **Loss of DNA methylation and histone H4 lysine 20 trimethylation in human breast cancer cells is associated with aberrant expression of DNA methyltransferase 1, Suv4-20 h2 histone methyltransferase and methyl-binding proteins.** *Cancer Biol Ther* 2006, **5**:65–70.
18. Elsheikh SE, Green AR, Rakha EA, Powe DG, Ahmed RA, Colins HM, Soria D, Garibaldi JM, Paish CE, Ammar AA, Grainge MJ, Ball GR, Abdelghany MK, Martinez-Pomares L, Heery DM, Ellis IO: **Global histone modifications in breast cancer correlate with tumor phenotypes, prognostic factors, and patient outcome.** *Cancer Res* 2009, **69**:3802–3809.
19. Yokoyama Y, Hieda M, Nishioka Y, Matsumoto A, Higashi S, Kimura H, Yamamoto H, Mori M, Matsuura S, Matsuura N: **Cancer-associated upregulation of histone H3 lysine 9 trimethylation promotes cell motility in vitro and drives tumor formation in vivo.** *Cancer Sci* 2013, **104**:889–895.
20. Hayashi-Takanaka Y, Yamagata K, Wakayama T, Stasevich TJ, Kainuma T, Tsurimoto T, Tachibana M, Shinkai Y, Kurumizaka H, Nozaki N, Kimura H: **Tracking epigenetic histone modifications in single cells using Fab-based live endogenous modification labeling.** *Nucleic Acids Res* 2011, **39**:6475–6488.
21. Chandra T, Kirschner K, Thuret JY, Pope BD, Ryba T, Newman S, Ahmed K, Samarajiwa SA, Salama R, Carroll T, Stark R, Janky R, Narita M, Xue L, Chicas A, Nũnez S, Janknecht R, Hayashi-Takanaka Y, Wilson MD, Marshall A, Odom DT, Babu MM, Bazett-Jones DP, Tavaré S, Edwards PA, Lowe SW, Kimura H, Gilbert DM, Narita M: **Independence of repressive histone marks and chromatin compaction during senescent heterochromatic layer formation.** *Mol Cell* 2012, **47**:203–214.
22. Shaker M, Yokoyama Y, Mori S, Tsujimoto M, Kawaguchi N, Kiyono T, Nakano T, Matsuura N: **Aberrant expression of disintegrin-metalloprotease proteins in the formation and progression of uterine cervical cancer.** *Pathobiology* 2011, **78**:149–161.

23. Tanaka H, Nishioka Y, Yokoyama Y, Higashiyama S, Matsuura N, Matsuura S, Hieda M: **Nuclear envelope-localized EGF family protein amphiregulin activates breast cancer cell migration in an EGF-like domain independent manner.** *Biochem Biophys Res Commun* 2012, **420**:721–726.
24. Sakamoto G, Inaji H, Akiyama F, Haga S, Hiraoka M, Inai K, Iwase T, Kobayashi S, Sakamoto G, Sano M, Sato T, Sonoo H, Tsuchiya S, Watanabe T, Japanese Breast Cancer Society: **General rules for clinical and pathological recording of breast cancer 2005.** *Breast Cancer* 2005, **12**:S1–S27.
25. Schotta G, Lachner M, Sarma K, Ebert A, Sengupta R, Reuter G, Reinberg D, Jenuwein T: **A silencing pathway to induce H3-K9 and H4-K20 trimethylation at constitutive heterochromatin.** *Genes Dev* 2004, **18**:1251–1262.
26. Kourmouli N, Jeppesen P, Mahadevhaiah S, Burgoyne P, Wu R, Gilbert DM, Bongiorni S, Prantera G, Fanti L, Pimpinelli S, Shi W, Fundele R, Singh PB: **Heterochromatin and tri-methylated lysine 20 of histone H4 in animals.** *J Cell Sci* 2004, **117**:2491–2501.
27. Park YS, Jin MY, Kim YJ, Yook JH, Kim BS, Jang SJ: **The global histone modification pattern correlates with cancer recurrence and overall survival in gastric adenocarcinoma.** *Ann Surg Oncol* 2008, **15**:1968–1976.
28. Song JS, Kim YS, Kim DK, Park SI, Jang SJ: **Global histone modification pattern associated with recurrence and disease-free survival in non-small cell lung cancer patients.** *Pathol Int* 2012, **62**:182–190.
29. **MENT: methylation and expression database of normal and tumor tissues.** [http://mgrc.kribb.re.kr:8080/MENT]
30. Baek SJ, Yang S, Kang TW, Park SM, Kim YS, Kim SY: **MENT: methylation and expression database of normal and tumor tissues.** *Gene* 2013, **518**:194–200.
31. Holliday DL, Speirs V: **Choosing the right cell line for breast cancer research.** *Breast Cancer Res* 2011, **13**:215.
32. Leong SP, Shen ZZ, Liu TJ, Agarwal G, Tajima T, Paik NS, Sandelin K, Derossis A, Cody H, Foulkes WD: **Is breast cancer the same disease in Asian and Western countries?** *World J Surg* 2010, **34**:2308–2324.
33. Hahn M, Dambacher S, Dulev S, Kuznetsova AY, Eck S, Wörz S, Sadic D, Schulte M, Mallm JP, Maiser A, Debs P, von Melchner H, Leonhardt H, Schermelleh L, Rohr K, Rippe K, Storchova Z, Schotta G: **Suv4-20 h2 mediates chromatin compaction and is important for cohesin recruitment to heterochromatin.** *Genes Dev* 2013, **27**:859–872.
34. Jørgensen S, Schotta G, Sørensen CS: **Histone H4 lysine 20 methylation: key player in epigenetic regulation of genomic integrity.** *Nucleic Acids Res* 2013, **41**:2797–2806.
35. Madsen MW, Briand P: **Relationship between tumorigenicity, in vitro invasiveness, and plasminogen activator production of human breast cell lines.** *Eur J Cancer* 1990, **26**:793–797.
36. Kelly T, Yan Y, Osborne RL, Athota AB, Rozypal TL, Colclasure JC, Chu WS: **Proteolysis of extracellular matrix by invadopodia facilitates human breast cancer cell invasion and is mediated by matrix metalloproteinases.** *Clin Exp Metastasis* 1998, **16**:501–512.
37. Gerlitz G, Bustin M: **The role of chromatin structure in cell migration.** *Trends Cell Biol* 2011, **21**:6–11.
38. Gerlitz G, Livnat I, Ziv C, Yarden O, Bustin M, Reiner O: **Migration cues induce chromatin alterations.** *Traffic* 2007, **8**:1521–1529.
39. Gerlitz G, Bustin M: **Efficient cell migration requires global chromatin condensation.** *J Cell Sci* 2010, **123**:2207–2217.
40. Moody SE, Sarkisian CJ, Hahn KT, Gunther EJ, Pickup S, Dugan KD, Innocent N, Cardiff RD, Schnall MD, Chodosh LA: **Conditional activation of Neu in the mammary epithelium of transgenic mice results in reversible pulmonary metastasis.** *Cancer Cell* 2002, **2**:451–461.
41. Palmieri D, Bronder JL, Herring JM, Yoneda T, Weil RJ, Stark AM, Kurek R, Vega-Valle E, Feigenbaum L, Halverson D, Vortmeyer AO, Steinberg SM, Aldape K, Steeg PS: **Her-2 overexpression increases the metastatic outgrowth of breast cancer cells in the brain.** *Cancer Res* 2007, **67**:4190–4198.
42. Tan M, Yao J, Yu D: **Overexpression of the c-erbB-2 gene enhanced intrinsic metastasis potential in human breast cancer cells without increasing their transformation abilities.** *Cancer Res* 1997, **57**:1199–1205.
43. Cao Q, Yu J, Dhanasekaran SM, Kim JH, Mani RS, Tomlins SA, Mehra R, Laxman B, Cao X, Yu J, Kleer CG, Varambally S, Chinnaiyan AM: **Repression of E-cadherin by the polycomb group protein EZH2 in cancer.** *Oncogene* 2008, **27**:7274–7284.
44. Chase A, Cross NC: **Aberrations of EZH2 in cancer.** *Clin Cancer Res* 2011, **17**:2613–2618.
45. Pang J, Toy KA, Griffith KA, Awuah B, Quayson S, Newman LA, Kleer CG: **Invasive breast carcinomas in Ghana: high frequency of high grade, basal-like histology and high EZH2 expression.** *Breast Cancer Res Treat* 2012, **135**:59–66.
46. Chen MW, Hua KT, Kao HJ, Chi CC, Wei LH, Johansson G, Shiah SG, Chen PS, Jeng YM, Cheng TY, Lai TC, Chang JS, Jan YH, Chien MH, Yang CJ, Huang MS, Hsiao M, Kuo ML: **H3K9 histone methyltransferase G9a promotes lung cancer invasion and metastasis by silencing the cell adhesion molecule Ep-CAM.** *Cancer Res* 2010, **70**:7830–7840.
47. Kapoor-Vazirani P, Kagey JD, Vertino PM: **SUV420H2-mediated H4K20 trimethylation enforces RNA polymerase II promoter-proximal pausing by blocking hMOF-dependent H4K16 acetylation.** *Mol Cell Biol* 2011, **31**:1594–1609.
48. Stender JD, Pascual G, Liu W, Kaikkonen MU, Do K, Spann NJ, Boutros M, Perrimon N, Rosenfeld MG, Glass CK: **Control of proinflammatory gene programs by regulated trimethylation and demethylation of histone H4K20.** *Mol Cell* 2012, **48**:28–38.
49. Henckel A, Nakabayashi K, Sanz LA, Feil R, Hata K, Arnaud P: **Histone methylation is mechanistically linked to DNA methylation at imprinting control regions in mammals.** *Hum Mol Genet* 2009, **18**:3375–3383.
50. Copeland RA, Solomon ME, Richon VM: **Protein methyltransferases as a target class for drug discovery.** *Nat Rev Drug Discov* 2009, **8**:724–732.
51. Richon VM, Johnston D, Sneeringer CJ, Jin L, Majer CR, Elliston K, Jerva LF, Scott MP, Copeland RA: **Chemogenetic analysis of human protein methyltransferases.** *Chem Biol Drug Des* 2011, **78**:199–210.
52. Giannini G, Cabri W, Fattorusso C, Rodriquez M: **Histone deacetylase inhibitors in the treatment of cancer: overview and perspectives.** *Future Med Chem* 2012, **4**:1439–1460.

doi:10.1186/bcr3681
Cite this article as: Yokoyama *et al.*: Loss of histone H4K20 trimethylation predicts poor prognosis in breast cancer and is associated with invasive activity. *Breast Cancer Research* 2014 16:R66.

JOURNAL OF PALLIATIVE MEDICINE
Volume 17, Number xx, 2014

DOI: 10.1089/jpm.2014.0099

Factors that Delay Treatment of Symptomatic Metastatic Extradural Spinal Cord Compression

Yoichiro Tsukada, MD,[1,2] Naoki Nakamura, MD, PhD,[1] Sachiko Ohde, EdM,[3] Keiko Akahane, MD,[1] Kenji Sekiguchi, MD, PhD,[1] and Atsuro Terahara, MD, PhD[2]

Abstract

Background: Treatment delays of metastatic extradural spinal cord compression (MESCC) sometimes have been reported, but reasons for its delay have remained unclear. The purpose of this study was to assess which clinical factors are associated with treatment delays in neurologically symptomatic MESCC in the hospital settings.

Methods: We reviewed medical records of MESCC patients in our institute who had at least one progressive neurological symptom (weakness, sensory changes, urinary retention, or nerve root pain), were diagnosed by magnetic resonance imaging (MRI), and were treated with at least radiotherapy. The number of days prior to treatment initiation were counted and defined as follows: from the patients' first physician visit to our hospital until MRI diagnosis [T1 (days)], from MRI diagnosis to treatment [T2 (days)], and from patients' first visit to treatment [T1 + 2 (days)]. Nine clinical factors that could potentially delay treatment were analyzed for each period.

Results: Forty-three episodes of MESCC met the inclusion criteria. Median days in T1 + 2 was 3 days (range: 0–22). T1 and T1 + 2 were significantly higher in patients with normal walking status than in those with deterioration or inabilities to walk (T1 + 2, 7 days versus 3 days, median, $p < 0.001$). The number of days was higher in all periods when it included weekends (T1 + 2, 7 days versus 2 days, median, $p < 0.001$).

Conclusions: Our findings suggest that normal walking status at the first physician visit and inclusion of weekends during the pretreatment periods were factors that resulted in treatment delays even for MESCC patients with emergency neurological symptoms.

Introduction

METASTATIC EXTRADURAL SPINAL CORD COMPRESSION (MESCC) is one of the most devastating complications of metastatic neoplasms. Defined as spinal cord or cauda equina compression by either direct pressure or induction of vertebral collapse or instability by metastatic spread or direct extension of malignancy,[1] the overall cumulative probability of experiencing at least one episode of MESCC in the 5 years preceding death from cancer has been estimated to be 2.5%,[2] When left untreated, MESCC can cause irreversible paralysis, sensory loss, and sphincter dysfunction.[3] Patients with MESCC generally require early definitive treatment such as surgery and radiotherapy or radiotherapy alone to prevent such permanent neurological deficits.[1] The emergent nature of the disease is highlighted by several previous studies demonstrating that earlier diagnosis and treatment leads to better neurological outcomes.[4–9] Therefore, symptomatic MESCC patients should be managed emergently to minimize treatment delays.[3]

There are two guidelines that are followed regarding the time between diagnosis and treatment.[1,10] In accordance with the first published guideline, current cancer patients with suspected MESCC should undergo diagnostic magnetic resonance imaging (MRI) examination within 24 hours, with definitive treatment initiated within 24 hours after diagnosis.[1] As per subsequent guidelines, surgical consultation should be obtained within 24 hours of radiographic diagnosis of MESCC.[10] Despite these guidelines, treatment delays continue to occur.[11–14] Husband stated that failure to diagnose MESCC and failure to adequately and expeditiously investigate, refer, and treat MESCC patients were the primary

[1]Department of Radiation Oncology, St. Luke's International Hospital, Tokyo, Japan.
[2]Department of Radiology, Toho University Omori Medical Center, Tokyo, Japan.
[3]Center for Clinical Epidemiology, St. Luke's Life Science Institute, Tokyo, Japan.
Accepted September 22, 2014.

causes of delay and consequent functional deterioration.[14] However, few reports have quantitatively assessed the factors that may affect total time to diagnosis and treatment after the initial physician encounter among MESCC patients. The purpose of this study was to determine the clinical and other logistical factors associated with delay in the diagnosis and treatment of neurologically symptomatic MESCC patients in acute hospital settings.

Methods

We retrospectively reviewed medical records of patients who received radiotherapy to the spinal or sacral area between March 2003 and April 2012 at St Luke's International Hospital, a tertiary medical care center in Tokyo, Japan. Of these, data for emergent MESCC patients were extracted according to the following criteria: 1) presence of progressive neurological symptoms, including weakness in at least one limb, sensory changes, urinary retention requiring a urinary catheter, or nerve root pain; 2) MRI read by senior radiologists demonstrating malignant neoplasms or metastases in the vertebral body with compression of spinal cord or cauda equina from outside the dura; and 3) treatment of MESCC with radiotherapy combined with surgery, or radiotherapy alone. Nerve root pain was defined as pain in unilateral or bilateral dermatomal distribution.[12] Symptoms of numbness and tingling, shooting, or burning sensations were regarded as nerve root pain.[1,2] Patients with radiographically diagnosed MESCC, but who were asymptomatic or had no neurological symptoms, were excluded, limiting our population to those warranting emergent treatment.

The number of days was calculated from the onset of the neurological symptoms to when definitive treatment was initiated. Treatment was categorized into three periods as illustrated in Figure 1: from first physician visit until MRI diagnosis [T1 (days)], from MRI diagnosis to treatment [(T2 (days)], and from first physician visit until treatment [(T1 + 2 (days)]. For example, if a patients' first visit to the physician was on Friday and MRI was performed the following Monday, T1 was defined as 3 days. First physician visit was defined as the day on which progressive neurological symptoms were first recorded by the physician in a series of consecutive events related to MESCC.

This study was approved by the institutional review board of St Luke's International Hospital, number 12-R001.

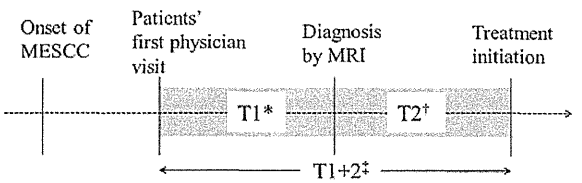

FIG. 1. Timeline of treatment process of MESCC from the day the patient first visited a physician until treatment initiation, from left to right on a time scale. *Total number of days from the day patient first visited a physician until diagnosis by MRI after the development of MESCC; †total number of days from diagnosis until treatment; ‡total number of days from the day the patient first visited a physician until start of treatment.

Evaluation of delaying factors

To identify the factors that were associated with delays in each of the time periods, baseline patient characteristics were extracted. In addition, six factors clinically relevant to MESCC and present at first physician visit were included in this analysis based on previous literature,[1,12,15,16] including prior MESCC episodes (yes or no),[1] known bone metastases (yes or no),[1] known history of malignancy (yes or no),[12,15] known vertebral metastases (yes or no),[16] walking status (yes or no),[16] and insertion of urinary catheter at first visit (yes or no).[16] Sensory changes, nerve root pain, and back pain were not included as covariates, as these symptoms were largely subjective and recording in patient records varied.

In addition, weekend days (Saturday or Sunday) during an MESCC-related sequence of events was recorded, to assess the relationship between the day of the week and time to treatment. Patients were further classified into two groups, based on whether or not a weekend day was included in each period. When time periods included either a Saturday or a Sunday, patients were classified as the "weekend group." Otherwise, they were classified as the "weekday group." For example, if a patient visited a physician on Friday, obtained an MRI the following Monday, and received treatment by Friday of that same week, the patient was categorized as the weekend group for T1 and weekday group for T2.

During this study period, all clinical departments in the hospital were open from Monday to Friday during the daytime hours (9:00 a.m. to 5:00 p.m.). The emergency department was open 24 hours all days of the week, and accessible to anyone on a walk-in basis or via ambulance. MRIs were available anytime depending on need. Physicians were able to consult other subspecialties at any time including the weekends. Weekend surgery and radiotherapy were available for emergent patients as needed. Type of initial imaging studies and subsequent subspecialist consultation were dependent on the assessment of the attending physician for patients suspected of MESCC.

Statistical analyses

The analysis of delay was performed using the Kaplan-Meier method, and the log-rank tests were used in univariate analysis to examine differences between the prognostic value of each possible factor and its effect of the length of T1, T2, and T1 + 2. Given the small sample size, multivariate analysis was not attempted. The level of statistical significance was set at $\alpha = 0.05$. SPSS® version 20 software (SPSS, Inc., Chicago, IL) was used to perform all statistical analyses.

Results

Of 335 patients who received radiotherapy to vertebral or sacral areas during the study period, 43 episodes (cases) of MESCC in 41 patients met all inclusion criteria. Patient characteristics and associated neurological symptoms at first visit are summarized in Table 1. The median age at the time of physician visit was 63 years (range, 34–85 years), and 42% ($n = 18$) of the patients were male and 58% ($n = 25$) were female. The most frequent primary tumor among the study population was breast cancer (33%, $n = 14$), followed by lung cancer in (21%, $n = 9$). The most frequently compressed section for lesions involving the vertebral body was thoracic

TABLE 1. PATIENT CHARACTERISTICS AND SYMPTOMS AT FIRST VISIT TO A PHYSICIAN

	Number of patients (%)
Sex	
Male	18 (42)
Female	25 (58)
Age (years)	63 (range, 34–85)
Site of primary malignancy	
Breast	14 (33)
Lung	9 (21)
Prostate	3 (7)
Colon	3 (7)
Renal cell	3 (7)
Others	11 (26)
Treatment methods	
Radiotherapy	43 (100)
Surgery with radiotherapy	0 (0)
Level of compression	
Cervical	8 (15)
Thoracic	33 (63)
Lumbar	10 (19)
Sacral	1 (2)
Medical history	
Known history of malignancy at first visit	37 (86)
Known history of MESCC at first visit	4 (9)
Known bone metastases at first visit	26 (60)
Known vertebral metastases at first visit	26 (60)
Stage IV of malignancy at initial diagnosis	15 (35)
Walking disturbance	
Unable to walk	12 (28)
Able to walk with deterioration	16 (37)
Able to walk without deterioration	9 (21)
Unknown	6 (14)
Sensory changes	
Present	14 (33)
Absent	9 (21)
Unknown	20 (47)
Nerve root pain	
Present	28 (65)
Absent	7 (16)
Unknown	8 (19)
Need urinary catheter	
Need	6 (14)
Not needed	35 (81)
Unknown	2 (5)

MESCC, metastatic extradural spinal cord compression.

(65%). Seven cases had multiple compression sites (16%): one case was both cervical and thoracic (2%); five cases were thoracic and lumber (12%); and another one had cervical, thoracic, and lumber sites (2%). Radiotherapy alone was used in all cases, with no case patients undergoing surgery combined with radiotherapy. Four case patients had undergone previous treatment for MESCC, though previously treated sites differed from current compression sites in all patients.

Nine case patients (21%) were able to walk without deterioration, 16 (37%) were able to walk with some deterioration, and 12 case patients (28%) were unable to walk. Two (5%) were previously paralyzed due to other reasons, two (5%) could not be evaluated due to poor physical status, and two (5%) had insufficient medical records. All patients who were able to walk without deterioration manifested sensory changes, nerve root pain, or both. None of the patients experienced bladder disturbance alone; four cases (10%) required insertion of urinary catheters at first visit, and two case patients (5%) could not be evaluated as they already had a urinary catheter inserted prior to first visit. With regard to the days of the week, four case patients (9%) presented during the weekend, two (5%) underwent MRI on the weekend, and one (2%) received radiotherapy on the weekend.

Time from onset of MESCC to treatment

The median time from onset of MESCC to first physician visit was 3 days (range, 0–143; mean, 10). The median time from patients' first physician visit to diagnosis by MRI (T1) was one day (range, 0–20; mean, 3), with 26 cases (60%) being diagnosed within one day. On the other hand, T1 was >3 days for 12 cases (28%). Median time from diagnosis until initiation of radiotherapy (T2) was 2 days (range, 0–19; mean, 2). Among these, radiotherapy was initiated within one day for 21 cases (49%). T2 was >3 days for nine cases (21%). Moreover, median time from first visit until radiotherapy (T1+2) was 3 days (range, 0–22; mean, 5). T1+2 was >3 days for 21 cases (49%).

Delaying factors

We analyzed all 43 cases for factors of "sex," "age," "known history of malignancy," "known history of MESCC," "known bone/vertebral metastases," and "stage IV malignancy at initial diagnosis" using log rank tests. However, patients with missing data were excluded from two separate analyses. Out of the original 43 cases, 37 were additionally analyzed as "unable to walk or able to walk with deterioration," which excluded 6 patients. Also, 41 cases were analyzed as "need urinary catheter," excluding 2 more patients.

Patients who presented with normal walking abilities at their first physician visit waited significantly longer for treatment initiation compared with those who had some deterioration in walking ability or were unable to walk during T1 (median, 4 days versus 1 day, respectively; $p<0.001$) and T1+2 (median, 7 days versus 3 days, $p<0.001$) as shown in Table 2. In T2, the median number of days in each group was equivalent (median, 2 days versus 2 days, $p=0.085$), but a trend was observed toward earlier treatment in the group with deterioration of ambulation or inability to walk. The weekend group experienced a higher number of days compared with that for the weekday group in T1 (median, 6 days versus 1 day, $p<0.001$), T2 (median, 3 days versus 1 day, $p<0.001$), and T1+2 (median, 7 days versus 2 days, $p<0.001$) (Table 2). Figure 2 represents Kaplan-Meier plots showing cumulative rates to treatment initiation in periods T1+2 for normal walking versus other. Figure 3 represents Kaplan-Meier plots showing cumulative rates to treatment initiation in periods T1+2, but for weekend versus weekday groups. This is

TABLE 2. UNIVARIATE ANALYSIS OF TOTAL NUMBER OF DAYS REQUIRED FOR TREATMENT AND FACTORS IN EACH TREATMENT PERIOD

	Number of patients (n)	*T1 period*[b] *(day) (median)*	P *value*[a]	*T2 period*[c] *(day) (median)*	P *value*[a]	*T1+2 period*[d] *(day) (median)*	P *value*[a]
Sex							
Male	$n=18$	2	$p=0.607$	2	$p=0.423$	4	$p=0.224$
Female	$n=25$	1		1		3	
Age (years)							
≥63	$n=23$	1	$p=0.677$	2	$p=0.372$	4	$p=0.444$
<63	$n=20$	1		1		3	
Known history of malignancy at first visit							
Yes	$n=37$	1	$p=0.495$	1	$p=0.497$	3	$p=0.998$
No	$n=6$	1		3		4	
Known history of MESCC at first visit							
Yes	$n=4$	2	$p=0.509$	2	$p=0.916$	6	$p=0.697$
No	$n=39$	1		2		3	
Known bone/vertebral metastases at first visit							
Yes	$n=26$	1	$p=0.822$	1	$p=0.272$	3	$p=0.291$
No	$n=17$	1		2		4	
Stage IV malignancy at initial diagnosis							
Yes	$n=15$	1	$p=0.870$	1	$p=0.828$	3	$p=0.778$
No	$n=28$	1		2		4	
Unable to walk or able to walk with deterioration							
Yes	$n=28$	1	$p<0.001$	2	$p=0.085$	3	$p<0.001$
No	$n=9$	4		2		7	
Need urinary catheter							
Yes	$n=6$	3	$p=0.237$	2	$p=0.596$	4	$p=0.224$
No	$n=35$	1		2		3	
Including weekend							
Yes (Weekend group[e])	T1: $n=14$ T2: $n=12$ T1+2: $n=22$	6	$p<0.001$	3	$p<0.001$	7	$p<0.001$
No (Weekday group[f])	T1: $n=29$ T2: $n=31$ T1+2: $n=21$	1		1		2	

[a]log-rank test.
[b]Total number of days between a patient's first visit to a physician until MRI after the development of MESCC.
[c]Total number of days between MRI and initiation of treatment.
[d]Total number of days between patient's first physician visit and initiation of treatment.
[e]Weekends included.
[f]Weekends not included in each treatment period.
MESCC, metastatic extradural spinal cord compression; MRI, magnetic resonance imaging.

defined based on walking status at first visit to a physician and the number of days of the week, respectively.

Other factors including sex, age, known history of malignancy at first visit, known history of MESCC at first visit, known bone/vertebral metastases at first visit, stage IV malignancy at initial diagnosis, and need for urinary catheterization were not significant.

Discussion

The findings of this study suggest that walking status at first physician visit and inclusion of weekends for each of three periods are factors that are significantly associated with delays in time to diagnosis and treatment for MESCC patients.

Patients with progressive neurological symptoms including weakness, sensory changes, urinary retention, and nerve root pain, but with normal walking status are likely to be at high risk for treatment delays. Presumably, physicians may not regard progressive neurological symptoms as caused by MESCC or may wait before obtaining MRI in the setting of preserved gait function.

However, ambulatory status at both diagnosis of MESCC and at treatment initiation has been reported to be important prognostic factors for postradiotherapy walking status.[4–8]

Maranzono and Latini prospectively assessed the effects of radiotherapy and neurological functions in MESCC patients.[4] Of the 109 patients who were able to walk before radiotherapy, 107 patients had preserved their ambulant abilities after one month of treatment (98%). On the other hand, only 51 of 100 patients who were unable to walk regained gait function after one month of treatment (51%).

With regard to combined surgery and radiotherapy, according to a subgroup analysis of a randomized controlled trial performed by Patchell et al., pretreatment Frankel score was associated with longer ambulatory time after definitive treatment.[9] Frankel score is used for evaluating spinal cord function with higher scores representing better residual function.[17] These

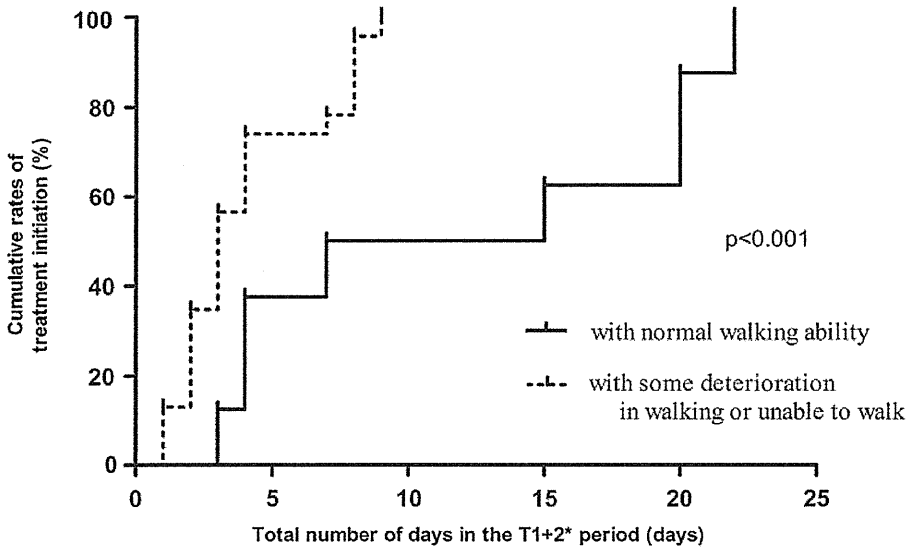

FIG. 2. Cumulative rates of treatment initiation in the T1 + 2* period based on patient's walking status. The solid line represents the patients with normal walking ability, and the dashed line represents patients who had some deterioration in walking or were unable to walk. *Total number of days from the day the patient first visited a physician until treatment initiation.

findings suggest that those patients with progressive neurological symptoms, but with normal walking status, benefit from early therapeutic intervention to preserve their walking ability, as well as patients with any deterioration of gait function. As such, it is necessary for physicians to pay very careful attention to diagnostic and treatment decisions for such patients.

Our results also suggest that weekends are factors for delay all pretreatment periods. Bell and Redelmeier revealed, in a cohort study of cases from 190 emergency departments, that a greater proportion of patients received urgent MRI on weekdays compared with weekends.[18] In our study, only two cases (5%) were diagnosed on weekends, despite the fact that MRI examinations were available on weekends. Fewer diagnoses made on weekends might be contributing to overall delays in time to treatment. Furthermore, many previous investigations showed that medical practice on weekends was

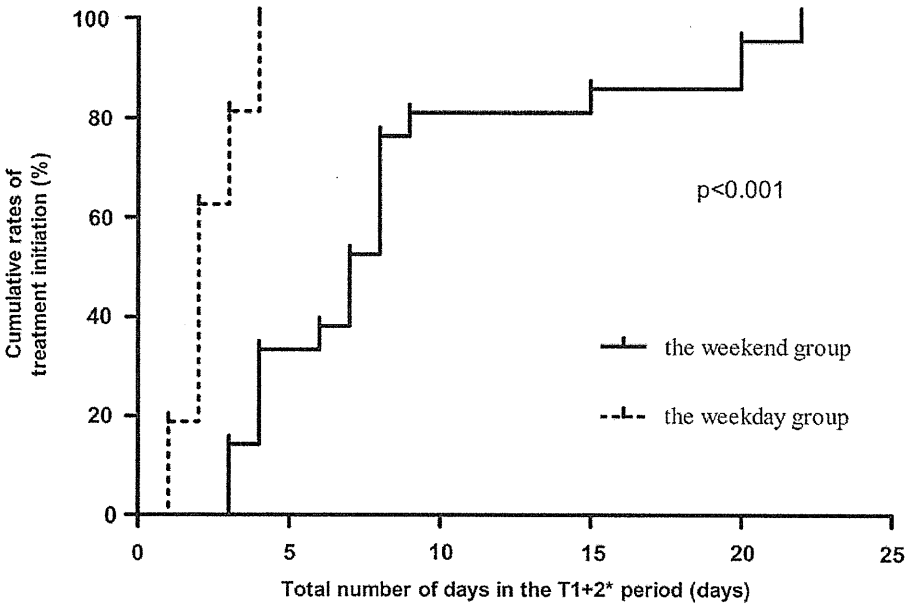

FIG. 3. Cumulative rates of treatment initiation in the T1 + 2* period based on the factor of the number of the days of the week in the two groups. The solid line represents the weekend group, and the dashed line represents the weekday group. *Total number of days from the day the patient first visited a physician until treatment initiation.

related with worse clinical outcomes in patients with some serious medical conditions, including ischemic stroke,[19] intracranial hemorrhage,[20] myocardial infarction,[21] ruptured abdominal aortic aneurysms,[22] and pulmonary embolism.[22] Bell and Redelmeier stated that possible reasons for worse medical outcomes on weekends were as follows: short staffing, less seniority and experience among those who do work on weekends, weekend staff having to cover for other health professionals and may be less familiar with the patients under their charge, fewer supervisors on weekends, and over-seeing the work of unfamiliar staff.[22] As for the management of symptomatic MESCC, insufficient support on weekends may also contribute to delays. Well-designed systematic support systems are warranted for weekend clinical practice for MESCC management.

In a previous study, the number of days from the development of MESCC to treatment was higher among women compared with men.[13] Other studies reported that patients with known malignancies received earlier treatment compared with those without known malignancies after developing MESCC.[12,15] These two factors could be associated with treatment delays.

In addition, we investigated the correlation between treatment delays and several high-risk and predictive factors for MESCC. First, according to the guidelines set by the National Institute for Health and Clinical Excellence of the UK, patients who have a history of MESCC and those with known bone metastases are considered to be at a high risk for developing MESCC.[1] Another study by Lu et al. investigated patients who were clinically suspected of having MESCC and judged to need further evaluation by MRI, and identified the following four independent factors predictive of MRI-confirmed MESCC: abnormal neurological examination, stage IV malignancy at initial diagnosis, known vertebral metastases, and middle or upper back pain.[16] Of these, we analyzed stage IV malignancy at initial diagnosis and known vertebral metastases. We substituted abnormal neurological examination with patient's walking status and need for urinary catheter at first physician visit, as these could be assessed via records reviews. However, with the exception of walking status, these high-risk and predictive factors for MESCC were not associated with earlier diagnosis and treatment.

In several institutions and regions, specific systems and treatment modalities have been developed to decrease treatment delays. For example, a remote consultation system, through which physicians are able to consult neurosurgeons at other hospitals, has been put into practice.[23] In addition, Lee et al. reported the introduction of a multidisciplinary clinical strategy for the diagnosis and treatment of suspected and definitive MESCC to reduce treatment delays at their institution.[24] These interventions were effective in decreasing time to treatment.

There were several limitations to this study. First, we excluded some patients, such as those who underwent other imaging examinations as a substitute for MRI, as well as patients who received MRI but did not receive radiotherapy. A small selection bias may have influenced our results. Second, in our study, we did not take subjective symptoms, and patients' and physicians' recognition into consideration. As per a previously published abstract,[11] patients who perceived that their symptoms are related to their previous cancer received treatment earlier compared with those who were unaware of their cancer-related symptoms. Moreover, based on our chart review, in one case where T2 was 19 days, a physician might not have regarded MESCC as an emergent complication, even though the physician charted the patient's aggressive neurological symptom and had suspected MESCC. Finally, interactions of multiple factors could not be assessed. For example, we observed several cases where T1 and T2 were both >3 days. This fact could not be explained only by the weekend factor, and some interactions of multiple factors would affect the delays. We think multivariate analysis may partly provide us with knowledge on how each factor affects time to treatment, though we did not conduct this analysis because of small sample size. Despite these limitations, Kaplan-Meier curves in Figure 2 and 3 show clear differences in T1 + 2 by walking status and days of the week. We consider our analysis to be meaningful in the clinical setting and expect larger studies to corroborate these results in the future.

Conclusions

Our findings suggest that normal walking status at the first physician visit and inclusion of weekends during the diagnostic and pretreatment periods are associated with delays in the treatment process for neurologically symptomatic MESCC patients. Physicians should be aware that patients with progressive neurological symptoms including weakness, sensory changes, urinary retention, and nerve root pain, but with normal walking status, are likely to be at risk for treatment delays and should be approached carefully to receive necessary emergency treatment. Moreover, well-designed systematic support systems for weekend clinical practices are needed to decrease the incidence of treatment delays.

Acknowledgments

This study was presented in part at the 25th Central Japan Meeting of Japanese Society for Radiation Oncology in 2012.

The authors appreciate the support of the Division of Analytical Research for Medical Informatics at St. Luke's International Hospital for assistance with data collection. The authors thank Dr. Gautam Deshpande from the Center for Clinical Epidemiology, St. Luke's Life Science Institute, and Dr. Rebecca Wong from the Department of Radiation Oncology, The Princess Margaret Cancer Centre, for their critical review of the manuscript.

Author Disclosure Statement

No competing financial interests exist.

References

1. The National Institute for Health and Clinical Excellence Clinical Guideline75: Metastatic spinal cord compression: Diagnosis and management of patients at risk of or with metastatic spinal cord compression. http://www.nice.org.uk/guidance/cg75/resources/guidance-metastatic-spinal-cord-compression.pdf (Last accessed October 17, 2014).
2. Loblaw DA, Laperriere NJ, Mackillop WJ: A population-based study of malignant spinal cord compression in Ontario. *Clin Oncol (R Coll Radiol)* 2003;15:211–217.
3. Loblaw DA, Perry J, Chambers A, et al.: Systematic review of the diagnosis and management of malignant extradural

spinal cord compression: The Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. *J Clin Oncol* 2005;23:2028–2037.
4. Maranzano E, Latini P: Effectiveness of radiation therapy without surgery in metastatic spinal cord compression: Final results from a prospective trial. *Int J Radiat Oncol Biol Phys* 1995;32:959–967.
5. Helweg-Larsen S, Sorensen PS, Kreiner S: Prognostic factors in metastatic spinal cord compression: A prospective study using multivariate analysis of variables influencing survival and gait function in 153 patients. *Int J Radiat Oncol Biol Phys* 2000;46:1163–1169.
6. Leviov M, Dale J, Stein M, et al.: The management of metastatic spinal cord compression: a radiotherapeutic success ceiling. *Int J Radiat Oncol Biol Phys* 1993;27:231–234.
7. Rades D, Karstens JH, Hoskin PJ,et al.: Escalation of radiation dose beyond 30 Gy in 10 fractions for metastatic spinal cord compression. *Int J Radiat Oncol Biol Phys* 2007;67:525–531.
8. Turner S, Marosszeky B, Timms I, et al.: Malignant spinal cord compression: A prospective evaluation. *Int J Radiat Oncol Biol Phys* 1993;26:141–146.
9. Patchell RA, Tibbs PA, Regine WF, et al.: Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: A randomised trial. *Lancet* 2005;366:643–648.
10. Loblaw DA, Mitera G, Ford M, et al.: A 2011 updated systematic review and clinical practice guideline for the management of malignant extradural spinal cord compression. *Int J Radiat Oncol Biol Phys* 2012;84:312–317.
11. Mitera G, Loblaw A: Delays from symptom onset to treatment in malignant spinal cord compression: Quantification and effect on pre-treatment neurological status [abstract]. 2004. ASCO annual meeting. http://meeting.ascopubs.org/cgi/content/abstract/22/14_suppl/8276 (Last accessed October 17, 2014).
12. Levack P, Graham J, Collie D, et al.: Don't wait for a sensory level—listen to the symptoms: A prospective audit of the delays in diagnosis of malignant cord compression. *Clin Oncol (R Coll Radiol)* 2002;14:472–480.
13. Solberg A, Bremnes RM: Metastatic spinal cord compression: Diagnostic delay, treatment, and outcome. *Anticancer Res* 1999;19:677–684.
14. Husband DJ: Malignant spinal cord compression: Prospective study of delays in referral and treatment. *BMJ* 1998;317:18–21.
15. McLinton A, Hutchison C: Malignant spinal cord compression: A retrospective audit of clinical practice at a UK regional cancer center. *Br J Cancer* 2006;94:486–491.
16. Lu C, Gonzalez RG, Jolesz FA, et al.: Suspected spinal cord compression in cancer patients: A multidisciplinary risk assessment. *J Support Oncol* 2005;3:305–312.
17. Frankel HL, Hancock DO, Hyslop G, et al.: The value of postural reduction in the initial management of closed injuries of the spine with paraplegia and tetraplegia. I. *Paraplegia* 1969;7:179–192.
18. Bell CM, Redelmeier DA: Waiting for urgent procedures on the weekend among emergently hospitalized patients. *Am J Med* 2004;117:175–181.
19. Saposnik G, Baibergenova A, Bayer N, et al.:Weekends: A dangerous time for having a stroke? *Stroke* 2007;38:1211–1215.
20. Crowley RW, Yeoh HK, Stukenborg GJ, et al.: Influence of weekend hospital admission on short-term mortality after intracerebral hemorrhage. *Stroke* 2009;40:2387–2392.
21. Kostis WJ, Demissie K, Marcella SW, et al.: Weekend versus weekday admission and mortality from myocardial infarction. *N Engl J Med* 2007;356:1099–1109.
22. Bell CM, Redelmeier DA: Mortality among patients admitted to hospitals on weekends as compared with weekdays. *N Engl J Med* 2001;345:663–668.
23. Fitzpatrick D, Grabarz D, Wang L, et al.:How effective is a virtual consultation process in facilitating multidisciplinary decision-making for malignant epidural spinal cord compression? *Int J Radiat Oncol Biol Phys* 2012;84:e167–e172.
24. Lee K, Tsou I, Wong S, et al.: Metastatic spinal cord compression as an oncology emergency: Getting our act together. *Int J Qual Health Care* 2007;19:377–381.

Address correspondence to:
Yoichiro Tsukada, MD
Department of Radiology
Toho University Omori Medical Center
6-11-1 Omori-nishi, Ota-ku
Tokyo 143-8541
Japan

E-mail: youichirou.tsukada@med.toho-u.ac.jp

Journal of
Oral Pathology & Medicine

doi: 10.1111/jop.12099

J Oral Pathol Med (2014) 43: 97–102

wileyonlinelibrary.com/journal/jop

Non-invasive objective evaluation of radiotherapy-induced dry mouth

Youko Fujimaki[1,2], Koichi Tsunoda[2], Shin-Ichi Ishimoto[3], Kazunari Okada[3], Makoto Kinoshita[1], Hiroshi Igaki[4], Atsuro Terahara[5], Takahiro Asakage[1], Tastuya Yamasoba[1]

[1]Department of Otolaryngology, Faculty of Medicine, Graduate School of Medicine, University of Tokyo, Tokyo, Japan; [2]Department of Artificial Organs and Otolaryngology, National Institute of Sensory Organs, Tokyo, Japan; [3]Department of Otolaryngology, Social Insurance Central General Hospital, Tokyo, Japan; [4]Department of Radiology, Faculty of Medicine, Graduate School of Medicine, University of Tokyo, Tokyo, Japan; [5]Department of Radiology, Toho University Omori Medical Center, Tokyo, Japan

BACKGROUND: Dry mouth is a common complaint in patients undergoing radiotherapy. Here, we employed the oral moisture meter Mucus III to evaluate dry mouth in head and neck tumor patients before and after they underwent radiotherapy.

METHODS: We recruited 17 newly diagnosed patients with pharyngeal squamous cell carcinoma or unknown primary squamous cell carcinoma, who received head and neck radiation therapy at Tokyo University Hospital in 2008–2010. The primary sites were the epipharynx ($n = 1$), oropharynx ($n = 6$), or hypopharynx ($n = 5$); it was unknown in five cases. Salivary function was assessed by a dry mouth questionnaire, resting saliva test, chewing gum test, and Mucus III, before ($n = 17$), immediately after radiotherapy ($n = 10$), and at 3 ($n = 9$) and 12 months after radiotherapy ($n = 11$).

RESULTS: The questionnaire, resting saliva test, and chewing gum test at 3 and 12 months after radiotherapy indicated a significantly decreased resting and stimulated whole saliva flow rate than prior radiotherapy ($P < 0.05$ and $P < 0.001$). In contrast, Mucus III results showed significant worsening of xerostomia at 12 months after radiotherapy ($P < 0.05$).

CONCLUSION: Mucus III has been proven to be an objective diagnostic tool for patients with serious dry mouth, such as in patients with Sjogren's syndrome. However, we did not find a perfect correlation between Mucus III and other objective (resting saliva and chewing gum) and subjective (questionnaire) measures of dry mouth. To precisely diagnose radiotherapy-induced dry mouth, further improvement to the method is needed.

Correspondence: Dr Youko Fujimaki, Department of Otolaryngology-Head and Neck Surgery, Faculty of Medicine, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Tokyo 113-8865, Japan. Tel: +81–3-3815-5411, Fax: +81-3-3814-9486, E-mail: yoko45f@yahoo.co.jp
Ethical approval number: 1523; Ethical approval obtained from the Tokyo University.
Accepted for publication May 16, 2013

J Oral Pathol Med (2014) **43:** 97–102

Keywords: head and neck cancer; xerostomia

Introduction

Dry mouth can be caused by various conditions such as hyposalivation due to Sjögren's syndrome, inflammation of the salivary gland and atrophy due to irradiation of head and neck tumors, mouth breathing due to nasal sinus disease and sleep apnea syndrome, and reduction in saliva secretion due to consumption of certain drugs (1–8). Dry mouth can lead to oral mucosal diseases, causing oral and oropharyngeal pain, oropharyngeal infections, dysphagia, cacogeusia, and difficulty in speaking (3).

Mouth dryness can be measured by several tests. Salivary secretion tests such as the chewing gum test, the Saxon test, and the paraffin test apply stimuli of variable intensities (9–16). They are useful for evaluating the amount of stimulated saliva, but not mucosal wetness in resting conditions (16). This is a problem for bed-ridden patients, dementia patients, and patients with dental prosthesis, in whom stimulated saliva tests are difficult to perform. Therefore, an objective evaluation method that did not depend on the patient's function was needed.

To take care of this need, an oral moisture meter (Mucus) was developed by Life Co. Ltd (Saitama, Japan) in 2001, based on the improved design of an original skin wetness meter (17). The tool works according to the principle of a condenser, which measures impedance with capacitive sensors, using the resonant frequency of the alternating current. The displayed number is not the actual value of the amount of water, but it is a relative value that reflects it. Therefore, units are not indicated. Thus, the moisture content of the mouth and tongue mucosae can be evaluated with this device (Fig. 1). The probe is placed against the oral and tongue mucosae for approximately within 5 s, and an alarm sounds at the end of the measurement. The probe tip (1 cm^2) touches the oral mucosa and tongue with a

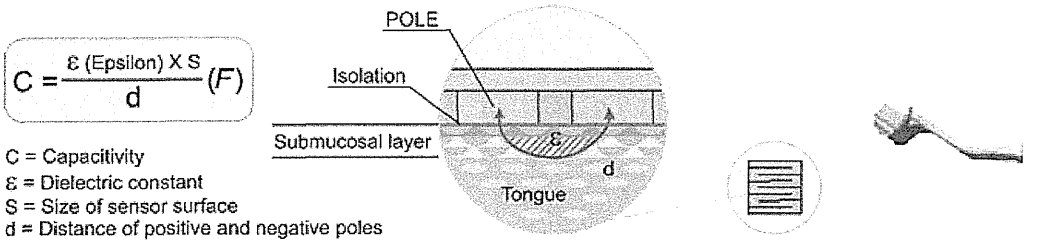

Figure 1 Measurement of the moisture content of the submucosal layer (about 50 μm under the mucosal surface) of the tongue was based on the principle of a condenser. The formula shown was used for calculation. As the value of '*S*' and '*d*' is constant, changes in '*C*' depend solely on '*ε*'. When the sensor is placed against the tongue, '*ε*' changes with the amount of moisture. In general, high moisture content gives high '*ε*' and '*C*' values, while low moisture content gives low '*ε*' and '*C*' values. Adapted from (18).

pressure of about 200 g/cm^2. After 27 mA (80 mW) of microelectrical current is delivered to the probe, the capacitance at the mucosal depth of 50 μm of the oral mucosa is quantified. Because the probe tip is covered with a sterile sensor cover (thickness, 12 μm), there is no risk of bacterial or viral infection. The tool is non-invasive and easy to operate. A digital display provides objective data.

However, this earlier model of Mucus had low reliability. To improve this, Ishimoto et al. pointed out the problems and came up with possible solutions to the manufacturer (18). This has led to the development of an improved version, the so-called Mucus III (Fig. 2). In an animal study, Ishimoto et al. established the reliability and usefulness of Mucus III (18). Later, Ishimoto et al. confirmed the reliability of Mucus III in healthy volunteers (standard value of the tongue's moisture content: 30.9 ± 1.8) and its usefulness in comparing the oral mucosa of patients with Sjogren's syndrome with that of controls (19). Currently, Mucus III is commercially marketed as MUCUS®.

To date, subjective questionnaire-based measures have been mainly used for the study of radiotherapy-induced dry mouth (20–24). We hypothesized that Mucus III could be as useful in the evaluation of radiotherapy-induced dry mouth as it was in the case of patients with Sjogren's syndrome.

The purpose of this study was to evaluate Mucus III for the assessment of oral dryness in head and neck cancer patients who have undergone radiation treatment. We also show the results of subjective (questionnaire) and objective (resting saliva and chewing gum) tests for comparison with the results of Mucus III.

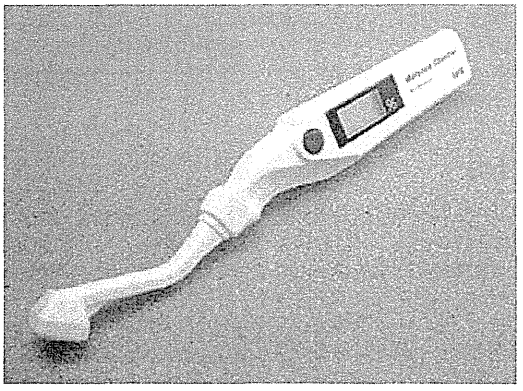

Figure 2 Mucus III device. Mucus III device measures 21.5 mm (width), 238 mm (length), and 41 mm (height), and weights 60 g.

Materials and methods

Subjects

From August 2008 to July 2010, 17 newly diagnosed patients with pharyngeal squamous cell carcinoma and unknown primary squamous cell carcinoma were recruited (Table 1).

All these patients underwent conventional radiotherapy (CRT) of the head and neck region at the Department of Otolaryngology, Tokyo University Hospital. The primary tumor site was classified into the epipharynx (n = 1), oropharynx (n = 6), hypopharynx (n = 5), or unknown (n = 5). Sixteen patients received a radiotherapy dose of 70 Gy, and one patient whose primary tumor site was unknown received a radiotherapy dose of 60 Gy. Fourteen patients received no medication (oral tablets or gel) during the follow-up period. Three patients were given a dose of pilocarpine hydrochloride to increase salivary secretion, but administration was stopped because of its side effects. The study was conducted in accordance with the Declaration of Helsinki and approved by the appropriate ethical committee. Informed consent was obtained from all the participants.

Assessment of mouth dryness

Four different tests (A–D) were applied to the enrolled participants before and after they underwent radiotherapy. Ten patients (9 men, 1 woman, age: 44–77 years, mean age: 61.1 years) were successfully evaluated before and immediately after the radiotherapy (within a maximum period of 11 days). The primary sites were the oropharynx (n = 3) and hypopharynx (n = 4); the site was unknown in three cases. The average radiation dose for the parotid glands was 45.4 ± 2.2 Gy. Nine cases (7 men, 2 women, age: 44–77 years, mean age: 60.2 years) were successfully evaluated before and 3 months after radiotherapy. The primary sites were the oropharynx (n = 4) and hypopharynx (n = 4), while it was unknown in one case. The average radiation dose for the parotid glands was 48.5 ± 4.2 Gy. Eleven cases (8 men, 3 women, age: 44–74 years, mean age: 58.8 years) were successfully evaluated before and 12 months after the radiotherapy; the primary sites were the nasopharynx (n = 1), oropharynx (n = 4), and hypopharynx (n = 3), while it was unknown in the three cases. The average radiation dose for the parotid glands was 43.3 ± 2.7 Gy.

Table 1 Clinical characteristics of the 17 patients enrolled in this study

No	*Sex*	*Age*	*Tumor site*	*TNM*	*Total radiation (Gy)*	*Chemotherapy*	*Immediately after*	*At 3 months*	*At 12 months*
1	M	65	OPX	T2N0M0	70	Yes	Yes	Yes	Yes
2	F	74	OPX	T2N0M0	70	Yes		Yes	Yes
3	F	67	OPX	T4aN0M1	70	Yes	Yes	Yes	Yes
4	M	59	OPX	T4aN1M0	70	Yes	Yes		
5	M	54	OPX	T4aN3	70	Yes			Yes
6	M	50	OPX	T4N2cMo	70	Yes		Yes	
7	M	77	HPX	T3N2aM1	70	Yes	Yes	Yes	
8	M	50	HPX	T2N1M0	70	Yes	Yes	Yes	Yes
9	M	62	HPX	T2N2M0	70	Yes			Yes
10	M	44	HPX	T4N2bM0	70	Yes	Yes	Yes	Yes
11	M	76	HPX	T2N3M0	70	Yes	Yes		
12	M	67	HPX	T3N0M0	70	Yes		Yes	
13	M	63	UP		60	Yes	Yes		Yes
14	M	59	UP		70	Yes	Yes		Yes
15	M	51	UP		70	Yes	Yes		Yes
16	M	48	UP		70	Yes		Yes	
17	F	58	EPX	T2bN1M0	70	Yes			Yes

EPX, epipharynx; HPX, hypopharynx; OPX, oropharynx; TNM, tumor, node, metastasis classification; UP, unknown primary.

Five cases (3 men, 2 women, age: 44–74 years, mean age: 60.0 years) were successfully evaluated before, 3 months, and 12 months after radiotherapy; the primary sites were the oropharynx (n = 3) and hypopharynx (n = 2), and it was unknown in three cases; the average radiation dose for the parotid glands was 42.4 ± 4.9 Gy.

A: Dry mouth questionnaire

A questionnaire for the subjective assessment of salivary dysfunction was designed based on the 8-item xerostomia questionnaire (20). The questionnaire consisted of eight questions regarding the sensation of mouth dryness and its influence on conversation and swallowing (Table 2). The participants were asked to grade each aspect with a score that ranged from 1 to 3, with a higher score denoting worse salivary function (21). The mean of the eight scores was calculated.

B: Resting saliva test

To evaluate resting salivary secretion, the patients were requested to keep spitting out saliva into a beaker during a period of 10 min, after which the total amount of saliva was measured (25).

C: Chewing gum test

To evaluate salivation upon stimulation, the patients were requested to chew gum (Free Zone; Lotte Co. Ltd, Tokyo, Japan) and keep spitting out saliva into a beaker during a period of 10 min, after which the total amount of saliva was measured (9–14). This mint-flavor, plate-like gum can also be used in patients with dentures, because it seldom sticks to the teeth.

Table 2 Questionnaire for subjective assessment of salivary dysfunction (20, 21)

1. Rate the difficulty you experience in speaking due to dryness
2. Rate the difficulty you experience in swallowing due to dryness
3. Rate the dryness of your mouth
4. Rate the dryness of your lips
5. Rate the dryness of your tongue
6. Rate the level of your thirst
7. Rate the stickiness you experience due to dryness
8. Rate how frequently you drink water for dryness

D: Measurement of oral moisture with Mucus III

The oral moisture meter Mucus III (Life Co. Ltd) was employed to measure the moisture content of the oral mucosa in resting conditions. The probe which was covered with a sterile sensor cover (thickness, 12 μm) was placed on the central part of the dorsal surface of the tongue about 10 mm from the tip for approximately 5 s. An alarm rang to provide the signal for the end of the measurement. A digital display provided objective data.

The measurements were carried out in the afternoon, 1–2 h after lunch at each time point, and in the following order: A: Dry mouth questionnaire, D: Measurement of oral moisture with Mucus III, B: Resting saliva test, C: Chewing gum test. Patients did not eat or drink for at least 60 min before measurements, nor did they smoke after diagnosis.

Statistical analysis

All data are expressed as the mean ± standard deviation (SD). Differences between two time points (before and immediately after, before and 3 months after, before and 12 months after, or 3 months and 12 months after radiotherapy) were examined for statistical significance using a paired t-test. A P-value of <0.05 was considered as significance thresholds.

Results

The dry mouth questionnaire (A), resting saliva test (B), and chewing gum test (C) showed that dry mouth symptoms were worsened immediately after radiotherapy as compared to before (2.47 ± 0.52 vs. 1.07 ± 0.10 [$P < 0.001$], 1.86 ± 1.38 vs. 5.51 ± 4.64 ml/10 min [$P < 0.05$], and 4.80 ± 5.35 vs. 24.15 ± 11.98 ml/10 min [$P < 0.001$], respectively). In the case of the Mucus III test (D), the reduction in oral moisture was not significantly different (30.00 ± 4.63 vs. 31.39 ± 1.27 [$P = 0.412$]) (Fig. 3).

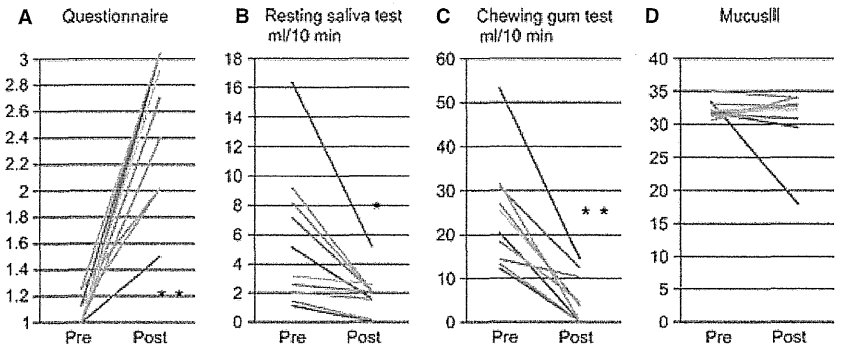

Figure 3 Results of the dry mouth questionnaire (A), resting saliva test (B), chewing gum test (C), and Mucus III test (D) before and immediately after radiotherapy (n = 10). *P < 0.05, **P < 0.001.

A similar trend in the results of the dry mouth questionnaire, resting saliva test, and chewing gum test was observed at 3 months after radiotherapy (2.68 ± 0.48 vs. 1.06 ± 0.12 [P < 0.001], 0.44 ± 0.53 vs. 7.04 ± 4.92 ml/10 min [P < 0.05], and 4.62 ± 4.64 vs. 22.66 ± 12.69 ml/10 min [P < 0.001], respectively). Again, the reduction in oral moisture was not significantly different in the case of the Mucus III test (26.69 ± 8.86 vs. 32.21 ± 1.91 [P = 0.096]) (Fig. 4). However, the decreasing trend was in accordance with the results of the other three tests.

At 12 months after radiotherapy, all four tests showed significant worsening of dry mouth symptoms, suggesting that subjective and objective reduction in salivation persisted for as long as 1 year (2.50 ± 0.42 vs. 1.06 ± 0.12 [P < 0.001], 0.72 ± 0.69 vs. 5.42 ± 4.39 ml/10 min [P < 0.05], 9.39 ± 4.81 vs. 23.86 ± 12.64 ml/10 min [P < 0.001], and 30.07 ± 1.73 vs. 31.94 ± 1.16 [P < 0.05], respectively) (Fig. 5).

Confirming the previous results, the five cases that were successfully evaluated before, 3 months, and 12 months after radiotherapy revealed significant differences in the dry mouth questionnaire results before radiotherapy and after 3 months, and before radiotherapy and after 12 months (1.10 ± 0.16 vs. 2.47 ± 0.58 [P < 0.05] and 1.10 ± 0.16

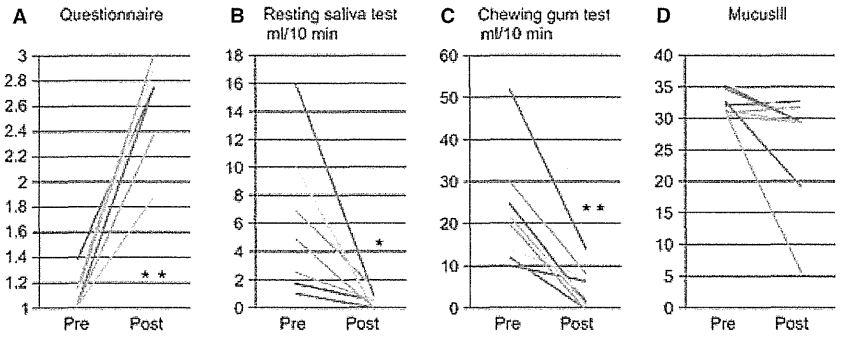

Figure 4 Results of the dry mouth questionnaire (A), resting saliva test (B), chewing gum test (C), and Mucus III test (D) before and 3 months after radiotherapy (n = 9). *P < 0.05, **P < 0.001.

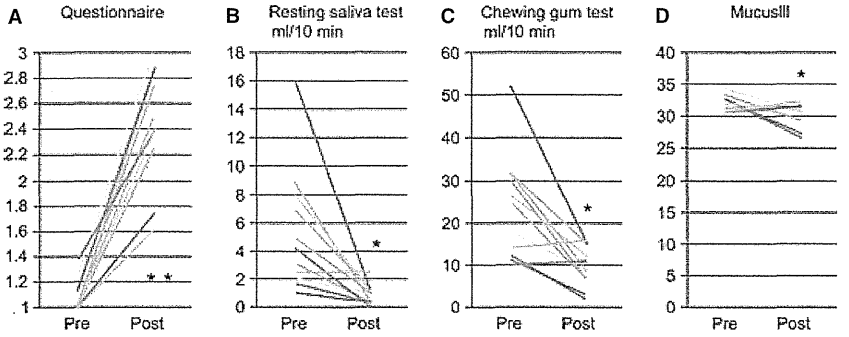

Figure 5 Results of the dry mouth questionnaire (A), resting saliva test (B), chewing gum test (C), and Mucus III test (D) before and 12 months after radiotherapy (n = 11).*P < 0.05, **P < 0.001.

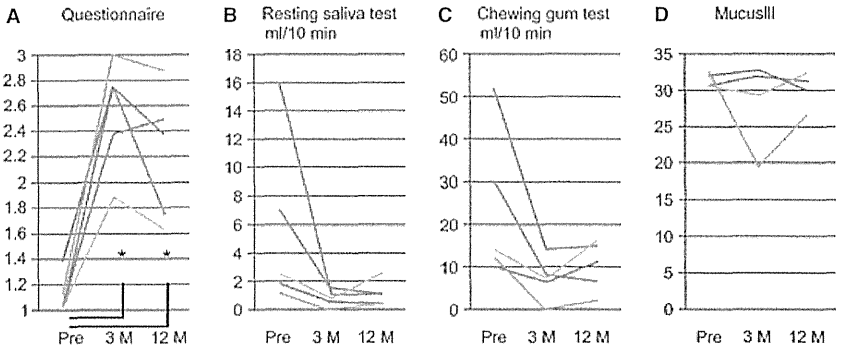

Figure 6 Results of the dry mouth questionnaire (A), resting saliva test (B), chewing gum test (C), and Mucus III test (D) before and 3 and 12 months after radiotherapy ($n = 5$). *$P < 0.05$.

vs. 2.27 ± 0.46 [$P < 0.05$], respectively). Comparison between the results at 3 months and 12 months after radiotherapy did not show a significant difference (2.47 ± 0.58 vs. 2.27 ± 0.46 [$P = 0.44$]); however, compared to 3 months after radiotherapy, 4 of 5 cases had improved mean scores at 12 months after radiotherapy. The resting saliva test, the chewing gum test, and Mucus III did not show significant differences between the same time points (Fig. 6). However, in the three tests, improvements in the mean scores at 12 months compared to 3 months after radiotherapy were observed (resting saliva test: 1.02 ± 0.89 vs. 0.74 ± 0.55 ml/10 min [$P = 0.52$]; chewing gum test: 10.10 ± 5.87 vs. 7.10 ± 4.98 ml/10 min [$P = 0.16$]; and Mucus III: 30.33 ± 2.17 vs. 29.04 ± 5.55 [$P = 0.50$]).

Discussion

Radiotherapy-induced dry mouth markedly reduces a patient's quality of life, and non-invasive objective evaluation tools are needed to help improve the management of radiotherapy side effects. Here, we tested the usefulness of the novel Mucus III in assessing mouth dryness in head and neck cancer patients who underwent radiotherapy. However, we found that Mucus III did not perform sufficiently well in reflecting dry mouth symptoms.

In this study, radiotherapy-induced dry mouth symptoms were identified subjectively and objectively by means of three different tests: a questionnaire, resting saliva test, and chewing gum test, immediately, 3 and 12 months after radiotherapy. Objective evaluation of oral moisture was obtained using Mucus III 12 months after radiotherapy. There was no significant difference seen immediately after the radiotherapy and 3 months after the radiotherapy. Unfortunately, because of the patients' physical and mental conditions and the difficulty with matching evaluation time points, we were unable to evaluate all 17 patients at each time point. Employing Mucus III to evaluate radiotherapy-induced dry mouth immediately after radiotherapy might not be the best option because inflammation of the oral mucosa is severe. On the other hand, 3 months after treatment, when the oral mucosa almost recovered from inflammation, application of Mucus III might be preferable. However, at 3 months after radiotherapy, Mucus III results showed a similar trend to the results of the other three tests, but the changes shown by Mucus III were not statistically significant. At 12 months after radiotherapy, dry mouth symptoms were evident in all four tests conducted, indicating that dry mouth was a long-term condition in these patients.

However, evaluating the data of 5 patients in a period of 1 year (Fig. 6), measurements at 12 months showed better improvement compared to the measurements obtained at 3 months after radiotherapy. Even though complete recovery from dry mouth symptoms is thought to be difficult or even almost impossible, the present results show that the process might not be entirely irreversible. This is consistent with the published literature (23, 24). To confirm this observation, a future study with a larger number of subjects and a longer follow-up period is necessary.

The results also indicate that Mucus III might not show consistent results across patients and/or time points. In case dry mouth is severe, and the absolute amount of saliva is reduced markedly, the value measured by Mucus III is also significantly lower, indicating its capacity to evaluate dry mouth precisely. However, when some degree of saliva secretion capacity remains, the measured value does not decrease significantly; in fact, it remains around normal values. Even if the relative value measured by Mucus III is lowered after irradiation, the absolute value is not significantly below the normal range. In short, the remaining saliva secretion capacity may not be sufficiently small to lower the absolute values measured by Mucus III; this might explain discrepancies in values compared to the other three tests.

Mucus III has proved its usefulness in the evaluation of hyposalivation in Sjogren's syndrome (6). However, in the present study, Mucus III did not perform sufficiently well in reflecting dry mouth symptoms resulting from radiation therapy. Importantly, in this study, there were no complaints of pain or discomfort associated with the probe. If this tool is revised and improved, it might help in the management of radiotherapy side effects, ultimately improving the quality of life after radiotherapy.

References

1. Daniels TE. Evaluation, differential diagnosis, and treatment of xerostomia. *J Rheumatol Suppl* 2000; **61**: 6–10.
2. Daniels TE, Wu AJ. Xerostomia – clinical evaluation and treatment in general practice. *J Calif Dent Assoc* 2000; **28**: 933–41.

3. Guputa A, Epstein JB, Sroussi H. Hyposalivation in elderly patients. *J Can Dent Assoc* 2006; **72**: 841–6.
4. Fox PC. Autoimmune diseases and Sjogren's syndrome: an autoimmune exocrinopathy. *Ann N Y Acad Sci* 2007; **1098**: 15–21.
5. Chambers MS, Garden AS, Kies MS, Martin JW. Radiation-induced xerostomia in patients with head and neck cancer: pathogenesis, impact on quality of life, and management. *Head Neck* 2004; **26**: 796–807.
6. Cheng SC, Wu WV, Kwong DL, Ying MT. Assessment of post-radiotherapy salivary glands. *Br J Radiol* 2011; **84**: 393–402.
7. Kakoei S, Haghdoost AA, Rad M, et al. Xerostomia after radiotherapy and its effect on quality of life in head and neck cancer patients. *Arch Iran Med* 2012; **15**: 214–18.
8. Dirix P, Nuyts S, van den Bogaert W. Radiation-induced xerostomia in patients with head and neck cancer. *Cancer* 2006; **107**: 2525–34.
9. Nogourani MK, Janghorbani M, Isfahan KR, Beheshti HM. Effects of chewing different flavored gums on salivary flow rate and pH. *Int J Dent* 2012; **2012**: 569327.
10. Olsson H, Spak CJ, Axell T. The effect of a chewing gum on salivary secretion, oral mucosal friction, and the feeling of dry mouth in xerostomic patients. *Acta Odontol Scand* 1991; **49**: 273–9.
11. Björnström M, Axéll T, Birkhed D. Comparison between saliva stimulants and saliva substitutes in patients with symptoms related to dry mouth. A multicentre study. *Swed Dent J* 1990; **14**: 153–61.
12. Miyawaki S, Torikai K, Natsume I, et al. Evaluation of two quantitative tests for salivary secretion–the chewing gum test and the Saxon test in normal subjects and in patients with Sjögren's syndrome. *Ryumachi* 1991; **31**: 22–7.
13. Risheim H, Arneberg P. Salivary stimulation by chewing gum and lozenges in rheumatic patients with xerostomia. *Scand J Dent Res* 1993; **101**: 40–3.
14. Mulligan R, Navazesh M, Wood GJ. A pilot study comparing three salivary collection methods in an adult population with salivary gland hypofunction. *Spec Care Dentist* 1995; **15**: 154–7.
15. Enberg N, Alho H, Loimaranta V, Lenander-Lumikari M. Saliva flow rate, amylase activity, and protein and electrocyte concentrations in saliva after acute alcohol consumption. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **92**: 292–8.
16. Kakinoki Y, Nishihara T, Arita M, Shibuya K, Ishikawa M. Usefulness of new wetness tester for diagnosis of dry mouth in disabled patients. *Gerodontology* 2004; **21**: 229–31.
17. Yamada H, Nakagawa Y, Nomura Y, et al. Preliminary result of moisture checker for Mucus in diagnosing dry mouth. *Oral Dis* 2005; **11**: 405–7.
18. Ishimoto S, Tsunoda K, Fujimaki Y, et al. Objective and non-invasive evaluation of dry mouth. *Auris Nasus Larynx* 2008; **35**: 89–93.
19. Ishimoto S, Tsunoda K, Akiya K, et al. Objective assessment of dry mouth using a non-invasive device. *Acta Otolaryngol* 2009; **129**: 1527–8.
20. Pai S, Ghezzi EM, Ship JA. Development of a visual analogue scale questionnaire for subjective assessment of salivary dysfunction. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **91**: 311–16.
21. Daly ME, Lieskovsky Y, Pawlicki T, et al. Evaluation of patterns of failure and subjective salivary function in patients treated with intensity modulated radiotherapy for head and neck squamous cell carcinoma. *Head Neck* 2007; **29**: 211–20.
22. Dirix P, Nuyts S, Vander Poorten V. The influence of xerostomia after radiotherapy on quality of life. Result of a questionnaire in head and neck cancer. *Support Care Cancer* 2008; **16**: 171–9.
23. Wijers OB, Levendag PC, Braaksma MM. Patients with head and neck cancer cured by radiation therapy: a survey of the dry mouth syndrome in long-term survivors. *Head Neck* 2002; **24**: 737–47.
24. Messmer MB, Thomsen A, Kirste S, Becker G, Momm F. Xerostomia after radiotherapy in the head & neck area: long-term observations. *Radiother Oncol* 2011; **98**: 48–50.
25. Márton K, Boros I, Fejérdy P, Madléna M. Evaluation of unstimulated flow rates of whole and palatal saliva in healthy patients wearing complete dentures and in patients with Sjogren's syndrome. *J Prosthet Dent* 2004; **91**: 577–81.

Acknowledgement

This study was supported by MEXT (Ministry of Education, Culture, Sports, Science and Technology) KAKENHI Grant Number 20791239.

Conflict of interests

The authors have no conflict of interests to declare.

特集 悪性リンパ腫の治療

4 眼-中枢神経悪性リンパ腫に対する放射線治療の実際

寺原敦朗*

はじめに

悪性リンパ腫は，悪性腫瘍の中では一般に放射線感受性が高く，放射線治療が一定の役割を果たしてきた。悪性リンパ腫は，さまざまなタイプのものがあり，そのタイプによって治療方針は異なる。以前は放射線治療が治療の中心となっているタイプも多かったが，化学療法の発達により放射線治療の役割は減ってきており，化学療法後のadjuvantとして用いられることが増え，また，用いられる線量も減少する傾向にある。放射線治療単独で治療が行われることが多い悪性リンパ腫は一部のタイプのみとなっているのが現状である。

眼科領域の悪性リンパ腫には，放射線治療が単独で用いられることが多く，高い局所制御率が得られている眼窩部のMALT lymphoma（mucosa-associated lymphoid tissue lymphoma）や，中枢神経浸潤を伴うことが多く，制御の難しい眼内悪性リンパ腫などがあるが，本稿では中枢神経悪性リンパ腫に対する治療も含め，放射線治療の実際について述べたい。

1 眼窩や眼球付属器の悪性リンパ腫

眼窩の悪性リンパ腫は，MALT lymphomaが多い。その他，結膜や涙腺などにみられることもある。Low grade, indolent typeのB cell lymphomaで，他の部位のMALT lymphomaと同様の治療が有効であり，同様の治療方針で治療が行われる。具体的には放射線治療単独で，30 Gy/15～20回程度の比較的低線量の照射により，90%以上の高い制御率が得られている。再発が2割程度に認められるが，多くは他の部位への再発である。

Hataらは，30例の眼窩MALT lymphomaに対する良好な放射線治療成績を報告している[1]。中央値30 Gyの照射により，5年全生存率，5年局所無増悪生存率はともに100%，5年非再発生存率は96%であった。5例にgrade 2の白内障が認められたが，眼内レンズ置換術により全例視力を回復しており，それ以外には照射による視力の低下は認められていない。

眼窩部の悪性リンパ腫として，次に多いのはびまん性大細胞性B細胞リンパ腫（diffuse large B cell lymphoma：DLBCL）である。他の部位におけるDLBCLと同様に，R-CHOPなどの化学療法後に，放射線治療が行われることが多く，残存腫瘍の有無によって30～40 Gy程度の線量が用いられている。治癒率は80%程度である。

眼窩病変に対する照射方法としては，照射野辺縁再発を避けるために，眼窩全体を照射野に含めることが多い。放射線による白内障の発生リスクを低下させるために，水晶体部を遮蔽することは，眼窩内に線量低下部位を生じさせることとなる。

* Atsurou TERAHARA　東邦大学医療センター大森病院放射線科
Key words：眼内悪性リンパ腫，中枢神経悪性リンパ腫，放射線治療，眼窩悪性リンパ腫

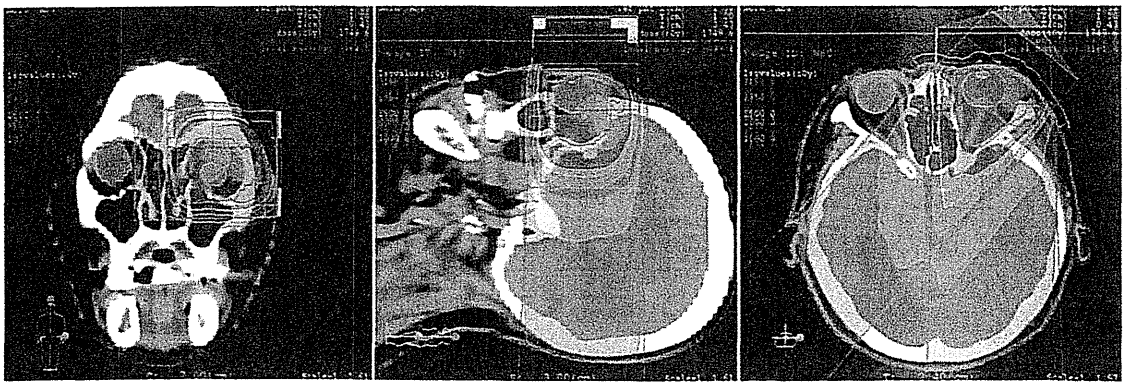

図1 左眼窩悪性リンパ腫に対する照射
前方からの wedge pair 2 門照射の線量分布図。

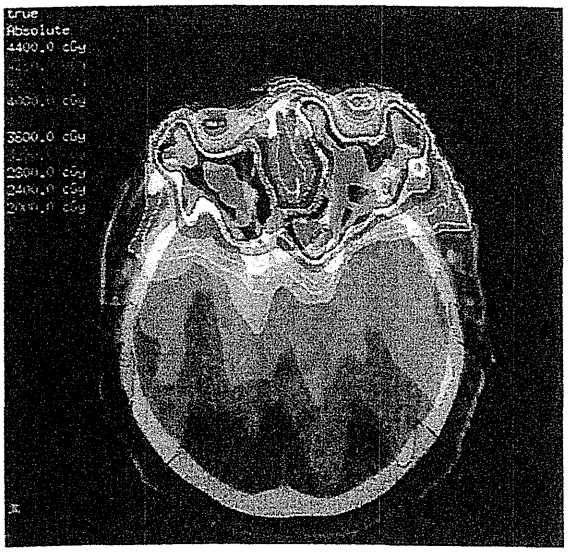

図2 両側眼窩悪性リンパ腫に対する強度変調放射線治療の線量分布図

その低線量域に再発するリスクを懸念して，眼窩全域に対して，前方からの wedge pair 2 門照射などの照射技法を用いた照射が行われる（図 1）．近年の照射技術の発達により可能となった強度変調放射線治療（IMRT：intensity modulated radiation therapy）を用いて，水晶体の線量を低減する試みも行われている（図 2）．眼瞼や結膜等の表層性病変に対しては，電子線を用いた照射が施行されることが多く，病変部位が水晶体からある程度離れている場合には，水晶体部を遮蔽するために鉛やタングステンの入ったコンタクトレンズ状の遮蔽器具を用いる場合もある。

2 眼内悪性リンパ腫

眼球内の悪性リンパ腫は，DLBCL が多いが，中枢神経への浸潤や再発も 60～80％に認められ，予後不良である。逆に中枢神経悪性リンパ腫からの眼球浸潤も 15～25％程度に認められる。最適な治療法はまだ確立されておらず，主として中枢神経悪性リンパ腫に準じた治療が行われている。眼内限局性病変に対しては，局所療法として眼球内の化学療法や眼球部への 30～36 Gy 程度の放射線治療のみが施行される場合もある。特に中枢神経浸潤が認められている場合には，高用量メトトレキサート（high dose MTX）を中心とした全身化学療法および局所への化学療法，さらに眼球部を含めた（あるいは外した）全脳照射 30～45 Gy 程度が行われることも多くなっている。

Mikami らが眼内悪性リンパ腫に対する放射線単独治療の成績を報告している[2]。明らかな中枢神経浸潤の確認されていない 22 例に対して，中央値 30 Gy（30～40 Gy）の放射線治療を施行し，3 年の局所制御率，全生存率，無増悪生存率はそれぞれ，95％，89％，49％で，局所制御は良好であった。グレード 3 以上の有害事象は 5 例に認められた白内障のみであり，許容範囲であったとしているが，55％において中枢神経再発が，照射後の中

央値28か月後に認められた。

東京大学では，メトトレキサートの硝子体内注射による局所の化学療法と，リツキシマブ，高用量メトトレキサート，ビンクリスチン，プロカルバジンの組み合わせによる全身化学療法(R-MPV)5コース施行後の比較的低線量の全脳照射(23.4 Gy)を組み合わせたプロトコールにて治療を施行しており[3]，その治療結果の解析がまたれる。

③ 中枢神経悪性リンパ腫

中枢神経悪性リンパ腫は，その多く(約90%)がDLBCLであり，多発病変として認められることも多く，前述のとおり，眼球浸潤も多い。年齢と全身状態(PS：performance status)が治療成績に影響するとされ，高齢やPSが不良の場合には，予後はより不良となる。放射線治療の奏効率は低くはないが，いったん完全寛解(CR：complete response)となっても再発が多く，放射線単独治療の成績は不良であり，中間生存期間は11～21か月程度である。そのため現在では，まずは高用量メトトレキサートや多剤併用(前述のMPVやR-MPV)の全身化学療法が施行され，その後に放射線治療の追加が検討されるようになっている。高齢者(60歳以上)においては，照射後の晩発性有害事象としての認知機能低下への懸念から，化学療法でCRとなった場合には，全脳照射は施行せずに経過観察することが推奨されている。60歳未満の場合，あるいは部分寛解(PR：partial response)以下やCR後の再発に対しては，全脳照射が施行される。また，PSや合併症の問題等で全身化学療法の施行が困難である場合には，全脳照射が施行されている。現在では，化学療法＋放射線治療により治療成績は改善しており，中間全生存期間は34～48か月程度，5年全生存率は26～51%程度まで向上している。

Nelsonらは1992年に，全脳照射40 Gyに局所照射20 Gyを追加する第2相試験(RTOG 8315)の結果を報告している[4]。中間生存期間11か月であり，再発が61%にみられ，そのうちの88%が追加局所照射野内であり，局所への追加照射の有用性は否定された。放射線治療のみでは限界があると考えられ，化学療法の併用が試みられるようになっていった。

Reniらは2001年に19のprospective seriesの解析を行い報告している[5]。高用量メトトレキサートを用いた全身化学療法の有用性が示された一方で，40 Gy以上の全脳照射や局所への追加照射は，全生存率の明らかな改善には寄与しておらず，また，化学療法でCRとなった症例においては，放射線治療を遅らせても全生存率の明らかな低下は認められなかったとしている。

DeAngelisらは2002年にRTOG 93-10の結果を報告している[6]。メトトレキサートの静注および脳室内注，ビンクリスチン，プロカルバジンを用いた化学療法(MPV)後に45 Gyの全脳照射(眼球浸潤が認められた場合には36 Gyまでは眼球も含めて照射)，さらに高用量シタラビンを用いるプロトコールで治療が行われ，中間全生存期間が36.9か月，中間非増悪生存期間が24か月と多施設共同の前向き試験で初めて化学放射線療法の有用性が示された。

Thielらは，2010年に，高用量メトトレキサートによる化学療法に，45 Gyの全脳照射を加える群に対して，全脳照射を加えずにイフォスファマイドによる化学療法を加えた群の成績が劣らないことを示すことを目的とした，非劣性試験(G-PCNSL-SG-1)の結果を報告している[7]。残念ながら設定された条件を満たすことはできず，非劣性は証明できなかったものの，中間生存期間は全脳照射群32.4か月，非全脳照射群37.1か月とほぼ同等の生存率が得られている。無増悪生存期間は全脳照射群が良好(中間でそれぞれ18.3か月および11.9か月)であったが，全脳照射群に神経毒性が多く認められており(それぞれ臨床的に49%および26%，画像的には71%および46%)，全脳照射の初期治療としての施行は推奨されないと

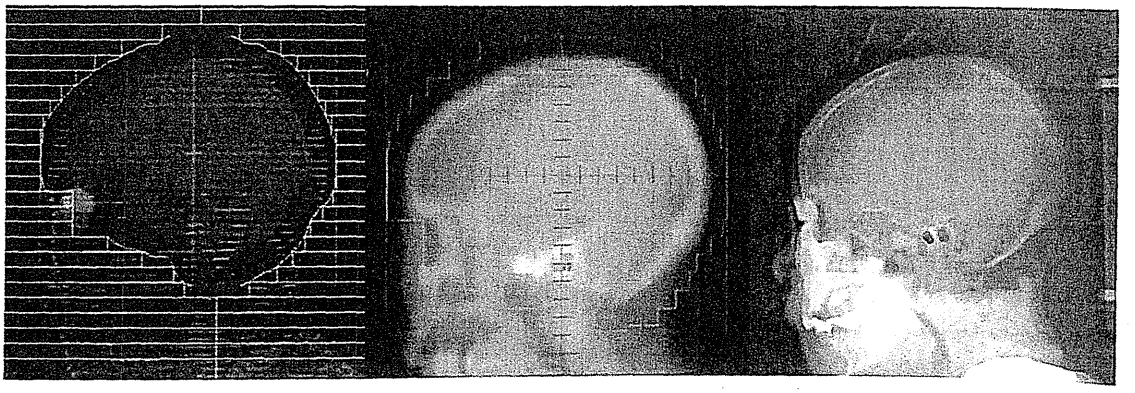

図3 中枢神経悪性リンパ腫に対する全脳照射＋眼球後部への照射野

結論づけている

中枢神経悪性リンパ腫に対する放射線治療は，腫瘍が脳内の広範囲に浸潤性に進展していくと考えられているため，局所照射ではなく全脳照射が行われる．眼球浸潤の頻度が高いことから，通常の全脳照射に加えて，眼球後部の網膜部を含めた照射野を設定する（図3）．前述のとおり，腫瘍部局所への追加照射の有効性は確認されていないため，全脳照射のみとすることが多い．また，眼球浸潤がある場合に，眼球局所への治療がどこまで必要であるかについては，確立した見解はない．30～40 Gy 程度まで眼球全体を含めて照射を行い，その後眼球前部を遮蔽する照射法もあるが，広く用いられてはおらず，メトトレキサートの硝子体内注射など局所への化学療法が行われることも多い．

線量については，化学療法後 CR となったのちに，全脳照射を追加する場合には 23.4～36 Gy 程度，PR 以下の場合や CR 後の再発の場合など病変が認められている場合には 36～45 Gy 程度の線量が推奨されている．全身状態不良等にて，長期予後が期待できない場合などには，30 Gy 10 回といった短期間の全脳照射が施行されることも少なくない．

化学療法と放射線治療の施行順序も重要なポイントであり，放射線治療の後に化学療法を施行した場合，神経毒性がより強くなるため，放射線治療は化学療法後に施行するべきである．

Grimm らは，International PCNSL Collaborative Group Report として，眼球浸潤のある中枢神経悪性リンパ腫の治療成績を解析して 2008 年に報告している[8]．眼球局所への治療（放射線治療あるいはメトトレキサートの硝子体内注射）を施行した群と，施行しなかった群とで比較したところ，全生存，無増悪生存は中間生存期間がそれぞれ 31 か月，18 か月で，中枢神経悪性リンパ腫の成績と同様であった．眼球部局所療法を施行することで，無増悪生存期間はやや延長（中間で 18 か月と 15 か月）したものの，眼球内の再発リスクは低減されておらず，全生存期間には差は認められなかった．

Blay らは，中枢神経悪性リンパ腫に対する高用量メトトレキサートを用いた治療について，後ろ向き試験の解析結果を 1998 年に報告している[9]．晩期神経毒性については，多変量解析の結果，放射線治療後の化学療法が相対リスク 11.5（95％信頼区間 2.76～32.0）であり，唯一の有意な因子であったとしている．

4 眼-中枢神経に対する放射線治療の有害事象

眼に対する放射線治療の急性有害事象としては，睫毛の脱毛，マイボーム腺や涙腺の機能低下による眼球乾燥や角膜炎，結膜炎などがある．これらの急性有害事象は，治療後は回復する場合が多いため，その後はあまり問題となることはない．

晩発性有害事象としては，眼球乾燥症，白内障，緑内障，網膜症，視神経障害などがある。眼球乾燥は24～26 Gy程度の線量から発生する可能性があり，照射容積や線量(一回線量および総線量)が増えることによって，そのリスクは高まり，発現時期も早くなると考えられている。白内障は5 Gy以下の低線量であっても発生する可能性があるが，発現する時期は通常数年以上経過してからである。線量が高くなると発現リスクが高くなり，発現までの期間も短くなる。手術によって視力の回復は可能ではあるが，水晶体への線量は可能な限り低減するべきである。放射線網膜症は，通常半年以降～数年後までの間に発生し，30～35 Gy程度の線量でも発生する可能性があるが，50 Gy以上の照射により，そのリスクが高くなるとされている。視神経障害は，通常分割照射では50 Gy以下で起こることはほとんどないと考えられ，54～55 Gy程度でもまれであり，55～60 Gyでは数%程度のリスク，60 Gyを超えると10%以上のリスクになるとされている。また，総線量のみならず，一回線量の要素も大きく影響する(一回線量が高いとリスクが高くなる)と考えられている。

これらの有害事象のリスク低減のために，前述したIMRTにより水晶体や涙腺，対側の眼窩に対する線量低減を行うことも試みられている。

中枢神経に対する放射線の急性有害事象としては，皮膚炎，頭痛，嘔気，疲労感などがあるが，照射後は回復するため，その後は通常問題となることはない。問題となるのは，晩発性有害事象である。中枢神経悪性リンパ腫の治療後に主に問題となるのは，認知機能の低下，白質脳症であるが，治療後半年以降～数年後に出現するため，長期生存をしないと問題になりにくい面もある。化学療法を施行することにより生存期間が延長してきたために，より問題になってきたともいえる。線量分割法の工夫も試みられたが，その毒性を明らかに低減することはできず，特に60歳以上の高齢者において，神経毒性のリスクが明らかに高い。全脳照射の線量を低減する試みも行われており，神経毒性が低減できる可能性が示唆されてきている。また，海馬の部分に照射される線量を低減することにより，認知機能低下のリスクを低減できる可能性も示唆されており[10]，IMRTを用いることで技術的にも可能であることも示されており[11][12]，実際の臨床応用を試みた試験の結果がまたれる。

DeAngelisらが報告したRTOG 93-10の結果において，治療成績は向上したものの，15%で重篤な晩発性神経毒性が認められており，10%では致命的なものであったことから，いかに神経毒性を減らしつつ，成績を向上させるかが課題と考えられた[6]。この臨床試験の再検討の結果がFisherらによって報告されている[13]。上記の神経毒性を低減することを目的に，化学療法後にCRが得られていた場合には，45 Gy/25回(1回1.8 Gy)から，36 Gy/30回，1回1.2 Gyで1日2回照射を行う過分割照射に線量分割法を変更して，総線量および一回線量を減らした治療が，試験の途中から行われた。その結果，全生存率および無増悪生存率には差は認められなかったが，重篤な神経毒性の頻度も変わらず，そのリスクを低減することはできなかった。

Abreyらは，MPV療法＋高用量シタラビンに全脳照射を加えた群と，神経毒性回避のために併用しなかった群との比較を行い，報告している[4]。全脳照射を施行した群では，60歳以上で83%と，60歳未満の6%に比較して神経毒性の発生率が明らかに高かった。照射しなかった群では神経毒性が認められたのは22例中1例のみであった。

Shahらは，さらなる全脳照射線量低減の試みについて報告している[5]。R-MPVを用いた化学療法を5～7サイクル施行し，CRと判定された場合には，全脳照射の線量を23.4 Gy/13回まで低減して治療を施行している(PR以下の場合には45 Gy/25回)。その結果，23.4 Gyの照射が施行された群では認知機能の低下は認められておら