Low-risk patients are candidates for radiotherapy alone, and such patients achieved favorable outcomes. Treatment for intermediate-risk patients involves consideration of whether or not radiotherapy alone is sufficient. Some of the patients experienced biochemical failure with carbon ion radiotherapy alone. However, patients with more advanced stage disease in the intermediate-risk group, namely T2c, showed favorable outcomes after the addition of hormone therapy. This suggests that hormone therapy may be advisable as a supplement for certain intermediate-risk patients.

In the case of high-risk patients, radiotherapy alone is considered to be insufficient. The five-year biochemical failure-free survival rate after radiotherapy with 66 Gy was approximately 30% (11). Increasing the radiation dose to 78 Gy using three-dimensional conformal radiotherapy or intensity-modulated radiation therapy improved biochemical failure-free survival rates compared to radiation with less than 72 Gy for high-risk patients (12-13). A radiation dose of 74 Gy for T3 patients with hormone therapy for 1-6 months yielded a biochemical failure-free survival rate of 46% after four years (14). For high-risk prostate cancer, therefore, high radiation doses greater than 72 Gy may be required for treatment, and such high doses may be used without serious adverse effects (15). The extension of the target volume to the pelvic area has been proposed (16), but because of the possible adverse effects on the neighboring organs, this technique is still controversial (17). Proton beam radiotherapy resulted in five-year biochemical-free survival rate of 48% in high-risk patients (18). Establishment of radiation modality was arranged from the results of initial protocols referring to carbon ion beam properties (19). After the initial protocols, the appropriate radiation dose was set at 66.0 GyE in 20 fractions. The cytocidal effect of this dose was assumed to be comparable to that of high doses of photons. Taking into account other beneficial properties, carbon ion radiotherapy may be considered to be one of the best treatment methods for prostate cancer. Acute and late morbidities associated with treatment are only minor and comparable to those associated with photon radiation (20).

The addition of hormone therapy has generally been recommended before, during and/or after radiotherapy to improve results for high-risk patients (21). In the literature, the reported durations of hormone therapy range between four months and five years (22). A consensus on the optimal duration has not yet been achieved. Hormone therapy for four months led to improved biochemical failure (22), but longer durations of hormone therapy, ranging from eight to thirty-six months, showed increased biochemical failure-free survival compared to either radiation alone or short-term hormone therapy (23-25). The RTOG 92-02 Trial showed that for high-risk patients 70 Gy of radiation with two years of hormone therapy led to 67% and 44% of biochemical failure-free rates at five and ten years, respectively (26-27). External beam radiotherapy with hormone therapy showed outcomes similar to those achieved with surgery (28-29). In the present study, high-risk patients were treated with adjuvant hormone therapy and this treatment seems to have achieved considerable biochemical failure-free outcomes in conjunction with carbon ion radiotherapy. Hormone therapy for two years may be sufficient. It is claimed that the addition of hormone therapy is generally credited with improving biochemical failure-free and clinical progression-free survivals, but has no benefit on overall survival. This is an important issue that needs to be further clarified. Recently, studies have reported adverse effects of hormone therapy (30), and trivialized its beneficial effects (31). On the contrary, the addition of hormone therapy is protective to the genitourinary and gastrointestinal tracts (32). Based on these findings, careful use of adjuvant hormone therapy may be beneficial. After biochemical failure, early induction of hormone therapy is more effective than delayed therapy (33). Salvage hormone treatment after failure as judged by the Phoenix criteria was also effective as shown in the present cohort. Factors influencing the response to hormone therapy included PSA-DT before the time of failure and the duration between radiotherapy and biochemical failure, suggesting a correlation with rapidly growing tumors.

A subset of high-risk patients progressed to a castration-resistant state, despite radiotherapy to the prostate and continuous hormone treatment. Most of these patients scarcely showed response to second-line hormone therapy. Clinically distant metastases may occur at certain times after biochemical failure (34, 35). Treatments for these patients were performed following EAU guidelines (36), but the patients progressed to a more severe disease state in general. The duration from the start of hormone therapy to biochemical failure in highly advanced prostate cancer patients, such as those at the metastatic stage, was generally one to two years and similar disease progression intervals were observed after radiotherapy. Factors affecting the rapid progression to a castration-resistant state included the time between radiotherapy and biochemical failure, and PSA kinetics including velocity and PSA-DT (37, 38), but other influencing factors have not been determined yet (39). Further advances are awaited in the development of treatment strategies for rapidly growing prostate cancer.

In summary, carbon ion radiotherapy is suitable and tolerable for the treatment of localized prostate cancer, especially for locally advanced stages.

Acknowledgements

The Authors acknowledge co-investigators from the Working Group for Genitourinary Tumors, the National Institute of Radiological Sciences of Japan. This work was partially supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References

1 Cancer Control and Information Services, National Cancer Centre, Japan, http://www.ganjoho.jp/ 2008

2 Tsuji H, Yanagi T, Ishikawa H, Kamada T, Mizoe J-E, Kanai T, Morita S,Tsujii H and Working Group for Genitourinary Tumors: Hypofractionated radiotherapy with carbon ion beams for prostate cancer. Int J Radiat Oncol Biol Phys *63*: 1153-1160. 2005

3 Akakura K, Tsujii H, Morita S, Tsuji H, Yagishita T, Isaka S, Ito H, Akaza H, Hata H, Fujime M, Harada M, Shimazaki J and Working Group for Genitourinary Tumors: Phase I/II clinical trials of carbon ion therapy for prostate cancer. Prostate *58*: 252-258. 2004.

4 Ishikawa H, Tsuji H, Kamada T, Yanagi T, Mizoe J-E, Kanai T, Morita S, Wakatsuki M, Shimazaki J, Tsujii H and Working Group for Genitourinary Tumors: Carbon ion radiation therapy for prostate cancer: Results of a prospective phase II study. Radiother Oncol *81*: 57-64, 2006

5 NCCN Clinical Practice Guidelines in Oncology V2, 2010,

6 Cox JD, Stetz J and Pajak TF; Toxicity criteria of the radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC). Int J Radiat Oncol Biol Phys *31*: 1341-1346 1995.

7 Roach III M, Hanks G, Thames H Jr, Schellhammer P, Shipley WU, Sokol GH and Sandler H: Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix consensus conference. Int J Radiat Oncol Biol Phys *65*: 965-74 2006.

8 Schmid H-P, McNeal JE and Stamy TA: Observations on the doubling time of prostate cancer, the use of serial prostate-specific antigen in patients with untreated disease as a measure of increasing cancer volume. Cancer *71*: 2031-2040, 1993.

9 Connolly D, Black A, Murray LJ, Napolitano G, Gavin A and Keane PF: Methods of calculating prostate-specific antigen velocity. Eur Urol *52*: 1044-1051, 2007

10 Nakamura K, Teshima T, Takahashi Y, Imai A, Koizumi M, Mitsuhashi N, Inoue T and Japanese PCS Working Subgroup of Prostate Cancer: Radical radiation therapy for prostate cancer in Japan: a patterns of care study report. Jpn J Clin Oncol *33*: 122-126, 2003.

11 D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, Tomazewski JE, Renshaw AA, Kaplan I, Beard CJ and Wein A: Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA *280*: 969-974, 1998.

12 Kupelian PA, Potters L, Khuntia D, Ciezki JP, Reddy CA, Reuther AM, Carison TP and Klein EA: Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy ≥72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. Int J Radiat Oncol Biol phys *58*: 25-33, 2004

13 Peeters STH, Heemsbergen WD, Koper PCM, van Putten WLJ, Slot A, Dielwart MFH, Bonffrer JMG, Incrocci L and Lebesque JV: Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol *24*: 1990-1996, 2006.

14 Liauw SL, Stadler WM, Correa D, Weichselbaum RR and Jani AB: Dose-escalated radiotherapy for high-risk prostate cancer: outcomes in modern era with short-term androgen deprivation therapy. Int J Radiol Oncol Biol Phys *77*: 125-130, 2010.

15 Talcott JA, Rossi C, Shipley WU, Slater JD, Niemierko A and Zietman AL: Patient-reported long-term outcomes after conventional and high-dose combined proton and photon radiation for early prostate cancer. JAMA *303*: 1046-1053, 2010.

16 Aizer AA, Yu JB, McKeon AM, Decker RH, Colberg JW and Peschel RE: Whole pelvic radiotherapy *versus* prostate only radiotherapy in the management of locally advanced or aggressive prostate adenocarcinoma. Int J Radiat Oncol Biol Phys *75*: 1344-1349, 2009.

17 Jereczek-Fossa BA and Orecchia R: Evidence-based radiation oncology: Definitive, adjuvant and salvage radiotherapy for non-metastatic prostate cancer. Radiother Oncol *84*: 197-215, 2007.

18 Slater JD, Rossi CJ Jr, Yonemoto LT, Bush DA, Jabola BR, Levy RP, Grove RI, Preston W and Slater JM: Proton therapy for prostate cancer: the initial Loma Linda University experience. Int J Radiat Oncol Biol Phy *59*: 348-352, 2004.

19 Kanai T, Endo M, Minohara S, Miyahara N, Koyama-Ito H, Tomura H, Matsufuji N, Futami Y, Fukumura A, Hiraoka T, Furusawa Y, Ando K, Suzuki M, Soga F and Kawachi K: Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. Int J Radiat Oncol Biol Phys *44*: 201-210, 1999.

20 Ishikawa H, Tsuji H, Kamada T, Hirasawa N, Yanagi T, Mizoe J-E, Akakura K, Suzuki H, Shimazaki J and Tsujii H; Risk factors of late rectal bleeding after carbon ion therapy for prostate cancer. Int J Radiat Oncol Biol Phys *66*: 1084-1091, 2006.

21 Schutz FAB and Oh WK: Neoadjuvant and adjuvant therapies in prostate cancer. Urol Clin N Am *37*: 97-104, 2010.

22 Roach III M, Bae K, Speight J, Wolkov HB, Rubin P, Lee J, Lawton C, Valicenti R, Grignon D and Pilepich MV: Short-term neoadjuvant androgen-deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. J Clin Oncol *26*: 585-591, 2008.

23 Souhami L, Bae K, Pilepiich M and Sandler H: Impact of the duration of adjuvant hormone therapy in patients with locally advanced prostate cancer treated with radiotherapy: a secondary analysis of RTOG 85-31. J Clin Oncol *27*: 2137-2143, 2009.

24 Bolla M, de Rreijke TM, van Tienhoven G, van den Bergh AC, Oddens J, Poortmans PM, Gez E, Kil P, Akdas A, Soete G, Kariakine O, van der Steen-Banasik EM, Musat E, Plerart M, Mauer ME, Collette L and EORTC Radiation Oncology Group and Genito-urinary Tract Cancer Group: Duration of androgen suppression in the treatment of prostate cancer. New Engl J Med *360*: 2516-2527, 2009.

25 Bria E, Cuppone F, Giannarelli D, Milella M, Ruggeri EM, Sperduti I, Pinnaro P, Terzoll E, Cognetti F and Carlini P: Does hormone treatment added to radiotherapy improve outcome in locally advanced prostate cancer? Meta-analysis of randomized trials. Cancer *115*: 3446-3456, 2009.

26 Hanks GE, Pajak TF, Porter A, Grignon D, Brereton H, Venkatesan V, Horwitz EM, Lawton C, Rosenthal SA, Sandler HM and Shipley WU: Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: The Radiation Therapy Oncology Group Protocol 92-02. J Clin Oncol *21*: 3972-3978, 2003.

27 Horwitz EM, Bae K, Hanks GE, Porter A, Grignon DJ, Brereton HD, Venkatesan V, Lawton CA, Rosenthal SA, Sandler HM and Shipley W: Ten-year follow-up of Radiation Therapy Oncology Group Protocol 92-02: a Phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. J Clin Oncol *26*: 2497-2504, 2008.
28 Arcangeli G, Strigari L, Arcangeli S, Petrongari MG, Saracino B, Gomellini S, Papalia R, Simone G, De Carli P and Gallucci M: Retrospective comparison of external beam radiotherapy and radical prostatectomy in high-risk, clinically localized prostate cancer. Int J Radiat Oncol Biol Phys *75*: 975-982, 2009.
29 Zelefsky MJ, Eastham JA, Cronin AM, Fuks Z, Zhang Z, Yamada Y, Vickers A and Scardino PT: Metastasis after radical prostatectomy or external beam radiotherapy for patients with clinically localized prostate cancer: a comparison of clinical cohorts adjusted for case mix. J Clin Oncol *28*: 1508-1513, 2010.
30 Taylor LG, Canfield SE and Du XL: Review of major adverse effects of androgen-deprivation therapy in men with prostate cancer. Cancer *115*: 2388-2399, 2009.
31 Krauss D, Kestin L, Ye H, Brabbins D, Ghilezan M, Gustafson G, Vicini F and Martinez A: Lack of benefit for the addition of androgen-deprivation therapy to dose-escalated radiotherapy in the treatment of intermediate- and high-risk prostate cancer. Int J Radiat Oncol Biol Phys. [doi 10.1016/ijrobp.2010.04.004 epub]
32 Lawton CA, Bae K, Pilepich M, Hanks G and Shipley W: Long-term treatment sequelae after external beam irradiation with or without hormonal manipulation for adenocarcinoma of the prostate: analysis of radiation therapy oncology group studies 85-31, 86-10, and 92-02. Int J Radiat Oncol Biol Phys *70*: 437-441, 2008.
33 Souhami L, Bae K, Pilepich M and Sandler H: Timing of salvage hormone therapy in prostate cancer patients with unfavorable prognosis treated with radiotherapy: a secondary analysis of radiation therapy oncology group 85-31. Int J Radat. Oncol Biol Phys. [doi 10.1016/ijrobp.2009.10.007 epub]
34 Buyyounouski MK, Hanlon AL, Horwitz EM and Pollack A: Interval to biochemical failure highly prognostic for distant metastasis and prostate cancer-specific mortality after radiotherapy. Int J Radiat Oncol Biol Phys *70*: 59-66, 2008.
35 Morgan PB, Hanlon AL, Horwitz EM, Buyyounouski MK, Uzzo RG and Pollack A: Timing of biochemical failure and distant metastatic disease for low-, intermediate-, and high-risk prostate cancer after radiotherapy. Cancer *110*: 68-80, 2007.
36 Heidenreich A, Aus G, Bolla M, Joniau S, Matveev VB, Schmid HP and Zattoni F: EAU Guidelines on prostate cancer. Eur Urol *53*: 68-80, 2008.
37 Prout-Lima C, Taylor JMG, Williams SG, Ankerst DP, Liu N, Kestin LL, Bae K and Sandler HM: Determinants of change in prostate-specific antigen over time and its association with recurrence after external beam radiation therapy for prostate cancer in five large cohorts. Int J Radiat Oncol Biol Phys *72*: 782-791, 2008.
38 Denham JW, Steigler A, Wilcox C, Lamb DS, Joseph D, Atkinson C, Tai K-H, Spry NA, Gleeson PS and D'Este C: Why are pretreatment prostate-specific antigen levels and biochemical recurrence poor predictors of prostate cancer survival? Cancer *115*: 4477-4487, 2009.
39 Roach III M, Waldman F and Pollack A: Predictive models in external beam radiotherapy for clinically localized prostate cancer. Cancer *115 (13 suppl)*: 3112-3120, 2009.

Received October 3, 2010
Revised November 6, 2010
Accepted November 9, 2010

前立腺癌患者における quality of life（QOL）効用値の評価：QOL 効用値指標 EQ-5D および VAS と健康関連 QOL 質問表 SF-36 および EPIC との比較

[1] 東京厚生年金病院泌尿器科，[2] 大阪大学大学院医学系研究科医療経済産業政策学，
[3] 東京医科歯科大学大学院医歯学総合研究科環境社会医歯学系医療政策学講座医療経済学分野

赤倉功一郎[1]　松崎香奈子[1]　小林　孝至[1]　木藤　宏樹[1]
溝口　研一[1]　富川聖恵麗[1]　田倉　智之[2]　川渕　孝一[3]

EVALUATION OF UTILITY INDEX OF QUALITY OF LIFE (QOL) IN PROSTATE CANCER PATIENTS : COMPARISON OF QOL UTILITY INDEX EuroQol-5D (EQ-5D) AND VISUAL ANALOGUE SCALE (VAS) WITH HEALTH-RELATED QOL QUESTIONNAIRES SF-36 AND EPIC

Koichiro Akakura[1], Kanako Matsuzaki[1], Takashi Kobayashi[1], Hiroki Kitoh[1], Ken-ichi Mizoguchi[1], Grace Tomikawa[1], Tomoyuki Takura[2] and Koichi Kawabuchi[3]

[1]*Department of Urology, Tokyo Kosei Nenkin Hospital*
[2]*Department of Health Economics and Industrial Policy, Osaka University Graduate School of Medicine*
[3]*Public Health Department of Health Science Policies, Health Care Economics, Tokyo Medical and Dental University Graduate School of Medical and Dental Sciences*

日本泌尿器科学会雑誌　第 102 巻　第 1 号　別刷

原　著　Original Article

前立腺癌患者における quality of life（QOL）効用値の評価：QOL 効用値指標 EQ-5D および VAS と健康関連 QOL 質問表 SF-36 および EPIC との比較

[1] 東京厚生年金病院泌尿器科，[2] 大阪大学大学院医学系研究科医療経済産業政策学，
[3] 東京医科歯科大学大学院医歯学総合研究科環境社会医歯学系医療政策学講座医療経済学分野
赤倉功一郎[1]　松崎香奈子[1]　小林　孝至[1]　木藤　宏樹[1]
溝口　研一[1]　富川聖恵麗[1]　田倉　智之[2]　川渕　孝一[3]

要旨：

（目的）局所前立腺癌の治療法として様々な選択肢があるが，その比較には医療経済的評価が不可欠である．また，費用対効用分析においては，単なる生存期間の比較ではなく QOL を加味した質調整生存年（QALY：quality adjusted life year）の評価が重要である．そこで，QALY 算出に最も広く用いられている QOL 効用値指標である EuroQol-5D（EQ-5D）ならびに visual analogue scale（VAS，0～100 points）の前立腺癌患者における有用性を検討した．

（対象と方法）前立腺癌患者 81 例を対象として，包括的および前立腺癌特異的 QOL 調査票である SF-36 と EPIC を用いて，EQ-5D と VAS との関連を調べた．

（結果）SF-36 の全ての下位尺度において EQ-5D および VAS との有意な相関を認めた．一方，EPIC の下位尺度である排尿，排便，性，ホルモンに関しては QOL 効用値指標に大きな影響はなかった．SF-36 の結果から VAS 効用値を変換算出すると，実際に得られた値と有意で強い相関がみられた（相関係数 0.53, $p<0.0001$）．

（結論）前立腺癌患者において EQ-5D ならびに VAS を用いた QOL 効用値指標の算出が妥当であり，費用対効用分析に用いる可能性が示された．また，これまでに蓄積されている SF-36 のデータを用いて QOL 効用値指標を変換算出できる可能性が示唆された．

（日泌尿会誌　102(1)：9～13, 2011）

キーワード：前立腺癌，費用対効用分析，質調整生存年（QALY）

緒　言

我が国においては，前立腺癌の罹患率および死亡率は近年上昇を続けており，今後も増加傾向を示すと推測されている[1]．また，人口の高齢化が進行するため，高齢者に多い前立腺癌の有病率は極めて高く，患者総数はさらに増大すると考えられる[2]．したがって，前立腺癌の治療法としては，治療効果が優れているのみならず，費用が適切であることが要求される．このため，前立腺癌に対する治療法の比較にあたっては医療経済的評価が不可欠である[3]．局所前立腺癌の治療法としては，様々な選択肢が存在している．いずれの治療法にも特徴，長所，短所があるが，その比較に際しては，抗腫瘍効果，有害事象やQOL(quality of life)への影響が考慮されるべきである．

一方，治療法別の費用対効用分析においては，単なる生存期間の比較ではなく，QOL 評価を加味した質調整生存年(QALY：quality adjusted life year)の評価が重要である[4]．健康関連 QOL の評価にはさまざまな調査票があるが，いずれも複数の測定尺度を含むため QALY 算出に直接用いることはできない．QALY 算出に最も広く用いられている QOL 効用値指標は EuroQol-5D (EQ-5D) ならびに visual analogue scale (VAS)[5][6]である．そこで，前立腺癌患者におけるこれらの QOL 効用値指標の有用性を明らかにするために，包括的および前立腺癌特異的 QOL 調査票である SF-36[7][8]と EPIC[9]を用いて，EQ-5D と VAS との関連を調べた．

対象・方法

東京厚生年金病院に通院中の前立腺癌患者 81 例を対象とした．年齢は 51～82 歳，平均 70.4±6.9 歳であった．主たる治療法としては，active surveillance(PSA 監視療法) 5 例，手術療法（前立腺全摘除術）22 例，放射線療法 38 例，内分泌療法 16 例であり，放射線療法の内訳は，小線源治療 3 例，リニアック外部照射 14 例，粒子線照射 21 例であった．14 例に再発ないし再燃を認め，67 例では再発・再燃なしであった．

受付日：2010 年 5 月 12 日，受理日：2010 年 8 月 12 日

付表　患者効用値（VAS：0～100点）の算出式

VAS＝社会生活機能得点×0.007＋身体機能得点×0.143＋心の健康得点×0.1＋日常役割機能（精神）得点×0.01＋体の痛み得点×0.04＋日常役割機能（身体）得点×0.024＋活力得点×0.182＋全体的健康感得点×0.31

表1　QOL効用値とSF36の関連

SF36（下位尺度8項目）	EQ-5D		VAS	
	相関係数	有意確率	相関係数	有意確率
身体機能	0.474	0.000	0.400	0.000
心の健康	0.251	0.025	0.254	0.030
日常役割機能（身体）	0.400	0.000	0.324	0.006
日常役割機能（精神）	0.295	0.008	0.291	0.013
体の痛み	0.455	0.000	0.401	0.000
全体的健康感	0.439	0.000	0.517	0.000
活力	0.376	0.001	0.401	0.000
社会生活機能	0.232	0.037	0.362	0.002

表2　QOL効用値とEPICの関連

EPIC（下位尺度4項目）	EQ-5D		VAS	
	相関係数	有意確率	相関係数	有意確率
排尿	0.125	0.273	0.300	0.010
排便	0.138	0.232	0.091	0.452
性	0.023	0.843	−0.023	0.852
ホルモン	0.167	0.147	0.120	0.322

2008年9月から12月に自己記入式の質問表によりアンケート調査を行った．QOL効用値指標としては，EQ-5DとVASスケールを用いた．EQ-5Dは，移動の程度，身の回りの管理，ふだんの活動，痛み/不快感，不安/ふさぎ込み，の5項目について3段階で評価する質問表であり，回答結果からQOL効用値が計算される．VASは，想像できる最も悪い健康状態（0ポイント）から想像できる最も良い健康状態（100ポイント）までの直線上に，現在の健康状態を自己評価しプロットするスケールである．包括的および前立腺癌特異的QOL尺度としては，それぞれSF-36およびEPICを使用した．また，SF-36の結果からVASへの変換式（付表）を用いてQOL効用値を算出し，実際の測定値と比較した[10]．

解析はDr. SPSS II（エス・ピー・エス株式会社，東京）を用いて行った．相関の解析にはPearsonの相関分析を使用し，$p<0.05$を有意とした．

結　果

全患者におけるEQ-5DおよびVASとSF-36との関連を下位尺度項目別に示す（表1）．SF-36の全ての下位尺度において，EQ-5DおよびVASとの相関が認められた．両者の相関係数は小さいものの統計学的に有意な相関であった．SF-36の8つの下位尺度のうちでは，身体機能とEQ-5D，全体的健康感とVASとの相関係数が比較的大きかった（図1，2）．全患者におけるEQ-5Dおよび

図1　EQ-5Dと身体機能（SF-36）

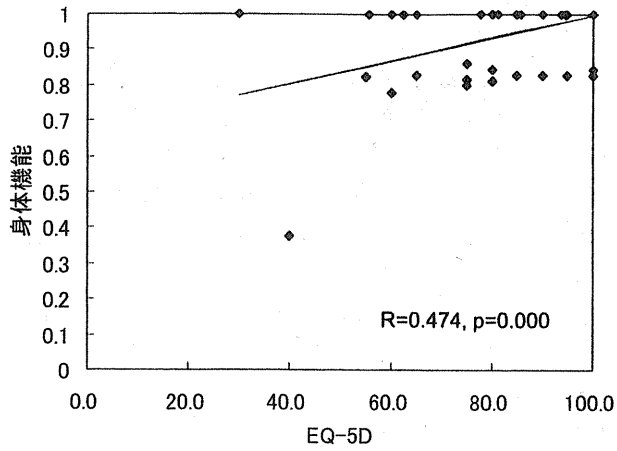


図2　VASと全体的健康感（SF-36）

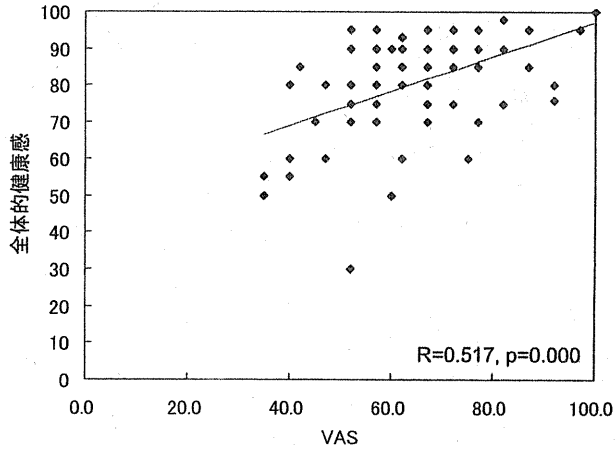
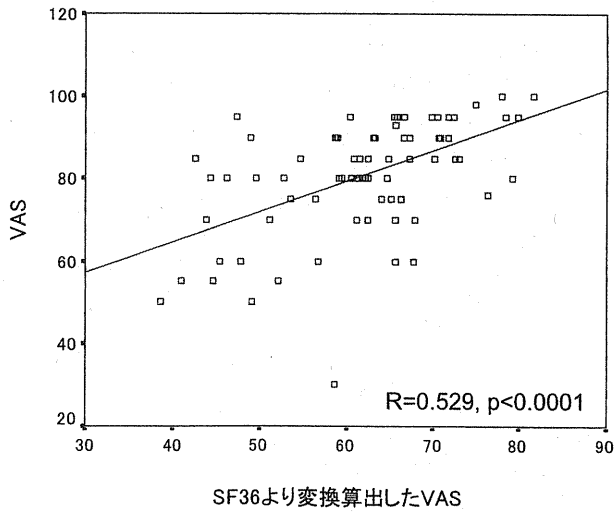


図3　SF-36より変換算出したVASとVAS実測値



VASとEPICとの関連を下位尺度項目別に示す(表2). EPICの排尿尺度とVASとの間に弱い相関を認めたが, それ以外に有意な相関を示すものはなかった. 放射線療法を受けた患者38例のみで解析を行ったところ, 同様に, EQ-5DおよびVASは, SF-36のすべての下位尺度との相関を認め, EPIC下位尺度との強い関連はなかった(data not shown).

EQ-5DとVASとの関連を検討すると, 両者には有意な相関が認められた(相関係数0.36, $p=0.0008$)[11]. 報告された方法によりSF-36の結果からVASスケールの効用値を変換算出すると, 実際に得られた値と有意で強い相関がみられた(相関係数0.53, $p<0.0001$, 図3).

年齢とEQ-5DおよびVASの間には相関はなかった. また, 治療法別にEQ-5DおよびVASを比較したが, 有意な差は認められなかった. 再発・再燃例では, EQ-5DおよびVASが低かったが, 有意な差ではなかった.

考　察

転移のない局所前立腺癌患者に対しては, 手術療法, 放射線療法, 内分泌療法, あるいはそれらの組み合わせなど, 多くの治療選択肢が提示される[12]. これらの比較においては, 抗腫瘍効果に基づく治療効果, 予測される有害事象のリスク以外に, QOLへの影響が重要視されるべきである. また, 医療経済的側面からみると, QOLへの影響を加味した質調整生存年(QALY)による評価が有用である[4].

前立腺癌患者における健康関連QOL評価には種々の質問票が用いられてきた. 包括的質問表としてはSF-36やSF-8, 癌特異的質問票ではEORTC QLQ-C30やFACT-G, 前立腺癌特異的質問表としてはFACT-PやUCLA-PCIやEPICなどが代表的である[7][13]~[17]. これらの質問票はいずれも複数の下位尺度からなっており, 全体として各患者のQOLを評価測定してQALYを算出することは困難であった. 一方, 各種治療法の費用対効用分析においては, QOLへの影響を加味した生存期間を比較することが要求される. そこで, QOL効用値指標を算出するためにEQ-5DやVASスケールが開発され使用されてきた.

今回の検討により, 前立腺癌患者において治療後のQOL効用値指標は一般的QOL評価の全ての下位尺度を反映することが明らかになった. すなわち, EQ-5DおよびVASは健康関連QOLのあらゆる側面から影響をうけていることが示唆され, 効用値評価として用いることは妥当であると考えられた. 一方, 前立腺癌に特異的なQOL下位尺度である排尿, 排便, 性, ホルモンに関しては, QOL効用値指標に大きな影響はなかった. 日本人前立腺癌患者では, 包括的QOL評価に挙げられているすべての下位尺度項目が, 自身の健康評価に重要であり, 疾患やその治療に関連する事象は容認可能であると推測される. また, SF-36のデータから変換算出したQOL効用値指標が, 直接測定したVASと強い相関を示したことより, SF-36質問表のデータが蓄積された前立腺癌患者コホートを費用対効用分析研究の対象として使用可能であることが示唆された.

以上より, 前立腺癌患者においてもEQ-5DならびにVASを用いたQOL効用値指標の算出が妥当であり, 費用対効用分析に用いる可能性が示された. 今回の検討は横断的研究であり, 患者背景や治療期間にばらつきがあったために, 治療法別にみてQOL効用値指標に有意差は認められなかった. 今後, 症例数を増やした縦断的研究により治療法別の比較が可能となると思われる. さらに, 生存期間とあわせてQALYを算出して, 各治療法を評価し比較することが望まれる.

本研究は, 平成20年度厚生労働省がん研究助成金および平成21年度厚生労働科学研究費補助金がん臨床研究事業の助成を受けて行われた.

文　献

1) 黒石哲夫, 広瀬かおる, 田島和雄：日本のがん死亡の将来予測. がん・統計白書—罹患/死亡/予後—2004, p 219—234, 篠原出版新社, 東京, 2004.
2) 大野ゆう子, 中村　隆, 大島　明：日本のがん罹患の将来推計. がん・統計白書—罹患/死亡/予後—2004, p 201—217, 篠原出版新社, 東京, 2004.
3) Peeters A., Grutters J.P., Pijls-Johannesma M., Reimoser S., De Ruysscher D., Severens J.L., Joore M.A. and Lambin P.: How costly is particle therapy? Cost analysis of external beam radiotherapy with carbon-ions, protons and photons. Radiother. Oncol., **95**, 45—53, 2010.
4) Siegel J.E., Torrance G.W., Russell L.B., Luce B.R., Weinstein M.C. and Gold M.R.: Guidelines for pharmacoeconomic studies. Recommendations from the panel on cost effectiveness in health and medicine. Pharmacoeconomics, **11**, 159—168, 1997.
5) EuroQol Group: EuroQol; a new facility for the measurement of health-related quality of life. Health Policy, **16**, 199—206, 1990.
6) 日本語版EuroQol開発委員会：日本語版EuroQolの開発. 医療と社会, **8**, 109—123, 1998.
7) Ware J.E.: The MOS 36-Item Short-Form Health Survey (SF-36) I. Conceptual framework and item selection. Med. Care, **30**, 473—483, 1992.
8) Fukuhara S., Bito S., Green J., Hsiao A. and Kurosawa K.: Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. J. Clin. Epidemiol., **51**, 1037—1044, 1998.
9) 竹上未紗, 鈴鴨よしみ, Sanda M.G., 賀本敏行, 並木俊一, 荒井陽一, 小川　修, 福原俊一, 筧　善行：Expanded Prostate Cancer Index Composite (EPIC) 日

本語版の開発：翻訳と文化的適合．日泌尿会誌，**96**，657—669，2005.

10) Shmueli A.: The relationship between the visual analog scale and the SF-36 scales in the general population: an update. Med. Decis. Making, **24**, 61—63, 2004.

11) König H.H., Born A., Matschinger H., Heinrich S., Riedel-Heller S.G., Angermeyer M.C. and Roick C.: Validity and responsiveness of the EQ-5D in assessing and valuing health status in patients with anxiety disorders. Health Qual. Life Outcomes, **8**, 47, 2010.

12) 日本泌尿器科学会：前立腺がん検診ガイドライン，金原出版，東京，2006.

13) Aaronson N.K., Ahmedzai S., Bergman B., Bullinger M., Cull A., Duez N.J., Filiberti A., Flechtner H., Fleishman S.B. and de Haes J.C.: The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J. Natl. Cancer Inst., **85**, 365—376, 1993.

14) Cella D.F., Tulsky D.S., Gray G., Sarafian B., Linn E., Bonomi A., Silberman M., Yellen S.B., Winicour P. and Brannon J.: The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J. Clin. Oncol., **11**, 570—579, 1993.

15) Esper P., Mo F., Chodak G., Sinner M., Cella D. and Pienta K.J.: Measuring quality of life in men with prostate cancer using Functional Assessment of Cancer Therapy-Prostate instrument. Urology, **50**, 920—928, 1997.

16) Litwin M.S., Hays R.D., Fink A., Ganz P.A., Leake B. and Brook R.H.: The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. Med. Care, **36**, 1002—1012, 1998.

17) Wei J.T., Dunn R.L., Litwin M.S., Sandler H.M. and Sanda M.G.: Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology, **56**, 899—905, 2000.

EVALUATION OF UTILITY INDEX OF QUALITY OF LIFE (QOL) IN PROSTATE CANCER PATIENTS: COMPARISON OF QOL UTILITY INDEX EuroQol-5D (EQ-5D) AND VISUAL ANALOGUE SCALE (VAS) WITH HEALTH-RELATED QOL QUESTIONNAIRES SF-36 AND EPIC

Koichiro Akakura[1], Kanako Matsuzaki[1], Takashi Kobayashi[1], Hiroki Kitoh[1], Ken-ichi Mizoguchi[1], Grace Tomikawa[1], Tomoyuki Takura[2] and Koichi Kawabuchi[3]

[1]*Department of Urology, Tokyo Kosei Nenkin Hospital*

[2]*Department of Health Economics and Industrial Policy, Osaka University Graduate School of Medicine*

[3]*Public Health Department of Health Science Policies, Health Care Economics, Tokyo Medical and Dental University Graduate School of Medical and Dental Sciences*

Abstract:

(Purpose) For the management of patients with localized prostate cancer, a number of therapeutic options are available. To compare the therapeutic modalities, it is important and necessary to evaluate economical aspects based on cost-effectiveness analysis. In addition, the survival time adjusted by quality of life (QOL), quality adjusted life year (QALY), is more reliable than the crude survival time. Thus, the usefulness of the commonly used QOL utility indexes, EuroQol-5D (EQ-5D) and visual analogue scale (VAS, 0–100 points), was investigated in prostate cancer patients.

(Patients and methods) A total of 81 patients with prostate cancer were included. The patients were asked to answer the four sets of questionnaires (EQ-5D, VAS, SF-36 and EPIC). The QOL utility indexes (EQ-5D and VAS) were evaluated in relation to the general and prostate cancer-specific QOL questionnaires (SF-36 and EPIC, respectively).

(Results) The results of EQ-5D and VAS were significantly correlated to all domains of the general QOL questionnaire (SF-36). On the contrary, no remarkable relationship of EQ-5D and VAS was observed with any domain (urinary, bowel, sexual or hormonal) of the prostate cancer-specific QOL questionnaire (EPIC). There was significant and close correlation between the actual values of VAS and the estimates of VAS calculated from SF-36 data ($R = 0.53$, $p < 0.0001$).

(Conclusions) The QOL utility indexes (EQ-5D and VAS) are pertinent to evaluation of QOL utility index in prostate cancer patients and can be utilized for cost-utility analysis. It is suggested that the accumulated data of SF-36 could be used by conversion to QOL utility index.

(Jpn. J. Urol 102(1): 9-13, 2011)

Keywords: prostate cancer, cost-effectiveness analysis, QALY (quality adjusted life year)

Received: May 12, 2010, Accepted: August 12, 2010

Lung Cancer 72 (2011) 355–359

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Klotho is a novel biomarker for good survival in resected large cell neuroendocrine carcinoma of the lung

Jitsuo Usuda[a,*], Shuji Ichinose[a], Taichirou Ishizumi[a], Keishi Ohtani[a], Tatsuya Inoue[a], Hisashi Saji[a], Masahiro Kakihana[a], Naohiro Kajiwara[a], Osamu Uchida[a], Masaharu Nomura[b], Hidemitsu Tsutsui[a], Tatsuo Ohira[a], Norihiko Ikeda[a]

[a] *Division of Thoracic Surgery 1, Department of Surgery 1, Tokyo Medical University, 6-7-1, Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan*
[b] *Department of Pathology, Tokyo Medical University, 6-7-1, Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan*

ARTICLE INFO

Article history:
Received 23 June 2010
Received in revised form 8 September 2010
Accepted 8 October 2010

Keywords:
Klotho
LCNEC
Lung cancer
Biomarker

ABSTRACT

Background: In terms of prognosis, large cell neuroendocrine carcinoma (LCNEC) differs distinctively from other non-small cell lung cancers, with the prognosis of LCNEC being poor, even for early-stage disease. Improvements in survival require a biomarker capable of defining a subset of patients destined to do poorly so that these patients can be targeted for additional therapies, including chemotherapy. In this study, we focused on the *Klotho* gene, which is an anti-aging gene known to be a potential tumor suppressor. We investigated whether the immunohistochemical expression of Klotho can predict survival patients with resected LCNEC.
Methods: The histological characteristics of patients receiving an initial diagnosis of LCNEC ($n=30$) at Tokyo Medical University Hospital were retrospectively reviewed, and multiple variables including stage, lymphangioinvasion, lymph node status and the expression of Klotho as identified using an immunohistochemical analysis, were assessed.
Results: Immunostaining for Klotho was mostly cytoplasmic, and Klotho expression was seen in 10 patients (33.3%) but not in 20 patients (66.7%). The expression of Klotho was significantly associated with a good outcome of resected patients with LCNEC and Klotho(−) was associated with increased LCNEC risk by multivariate analysis (hazard ratio 4.92, 95% confidence interval 1.04–23.24, $p=0.044$). Neither lymph node status nor lymphangioinvasion were significantly associated with a poor survival. However, among patients without lymph node metastasis or angioinvasion, the survival benefit of Klotho expression in the primary tumor was significantly higher, compared with that of patients without Klotho expression.
Conclusion: Klotho staining provides a new biomarker for a good outcome in patients with LCNEC, especially among patients without lymph node metastasis or lymphangioinvasion.

1. Introduction

In the World Health Organization (WHO) classification, large cell neuroendocrine carcinoma (LCNEC) is categorized as a variant of large cell carcinoma [1,2]. When LCNEC is combined with adenocarcinoma, squamous cell carcinoma, or giant cell carcinoma, it is categorized as combined LCNEC. LCNEC reportedly represents about 2–3% of all lung cancers, and the prognosis of LCNEC is poor, even for early-stage disease; the prognosis of stage I LCNEC is, in fact, poorer than that of the same stage of other non-small cell lung cancers [3–6]. Asamura et al. reported a study with a large sample size that was conducted in a retrospective, multi-institutional setting and included a critical review of the histological findings; the authors concluded that no prognostic difference was noted between LCNEC and small cell lung cancer (SCLC) [7].

Recently, we examined the clinical response of LCNEC to perioperative adjuvant chemotherapy and reported that perioperative chemotherapy may improve survival in patients with resected LCNEC [8]. Therefore, a biomarker capable of predicting either a good or poor outcome among patients with resected LCNEC is needed [9,10]. New molecular biomarkers, such as the excision repair cross-complementation group 1 protein, have attracted considerable interest with regard to the prediction of outcome among early-stage patients who have undergone resection [11].

The insulin-like growth factor (IGF) pathway is involved in the normal control of fetal development, tissue growth, and metabolism [12–14]. The IGF pathway has been implicated in the induction and maintenance of non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) [15]. Dziadziuszko et al. reported that elevated plasma levels of IGF-1 have been associated with

* Corresponding author. Tel.: +81 3 3342 6111; fax: +81 3 3349 0326.
E-mail address: jusuda@tokyo-med.ac.jp (J. Usuda).

0169-5002/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.lungcan.2010.10.008

an increased risk of lung cancer [16]. An immunohistochemical analysis demonstrated that intracellular IGF binding protein was highly expressed in lung adenocarcinomas, and the expression of IGF-messenger RNA-binding protein was higher in LCNECs than in SCLCs [17,18]. A number of IGF receptor inhibitors, including monoclonal antibodies and small molecule inhibitors, are currently undergoing testing in clinical trials [19,20].

Recently, the Klotho gene, which is a 1014-amino acid single-pass transmembrane protein first identified as an anti-aging gene, has been shown to function as an inhibitor of IGF pathways, and is a potential tumor suppressor in breast cancer [21–25]. Therefore, we hypothesized that the *Klotho* gene may play an important role in regulating cell growth and LCNEC proliferation and may predict the survival of patients with LCNEC. In this study, we investigated whether the immunohistochemical expression of Klotho can predict survival in resected LCNEC.

2. Materials and methods

2.1. Patient selection

Of 1400 patients who underwent surgical resection for primary lung cancer between January 1999 and December 2004 at our institution, 30 patients with LCNEC were enrolled in this study. According to the histological typing of lung and pleural tumors in the WHO International Histological Classification of Tumors, 3rd edition, LCNEC is classified as a variant of large cell carcinoma (LCC) [1–4]. Because previous studies reported a similar prognosis for pure and combined LCNEC, both forms are included in the present study [5–7]. An immunohistochemical analysis was performed to confirm the neuroendocrine differentiation of the tumors. For a definitive diagnosis of LCNEC, formalin-fixed paraffin sections were stained using a panel of neuroendocrine markers that included chromogranin A (CGA) (1:1500, Dako), synaptophysin (SYN) (1:100, Dako), and neural cell adhesion molecule (NCAM) (1:50, Novacastra), using standard methods [5–8]. All the histological specimens were diagnosed by experienced pathologists in the Department of Pathology, Tokyo Medical University Hospital. This study was conducted with the approval of the Ethical Committee of Tokyo Medical University.

2.2. Immunostaining for Klotho

Immunohistochemical staining was performed on 4-μM formalin-fixed, paraffin-embedded tissue sections [6,7,9]. The slides were deparaffinized in xylene and dehydrated in a graded ethanol series. Endogenous peroxidase was blocked with 0.3% H_2O_2 in methanol for 10 min. All the slides were heated to 95 °C by exposure to microwave irradiation for 20 min. The slides were then cooled for 1 h at room temperature and washed in phosphate buffer solution (PBS). Non-specific binding was blocked by pre-incubation with 1% BSA for 30 min. After washing with PBS, the slides were incubated for 1 h at room temperature with anti-Klotho antibody (kindly provided by Prof. Nabeshima, Kyoto Univ.). Antibody staining was considered positive if >10% of the tumor cells were stained, based on the use of a 10% cutoff level in several previous studies [26]. All the slides were examined by two observers without knowledge of the patients' clinical data [24–26].

2.3. Statistics

Clinical information was extracted from the medical records. The disease stage was based on the TNM classification using the International Union Against Cancer (UICC) staging system. Statistical analyses were performed using SPSS for Windows. The Kaplan–Meier method was used to determine survival [26–29].

Table 1
Clinicopathological characteristics of 30 patients with LCNEC.

Patient characteristics	No. of patients
No. of cases (%)	30
Age (mean)	40–82 (69.8)
Gender	
Male	27
Female	3
Surgical procedure	
Lobectomy	29
Pneumonectomy	1
p-Stage	
IA	2
IB	12
IIA	3
IIB	3
IIIA	4
IIIB	5
IV	1
Perioperative chemotherapy	
Yes	18
No	12
Alive	
Yes	12
No	18

Overall survival was defined as the time (in months) from the date of surgery until the time of death. We assessed the univariate effect of each variable on survival using the log-rank test for categorical predictors or the univariate Cox model for continuous predictors [26–29]. Variables were considered significant in the univariate analyses. Lymph node invasion, Klotho expression, and lymphangio invasion were candidates in this final model of 0.05 for entry into the model.

3. Results

The clinicopathologic characteristics of the patients are listed in Table 1. Their mean age at the time of surgery was 69.8 years (range, 40–82 years). Twenty-seven patients were men, and 3 patients were women. The surgical procedures that were performed included 29 lobectomies and 1 pneumonectomy. The distribution of pathological staging was 2 (6.7%) patients with stage IA, 12 (40%) with stage IB, 3 (10%) with stage IIA, 3 (10%) with stage IIB, 4 (13.3%) with stage IIIA, 5 (16.6%) with stage IIIB and 1 (3.3%) with stage IV. The median follow-up period was 45 months (range, 12–96 months); during the study period, 18 patients (60%) died and 12 patients survived for more than 60 months. We examined Klotho expression using an immunohistochemical analysis. As Fig. 1 shows, immunostaining for Klotho was mainly observed in the cytoplasm, and Klotho expression was seen in 10 patients (33.3%) but not in 20 patients (66.7%). We investigated whether Klotho staining might predict a good outcome. Fig. 2 shows the Kaplan–Meier survival curve for Klotho-positive patients (10 patients) and for Klotho-negative patients (20 patients). The expression of Klotho was significantly associated with survival in patients with resected LCNEC ($p = 0.013$). Klotho-negative patients with LCNEC had a worst overall survival and Klotho expression was an independent prognostic factor by multivariate analysis (hazard ratio = 4.92; 95% confidence interval: 1.04–23.24; $p = 0.044$) (Table 2). Neither lymph node status nor lymphangioinvasion were significantly associated with poor survival, as shown in Figs. 3 and 4. In this study, lymph node status was not a prognostic factor by multivariate analysis (hazard ratio = 1.99; 95% confidence interval: 0.72–5.47; $p = 0.185$) (Table 2). Among the nine patients with pathological stage IB, six patients without Klotho expression died and three patients with Klotho expression were still alive. However, among the 14 patients with a negative lymph node status, including

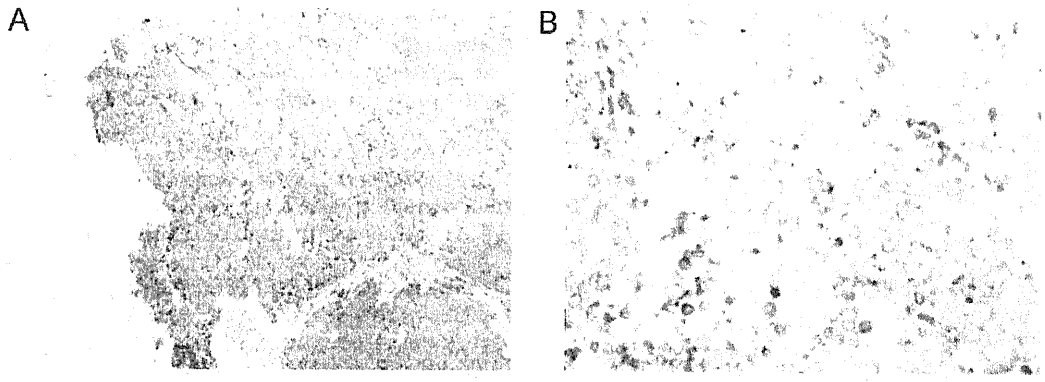


Fig. 1. Immunohistochemical staining with anti-Klotho antibody (KM2906) in resected LCNEC (A, 40×; B, 400×).

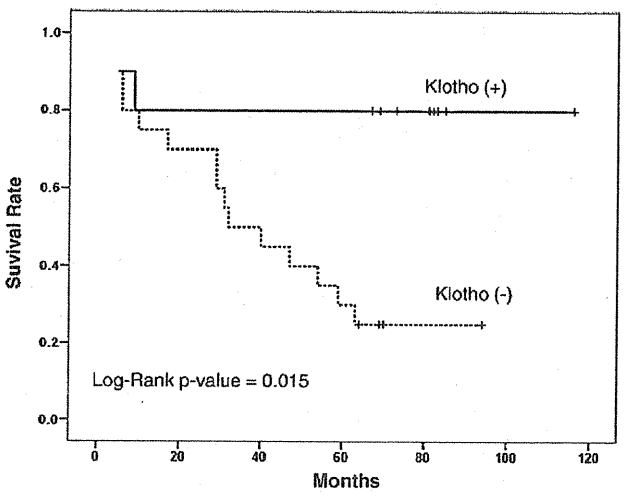


Fig. 2. Kaplan–Meier survival plot showing the survival of 30 patients with LCNEC who were positive ($n=10$) or negative ($n=20$) for Klotho expression. Patients with LCNEC and Klotho (+) expression have a significantly better prognosis than those with Klotho (−) expression ($P=0.015$).

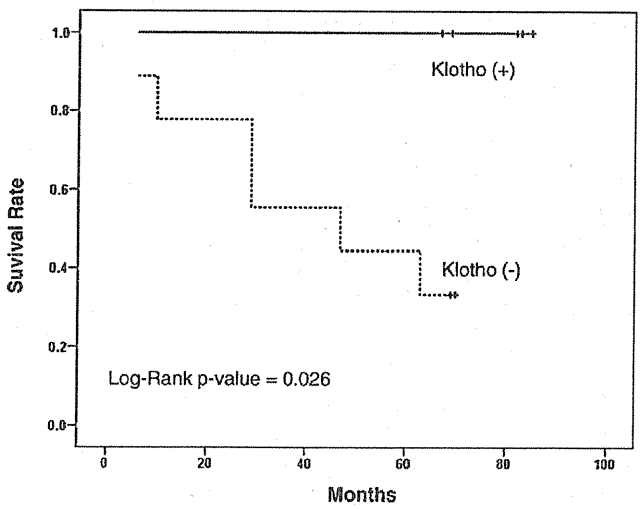


Fig. 3. Kaplan–Meier survival plot showing the survival of 14 patients with LCNEC but without lymph node metastasis. A significant difference in survival was observed between patients with Klotho (+) expression ($n=5$) and those with Klotho (−) expression ($n=9$). The prognosis of the patients with Klotho (+) expression was better than that of the patients with Klotho (−) expression ($P=0.026$).

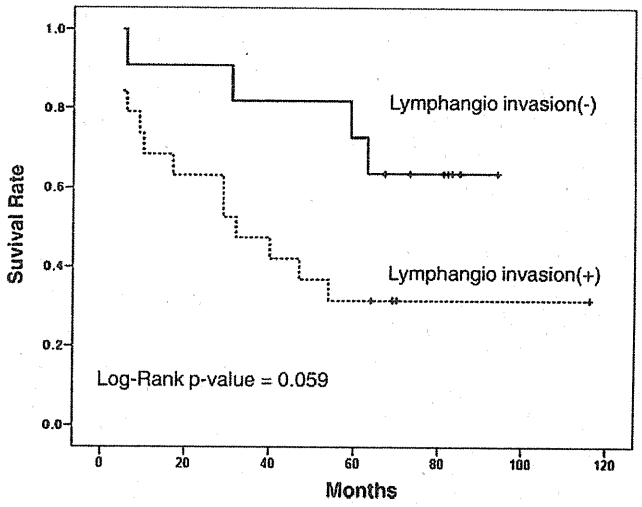


Fig. 4. Kaplan–Meier survival plot showing the survival of 30 patients with LCNEC and lymphangioinvasion (+) ($n=19$) or lymphangioinvasion (−) ($N=11$). Lymphangioinvasion did not significantly affect survival ($P=0.059$).

those with p-stage IA, IB, and IIA, 6 patients died and 8 patients were still alive. Of these 14 patients, 5 patients had Klotho expression and were alive and 9 patients did not have Klotho expression. Fig. 3 shows that among the 14 patients without lymph node metastasis, the survival curve of patients with Klotho expression in their primary tumors was significantly higher than that of patients without Klotho expression.

Vascular or lymphatic vessel invasion have both been suggested as potential markers of a poor outcome among stage IA

Table 2
Parameters related to overall survival (multivariate analysis).

	Cases	HR (95% CI)	P^a value
Klotho expression			
Positive	10	1	
Negative	20	4.92 (1.04–23.24)	0.044
Lymph node			
Meta (−)	14	1	
Meta (+)	16	1.99 (0.72–5.47)	0.185
Lymphangioinvasion			
Absent	11	1	
Present	19	1.93 (0.61–6.13)	0.264
Perioperative chemotherapy			
Yes	20	1	
No	10	1.98 (0.73–5.36)	0.181

[a] Tested in Cox regression model with Klotho expression, lymph node, lymphangio invasion, chemotherapy. HR, hazard ratio; CI, confidential interval.

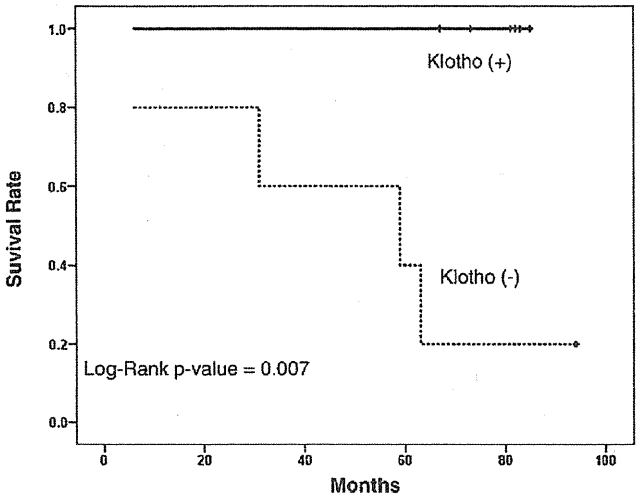


Fig. 5. Kaplan–Meier survival plot showing the survival of 11 patients with LCNEC but without lymphangioinvasion. A significant difference in survival was observed between the patients with Klotho (+) expression ($N=6$) and those with Klotho (−) expression ($N=5$). The prognosis of the patients with Klotho (+) expression was better than that of those with Klotho (−) expression ($P=0.007$).

patients, but the results have been controversial and inconsistent [7–10]. In this study, no significant difference in outcome was observed between patients with lymphangioinvasion and those without lymphangioinvasion, as shown in Fig. 4. Therefore, we focused on patients without lymphangioinvasion. As shown in Fig. 5, among the lymphangioinvasion-negative patients, the survival rate was significantly higher in those with Klotho expression in their primary tumors than in those without Klotho expression. These results suggest that the survival of patients with LCNEC who are lymph node negative or lymphangioinvasion negative might be strongly influenced by the presence of Klotho expression, and Klotho immunostaining was a highly significant prognostic marker for patients with resected LCNEC.

4. Discussion

Patients with LCNEC have a very poor prognosis, and Asamura et al. reported that the 5-year survival rates of patients with all disease stages were 40.3% for LCNEC and 35.7% for SCLC, with no significant difference noted between LCNEC and SCLC [7]. Considering the 5-year survival rate of stage I non-small cell lung cancer, the LCNEC histology is associated with a dismal prognosis, and LCNEC has almost the same prognosis as SCLC [7]. These two histologies also share similar clinicopathological features, such as a smoking history and male prevalence, and incomplete resection, and nodal involvement are significant prognostic factors for both LCNEC and SCLC.

Recently, the potential uses of neuronatin (NNAT), cytokeratin 7 (CK7), CK18, E-cadherin and β-catenin as differential markers for LCNEC and SCLC have been reported [7–11]. The existence of prognostic factors capable of predicting the survival rate of patients with LCNEC after curative resection remains uncertain. In the present study, although the number of resected LCNEC was relatively small, our data indicate that Klotho expression may predict the good outcome of patients with LCNEC and that Klotho expression is a prognostic factor after curative resection, and our data need to be verified in more larger cases.

Wolf et al. identified Klotho as a potent tumor suppressor gene in breast cancer, and Klotho expression may serve as a predictor of breast cancer risk among *BRCA 1* mutation carriers [24]. Moreover, Wolf et al. reported that Klotho overexpression specifically reduces the colony formation of breast cancer cell, and most of Klotho's growth inhibitory activities in the breast are mediated by the secreted protein [24,25]. Klotho expression may play an important role in improving the treatment outcome of patients with LCNEC.

We retrospectively analyzed the association between perioperative chemotherapy and the survival benefit of LCNEC and reported that perioperative chemotherapy is needed to improve the survival of patients with resected LCNEC [8]. Surgical resection alone did not appear to improve the prognosis of patients with LCNEC as previous reports [30,31]. In the present study, no significant difference between Klotho expression and the survival benefit of perioperative chemotherapy was noted for patients with LCNEC. Although the number of patients with LCNEC is relatively small and randomized controlled trials demonstrating a survival benefit of adjuvant chemotherapy are difficult to conduct, the association between Klotho expression and the survival benefit of perioperative chemotherapy for LCNEC should be further evaluated in larger multi-institutional trials.

In summary, we demonstrated that Klotho expression has a significant prognostic value in resected LCNEC of the lung. In the future, the evaluation of this marker may improve the personalization of the treatment in this aggressive histotype of lung cancer.

Conflict of interest statement

There was no financial support for the authors nor does any author have a financial relationship with a commercial entity that has an interest in this manuscript.

Acknowledgement

This study was supported in part by a Grant-in-Aid for Scientific Research (C) from Japan Society for the Promotion of Science (JSPS) (to JU) (KAKENHI 21591826).

References

[1] Travis WD, Linnoila RI, Tsokos MG, Hitchcock CL, Cutler GB, Nieman L, et al. Neuroendicrine tumors of the lung with proposed criteria for large-cell neuroendocrine cacinomas. Am J Surg Pathol 1991;15:529–53.
[2] Travis WD, Corrin B, Shimosato Y. Histological typing of lung and pleural tumors. In: World Health Organization International Hisotological Classification of Tumors. 3rd ed. Berlin: Springer Verlag; 1999.
[3] Desler CM, Ritter JH, Patterson GA, Ross E, Bailey MS, Wick MR, et al. Clinicalpathologic analysis of 40 patients with large cell neuroendocrine carcinoma of the lung. Ann Thorac Surg 1997;63:180–5.
[4] Cooper WA, Thourani VH, Gal AA, Lee RB, Mansour KA, Miller JI. The surgical spectrum of pulmonary neuroendocrine neoplasms. Chest 2001;119:14–8.
[5] Iyoda A, Hiroshima K, Toyozaki T, Haga Y, Baba M, Fujisawa T, et al. Clinical characterization of pulmonary large cell neuroendocrine carcinoma and large cell carcinoma with neuroendocrine morphology. Cancer 2001;91:1992–2000.
[6] Takei H, Asamura H, Maeshima A, Suzuku K, Kondo H, Niki T, et al. Large cell neuroendocrine carcinoma of the lung: a clinicopathologic study of eighty-seven cases. J Thorac Cardiovasc Surg 2002;124:285–92.
[7] Asamura H, Kameya T, Matsuno Y, Noguchi M, Tada H, Ishikawa Y, et al. Neuroendocrine neoplasm of the lung: a prognostic spectrum. J Clin Oncol 2006;24:70–6.
[8] Saji H, Tsuboi M, Matsubayashi J, Miyajima K, Shimada Y, Imai K, et al. Clinical response of large cell neuroendocrine carcinoma of the lung to perioperative adjuvant chemotherapy. Anticancer Drugs 2010;21:89–93.
[9] Paci M, Cavazza A, Annessi V, Putrino I, Ferrari G, De Franco S, et al. Large cell neuroendocrine carcinoma of the lung: a 10-year clinicopathologic retrospective study. Ann Thorac Surg 2004;77:1163–7.
[10] Okubo C, Minami Y, Tanaka R, Uchihara T, Anami Y, Furuya S, et al. Analysis of differentially expressed genes in neuroendocrine carcinimas of the lung. J Thorac Oncol 2006;1:780–6.
[11] Freidin B, McShane LM, Korn EL. Randomized clinical trials with biomarkers: design issues. J Natl Cancer Inst 2010;102:152–60.
[12] Bartucci M, Morelli C, Mauro L, Ando S, Surmacz E. Differential insulin-like growth factor I receptor signaling and function in estrogen receptor (ER)-positive MCF-7 and ER-negative MDA-MB-231 breast cancer cells. Cancer Res 2001;61:6747–54.

[13] Wolf I, Sadetzki S, Gluck I, Oberman B, Ben-David M, Papa MZ, et al. Association between diabetes mellitus and adverse characteristics of breast cancer at presentation. Eur J Cancer 2006;42:1077–82.
[14] Yee D. Targeting insulin-like growth factor pathways. Br J Cancer 2006;94:465–8.
[15] Zhang H, Fagan DH, Zeng X, Freeman KT, Sachdev D, Yee D. Inhibition of cancer cell proliferation and metastasis by insulin receptor downregulation. Oncogene 2010;29:2517–27.
[16] Dziadziuszko R, Camidge R, Hirsch FR. The insulin-like growth factor pathway in lung cancer. J Thorac Oncol 2008;3:815–8.
[17] London SJ, Yuan JM, Travlos GS, Gao YT, Wilson RE, Ross RK, et al. Insulin-like growth factor 1, IGF-binding protein 3, and lung cancer risk in a prospective study of men in China. J Natl Cancer Inst 2002;94:749–54.
[18] Chang YS, Wang L, Liu D, Mao L, Hong WK, Khuri FR, et al. Correlation between insulin-like growth factor-binding protein 3 promoter methylation and prognosis of patients with stage I non-small cell lung cancer. Clin Cancer Res 2002;8:3669–75.
[19] Cohen BD, Baker DA, Soderstrom C, Tkalcevic G, Rossi AM, Miller PE, et al. Combination therapy enhances the inhibition of tumor growth with fully human anti-type 1 insulin-like growth factor receptor monoclonal antibody CP-751, 871. Clin Cancer Res 2005;11:2063–73.
[20] Ji QS, Mulvihill MJ, Rosenfeld-Franklin M, Cooke A, Feng L, Mak G, et al. A novel, potent, and selective insulin-like growth factor-1 receptor kinase inhibitor blocks insulin-like growth factor-1 receptor signaling in vitro and inhibits insulin-like growth factor-1 dependent tumor growth in vivo. Mol Cancer Ther 2007;6:2158–67.
[21] Kuro-o M, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T, et al. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. Nature 1997;390:45–51.
[22] Matsumura Y, Aizawa H, Shiraki-Iida T, Nagai R, Kuro-o M, Nabeshima Y. Identification of the human klotho gene and its two transcripts encoding membrane and secreted Klotho protein. Biochem Biophys Res Commun 1998;242:626–30.
[23] Kurosu H, Yamamoto M, Clark JD, Pastor JV, Nandi A, Gurnari P, et al. Suppression of aging in mice by the hormone Klotho. Science 2005;309:1829–33.
[24] Wolf I, Levanon-Cohen S, Bose S, Ligumsky H, Sredni B, Kanety H, et al. Klotho: a tumor suppressor and modulator of the IGF-1 and FGF pathways in human breast cancer. Oncogene 2008;27:7094–105.
[25] Wolf I, Laitman Y, Rubinek T, Abramovitz L, Novikov I, Beeri R, et al. Functional variant of *KLOTHO*: a breast cancer risk modifier among BRCA1 mutation carriers of Ashkenazi origin. Oncogene 2010;29:26–33.
[26] Dhillon T, Mauri FA, Bellezza G, Cagini L, Barbareschi M, North BV, et al. Overexpression of the mammalian target rapamycin; a novel biomarker for poor survival in resected early stage non small cell lung cancer. J Thorac Oncol 2010;5:314–9.
[27] Lee YJ, Kim HT, Han JY, Yun T, Lee GK, Kim HY, et al. First-line gefitinib treatment for patients with advanced non-small cell lung cancer with poor performance status. J Thorac Oncol 2010;5:361–8.
[28] Nakao M, Yoshida J, Ishii G, Kawase A, Maeda R, Aokage K, et al. Prognostic impact of node involvement pattern in pulmonary pN1 squamous cell carcinoma patients. J Thorac Oncol 2010;5:504–9.
[29] Ignatius SH, Ziogas A, Zell JA. Primary signet-ring carcinoma (SRC) of the lung: a population-based epidemiologic study of 262 cases with comparison to adenocarcinoma of the lung. J Thorac Oncol 2010;5:420–7.
[30] Yamazaki S, Sekine I, Matsuno Y, Takei H, Yamamoto N, Kunitoh H, et al. Clinical responses of large cell neuroendocrine carcinoma of the lung to cisplatin-based chemotherapy. Lung Cancer 2005;49:217–23.
[31] Iyoda A, Hiroshima K, Moriya Y, Takiguchi Y, Sekine Y, Shibuya K, et al. Prospective study of adjuvant chemotherapy for pulmonary large cell neuroendocrine carcinoma. Ann Thorac Surg 2006;82:1802–7.

doi:10.1510/icvts.2010.251652

INTERACTIVE CARDIOVASCULAR AND THORACIC SURGERY

Interactive CardioVascular and Thoracic Surgery 12 (2011) 112-116

www.icvts.org

Work in progress report - Thoracic non-oncologic

Appropriate set-up of the da Vinci® Surgical System in relation to the location of anterior and middle mediastinal tumors

Naohiro Kajiwara[a,*], Masatoshi Kakihana[a], Norihiko Kawate[b], Norihiko Ikeda[a]

[a]Department of Surgery, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan
[b]Department of Health Science and Social Welfare, Waseda University School of Human Sciences, Tokyo 160-0023, Japan

Received 12 August 2010; received in revised form 22 October 2010; accepted 26 October 2010

Abstract

The da Vinci® Surgical System (dV) and its later version [da Vinci S® Surgical System (dVS)] have been used only in very few cases in selected thoracic surgical areas in Japan. Recently, we used the dV and dVS for various types of anterior and middle mediastinal tumors in clinical practice. We report our experience, and review the settings which depended on tumor location. Six patients gave written informed consent to undergo robotic surgery using the dV or dVS. We evaluated the feasibility, safety and appropriate settings of this system for the surgical treatment of mediastinal tumors. Tumor dissection was performed by two specialists in thoracic surgery certified to use the dV and dVS, and another specialist who acted as an assistant. We were able to access difficult-to-reach areas like the mediastinum. All the resected tumors were classified as benign tumors histologically. Crucial to the success of these operations was the set-up of the dV, which varied according to the location of mediastinal tumors. Robotic surgery enables various types of mediastinal tumor dissection more safely and easily than conventional video-assisted thoracoscopic surgery (VATS). The dV requires the appropriate set-up configuration, which varies according to the location of the mediastinal tumor.

Keywords: Robotic surgery; da Vinci® Surgical System; Mediastinal tumor

1. Introduction

According to a 2007 national survey of 1914 institutions by the Japanese Association for Thoracic Surgery [1], 60.4% (33,696) of all thoracic surgery cases were performed using video-assisted thoracoscopic surgery (VATS), out of a total of 55,832 cases of all general thoracic surgery. This report also showed that VATS was used in 36.9% of mediastinal tumors. Standard thoracotomy is generally highly invasive and can involve difficult postoperative management. While VATS is less invasive than standard thoracotomy, there is also the problem of postoperative pain caused by the inevitable leverage of instruments on the chest wall during the procedure, and the difficulty of manipulation in the mediastinum. The development of robotic surgery raises the question of whether it can yield comparable results in terms of safety and curativity for thoracic disease, such as mediastinal tumors. The da Vinci® Surgical System (dV) and da Vinci S® Surgical System (dVS) (Intuitive Surgical, Inc, Sunnyvale, CA, USA) have been used in very few cases for the treatment of mediastinal tumors in Japan [2, 3] and the new type of dV, the dVS, has never been reported for as having been used in the treatment of mediastinal tumors in Japan.

We set out to establish a procedure for resection of various types of mediastinal tumors.

2. Methods

2.1. Patients

All patients who underwent mediastinal tumor dissection gave written informed consent to receive robotic surgery using the dV (first two cases) or dVS (last four cases), and the Institutional Review Committees of each institution gave their permission. The total number of patients was six cases, consisting of three pericardial cysts, one giant pericardial cyst, one bronchogenic cyst and one thymic cyst (both of the latter being located in the middle mediastinum). Procedures were performed between March and July 2010.

2.2. The dV and surgical procedure

The dV and the dVS (not the latest version with a separately-controlled robotic arm) (hereafter dV) consist of a surgeon's console connected to the body of the dV, a manipulator unit with three instrument arms, including a central arm to guide the endoscope camera, to which the surgeon's movements are transmitted [4, 5].

Typically, three 2-cm incisions and one 1-cm incision for an accessory port access are made. A camera incision is

*Corresponding author. Tel.: +81 3-3342-6111 (Ext. 5070); fax: +81 3-3349-0326.
E-mail address: naokjw@topaz.ocn.ne.jp (N. Kajiwara).

placed in the sixth to seventh intercostal space on the mid-postaxillary line. Another two incisions are placed in the appropriate intercostal spaces, depending on the location of the mediastinal tumor. An additional 1-cm incision is made for additional accessory port access.

To widen the typically narrow working thoracic space, CO_2 inflation of the thoracic space (high flow; 8–10 mmHg) was performed during the dV procedure.

3. Results

Tumor dissection was performed by two specialists in thoracic surgery certified by the manufacturer to use the dV, and another specialist in thoracic surgery was an assistant (Figs. 1 and 2). The dV was used for cases 1 and 2, and the dVS was used for cases 3–6. All the resected tumors were classified as benign cysts, such as pericardial cyst, bronchogenic cyst and thymic cyst histologically, as shown in Table 1 and Fig. 3.

For these procedures, the semi-lateral decubitus position, which enables an approach from the front side in cases where emergency access is required was found to be optimal. One table surgeon (assistant), working on the setting and replacement of instrument arms, was positioned opposite to the procedural side of the patient. Another surgeon was located behind the patient as a second assistant in case thoracotomy became necessary, as these were our first cases with the dV. The operating surgeon manipulated the dVS from the console, located apart from the operation table, but pointing in the same direction as the camera.

Details of the positioning of all units are shown in Fig. 2, and the instrument-arm placement, which depends on the localization of the mediastinal tumors, is shown in Fig. 3.

The average time to set up the dVS was 15.3 min, the average procedure time from roll-in to roll-out was 69 min.

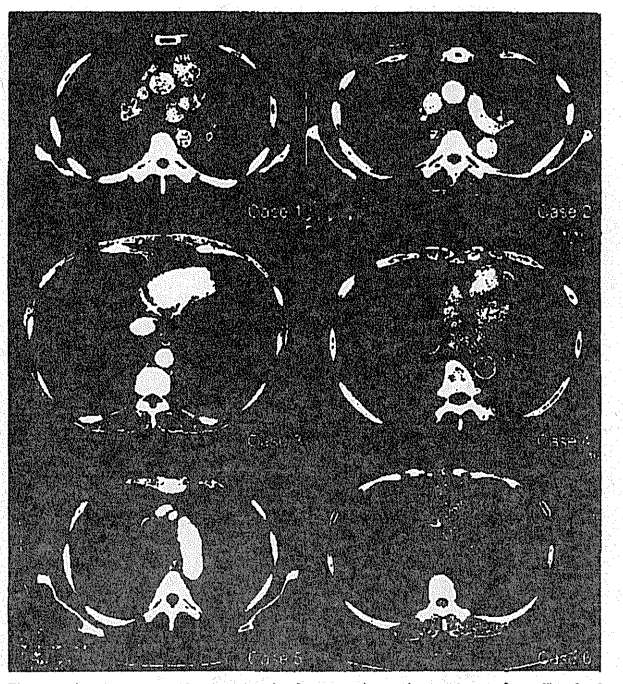


Fig. 1. Chest computed tomography images show the variety of mediastinal tumors in cases 1–6.

The average working time of the thoracic surgeons was 50.6 min, and average overall operation time was 111 min, from the start of skin incisions to wound closing, as shown in Table 1. The average total amount of bleeding was 25.8 ml.

The surgical procedure and techniques of robotic surgery closely resemble the standard open thoracotomy proce-

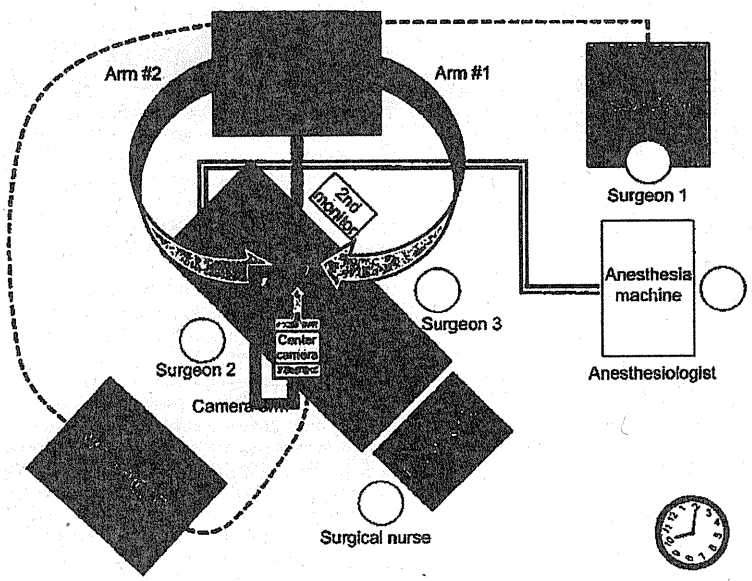


Fig. 2. Appropriate positioning of the dV, other instruments, thoracic surgeons, an anesthesiologist and a surgical nurse. The direction of the patient was based on clock positioning. The dV consists of a surgeon's console connected by wires to the body of the dV and a manipulator unit with three instrument arms. The dVS was rolled in from the 2 o'clock direction. dV, da Vinci® Surgical System; dVS, da Vinci S® Surgical System.

Table 1. The contents and results of operation using the dV

Patient no.	Sex	Age (years)	Pathological diagnosis	Side	Location	Tumor size (mm)	Total operation time (m)	Time of da Vinci setting (m)*	Time of roll in-to-out (m)	da Vinci working time (m)	Bleeding (g)	Complication	Postoperative pain (VAS)†	Drainage time (days)	Hospitalization time (days)
1	M	44	Pericardial cyst	Right	Upper anterior	31×64	105	17	73	56	50	None	0	2	11‡
2	M	47	Thymic cyst	Left	Upper anterior	31×24×16	114	18	78	60	65	None	0	2	6
3	M	48	Pericardial cyst	Right	Lower anterior	42×34×22	122	22	70	40	10	None	0	2	4
4	M	60	Giant pericardial cyst	Right	Middle–lower anterior	131×94×94	118	15	65	45	10	None	0	2	6
5	F	54	Bronchogenic cyst	Right	Upper anterior	40×35	145	10	99	88	10	None	0	2	5
6	F	53	Pericardial cyst	Right	Lower anterior	41×25	62	10	29	15	10	None	0	3	5
Average		51					111	15.3	69	50.6	25.8		0	2.2	6.2

*'Time of dV setting' means the time from roll-in to the start of use of the dV, †VAS (visual analog scale); we evaluated the scale at the time of discharge from hospital, ‡Longer hospitalization at request of patient.

Fig. 3. This figure shows the appropriate placement of instrument arm ports and mediastinal tumor location in each case (cases 1–6). ① Shows the position of the 3-D camera port, ② shows the position of the instrument arm #2 port, ③ shows the position of the instrument arm #1 port and ④ shows the position of the accessory port. Case 1: left semi-lateral position (2 o'clock) ① seventh intercostal in mid-axillary line, ② fifth intercostal in posterior–axillary line, ③ fifth intercostal in anterior–axillary line; case 2: right semi-lateral position (10 o'clock) ① seventh intercostal in mid-axillary line, ② fourth intercostal in anterior–axillary line, ③ sixth intercostal in posterior–axillary line; case 3: left semi-lateral position (3 o'clock) ① seventh intercostal in mid-axillary line, ② fourth intercostal in mid-anterior axillary line, ③ eighth intercostal in anterior–axillary line, ④ sixth intercostal in mid-posterior axillary line, (④ a was only marked, not opened); case 4: left semi-lateral position (4 o'clock) ① sixth intercostal in mid-axillary line, ② fourth intercostal in anterior–axillary line, ③ eighth intercostal in mid-anterior axillary line, ④a ninth intercostal in posterior–axillary line, ④b fifth intercostal in mid-axillary line, (④b was only marked, not opened); case 5: left semi-lateral position (2 o'clock) ① seventh intercostal in mid-axillary line, ② fifth intercostal in mid-posterior axillary line, ③ fifth intercostal in anterior–axillary line, ④ seventh intercostal in posterior–axillary line; case 6: left semi-lateral position (4 o'clock) ① fifth intercostal in mid-posterior axillary line, ② third intercostal in anterior–axillary line, ③ eighth intercostal in mid-axillary line, ④ seventh intercostal in posterior–axillary line.

dure, in spite of the fact that the robotic surgery is guided by a video-assisted system.

4. Discussion

The VATS technique, generally accepted as a safe procedure in patients with mediastinal tumors, has the advantages of minimally-invasive surgery (MIN) with little tissue trauma, short hospitalization, less pain and good cosmetic results, compared with standard thoracotomy [6]. However, conventional VATS is challenged by the narrow anatomical structure of the mediastinum, the most severe aspect being the limited movement of VATS instruments.

Telerobotic surgery evolved in the US to improve standard MIN techniques, and the dV has been approved by the US Food and Drug Administration. About 1500 dVS are used worldwide in various fields, such as cardiovascular thoracic surgery, urology, gynecology and gastrointestinal surgery. However, in Japan only 13 hospitals possessed this system as of the end of June 2010.

This system is now used frequently in the clinical setting [7–12]. Surgery using the dV is performed with robot arms inserted via the surgical ports as in conventional VATS, with an endoscope which provides a three-dimensional (3-D) high-resolution binocular view of the surgical field, and is capable of a 12-fold enlarged view. This enhances safety compared with conventional VATS for almost all surgeons.

The operative arm of the dV, the EndoWrist® instrument system, with maneuverability capable of seven degrees of freedom and two degrees of axial rotation, replicates human wrist-like movements. The EndoWrist® system has various functions, including three-step motion scaling (no scale 2:2, fine 3:1, ultra fine 5:1) and eliminates the physiological vibrations of the hands of the surgeon.

If the dV is used in mediastinal surgery, the field of thoracic surgery will benefit from the combined advantages of standard thoracotomy and VATS [13–15]. However, very few institutions perform robot-assisted thoracic surgery routinely. In particular, there are few reports of cases of robotically-operated mediastinal tumors in Japan [2, 3]. Several factors seem to be related to this. First, the dV is not yet approved by the Japanese Ministry of Health, Labor and Welfare, and second, it is expensive.

We set out to determine the feasibility and safety of the dVS in performing mediastinal tumor dissection clinically and to contribute to the future establishment of guidelines for operation and certification.

Our operation time was similar to conventional VATS for tumor resection. The total amount of bleeding during surgery was 10–65 ml (average 25.8 ml), similar to conventional VATS for mediastinal tumors. Dissection of mediastinal tumors with this system enables accurate, simple and safe operation by the surgeon, because the range of motion of the robot arms within small spaces, such as the thorax is extremely extensive.

The learning curve for dV setting and manipulation time is very short, especially for those experienced in conventional VATS for thoracic surgery. This is the greatest difference from conventional VATS, in which the surgery cannot be performed safely if the surgeon is not accomplished at operating long rigid instruments. This is one reason why robotic surgery is regarded as a continuation of the evolution of standard thoracotomy. However, the differences between robotic surgery and standard thoracotomy include the advantages of the 12-fold enlarged operative field of robotic surgery, and the ability to access difficult-to-reach areas like the mediastinum.

The relation between the tumor location and angle of the dVS is also crucial in the pre-setting stage. The most important part of these operations is setting the positions and direction of the dV as shown in Fig. 2, and the instrument-arm points depended on the location of mediastinal tumors as shown in Fig. 3. Alteration of the positions of the dV is necessary for each case of mediastinal tumor, and port placement is the most important part of the procedure for mediastinal tumors, as shown in Fig. 3.

Four surgical ports (all skin incisions were about 2 cm) were used in this procedure. One port was used for the 3-D camera placed in the sixth to seventh intercostal space on the mid-axillary line, another two ports were used for the right arm (scissors) and the left arm (a grasper) placed in different intercostal spaces as shown in Fig. 3. If the tumor was located in the right upper-middle zone of the mediastinum (cases 1 and 5), the patients would be positioned in a left semi-lateral position. The dVS was rolled in from the direction of 2 o'clock. The camera port was positioned at the sixth to seventh intercostal space on the mid-axillary line, the right arm positioned at the fourth to fifth intercostal space on the posterior axillary line, and the left arm positioned at the fifth to sixth intercostal space in the anterior–axillary line. However, if the tumor was located in the lower zone of the mediastinum (cases 4 and 6), the dVS was rolled-in from the direction of 4 o'clock. Then, the camera-port was positioned at the fifth to sixth intercostal space on the mid-axillary line, the right arm positioned at the third to fourth intercostal space in the anterior–axillary line and the left arm positioned at the eighth intercostal space in the mid-anterior axillary line. For tumors located in the left thorax, the system and instrument ports positions were reversed.

The fourth port, used as an assisting trocar for other devices, was placed at least 5 cm apart from the other ports, to prevent instrument arms clashing. The positioning of accessory ports, also shown in Fig. 3, was adjusted in every case for optimal manipulation. The use of various types of surgical arms was attempted for tumor dissection, such as the monopolar curved scissors, Maryland bipolar forceps and Cadiere forceps. In our experience, most manipulations were performed with the monopolar curved scissors for arm #1 and Cadiere forceps for arm #2. This was very useful for tumor resection, allowing free movement, and the 3-D high-vision camera contributed to tumor dissection at the mediastinum with a visual sensation similar to open standard thoracotomy, which is an advantage over conventional VATS.

Other devices, such as a continuous-suction and washing device are also very useful in robotic surgery.

In case 4 (giant pericardial cyst), drainage using a continuous-suction device before resection was very useful for such a large pericardial cyst.

However, the dV still has some unresolved issues. The main limitation for robotic surgery is the lack of sufficient

dedicated instruments, such as robotic surgery tissue-sealing devices and stapler arms. At present, surgeons must use current thoracic surgery devices as substitutes. In our experience, it was sometimes difficult to judge the amount of strength to apply when tying sutures. This issue needs to be solved in the near future. Until such time, combined use with tissue-sealing devices is possible for the cutting of small vessels.

Another issue is the system of medical insurance coverage in Japan. This robotic system is not yet recognized by the Ministry of Health, Labor and Welfare and therefore, is not covered by existing public insurance. We hope that its status will soon be recognized by the national insurance system. Among societies devoted to surgeries of various organs, standardized rules and guidelines regarding the indications for robotic surgery, training systems, techniques, certification and financial aspects are beginning to be established in Japan.

5. Conclusions

Robotic surgery using the dV yields results similar to those of standard surgical procedures, and yet appears safer, and the instrumentation is easier to use, than conventional VATS for the surgical treatment of mediastinal tumors. However, the positioning of all units and the location of instrument arm ports need suitable directional setting, which depends on the tumor location.

Acknowledgements

The authors are grateful to Roderick J. Turner and Patrick Barron of the Department of International Medical Communications at Tokyo Medical University for reviewing the English manuscript.

References

[1] Ueda Y, Fujii Y, Udagawa H. Thoracic and cardiovascular surgery in Japan during 2007. Gen Thorac Cardiovasc Surg 2009;57:488–513.

[2] Yoshino I, Hashizume M, Shimada M, Tomikawa M, Tomiyasu M, Suemitsu R, Sugimachi K. Thoracoscopic thymomectomy with the da Vinci computer-enhanced surgical system. J Thorac Cardiovasc Surg 2001; 122:783–785.

[3] Yoshino I, Hashizume M, Shimada M, Tomikawa M, Sugimachi K. Video-assisted thoracoscopic extirpation of a posterior mediastinal mass using the da Vinci computer enhanced surgical system. Ann Thorac Surg 2002;74:1235–1237.

[4] Bodner J, Wykypiel H, Wetscher G, Schmid T. First experiences with the da Vinci operating robot in thoracic surgery. Eur J Cardiothorac Surg 2004;25:844–851.

[5] Giulianotti PC, Buchs NC, Caravaglios G, Bianco FM. Robot-assisted lung resection: outcomes and technical details. Interact CardioVasc Thorac Surg 2010;11:388–392.

[6] Inada K, Shirakusa T, Yoshinaga Y, Yoneda S, Shiraishi T, Okabayashi K, Iwasaki A, Kawahara K. The role of video-assisted thoracic surgery for the treatment of lung cancer: lung lobectomy by thoracoscopy versus the standard thoracotomy approach. Int Surg 2000;85:6–12.

[7] Park BJ, Flores RM, Rusch VW. Robotic assistance for video-assisted thoracic surgical lobectomy: technique and initial results. J Thorac Cardiovasc Surg 2006;131:54–59.

[8] Gharagozloo F, Margolis M, Tempesta B, Strother E, Najam F. Robot-assisted lobectomy for early-stage lung cancer: report of 100 consecutive cases. Ann Thorac Surg 2009;88:380–384.

[9] Dolezel J, Vicek P. Robot-assisted pulmonary lobectomy. Bratisl Lek Listy 2008;109:251–253.

[10] Dolezel J, Jedlicka V, Capov I. Robot-assisted pulmonary lobectomy–our first experiences. Rozhl Chir 2008;87:121–123; discussion 124. Czech.

[11] Gharagozloo F, Margolis M, Tempesta B. Robot-assisted thoracoscopic lobectomy for early-stage lung cancer. Ann Thorac Surg 2008;85:1880–1885; discussion 1885–1886.

[12] Morgan JA, Ginsburg ME, Sonett JR, Argenziano M. Thoracoscopic lobectomy using robotic technology. Heart Surg Forum 2003;6:E167–E169.

[13] Savitt MA, Gao G, Furnary AP, Swanson J, Gately HL, Handy JR. Application of robotic-assisted techniques to the surgical evaluation and treatment of the anterior mediastinum. Ann Thorac Surg 2005;79:450–455; discussion 455.

[14] Bodner J, Wykypiel H, Greiner A, Kirchmayr W, Freund MC, Margreiter R, Schmid T. Early experience with robot-assisted surgery for mediastinal masses. Ann Thorac Surg 2004;78:259–265; discussion 265–266.

[15] DeRose JJ Jr, Swistel DG, Safavi, Connery CP, Ashton RC Jr. Mediastinal mass evaluation using advanced robotic techniques. Ann Thorac Surg 2003;75:571–573.

Lasers in Surgery and Medicine 43:749–754 (2011)

New Aspects of Photodynamic Therapy for Central Type Early Stage Lung Cancer

Norihiko Ikeda, MD, PhD,[1]* Jitsuo Usuda, MD, PhD,[1] Harubumi Kato, MD, PhD,[2] Taichiro Ishizumi, MD, PhD,[1] Shuji Ichinose, MD, PhD,[1] Keishi Otani, MD, PhD,[1] Hidetoshi Honda, MD, PhD,[1] Kinya Furukawa, MD, PhD,[3] Tetsuya Okunaka, MD, PhD,[4] and Hidemitsu Tsutsui, MD, PhD[1]

[1]*Department of Surgery, Tokyo Medical University, Tokyo, Japan*
[2]*Department of Thoracic Surgery, Niizashiki Chuo Hospital, Saitama, Japan*
[3]*Department of Thoracic Surgery, Ibaragi Medical Center, Tokyo Medical University, Ibaragi, Japan*
[4]*Respiratory Disease Center, Sanno Hospital, Tokyo, Japan*

Background: and Objective Photodynamic therapy (PDT) has come to be considered as the first choice of treatment for central type early stage lung cancer (CELC). Recent advances in the ability to diagnose CELC, and in photosensitizers, as well as sophisticated clinical management, may improve the therapeutic outcome and expand the indications of PDT.

Materials and Methods: We made the search for papers on PDT for lung cancer to select the most relevant articles. Based on this review and our recent data, we discussed the best available evidence for the diagnosis, the definition of indications, photosensitizers, and clinical management with regard to PDT.

Results: To obtain complete response (CR) by PDT, the selection of the indications is extremely important, including the extent of the tumor on the bronchial surface and the depth of invasion in the bronchial wall. The development of autofluorescence bronchoscopy (AFB) and endobronchial ultrasonography (EBUS) have had a large impact on diagnostic bronchoscopy for CELC. CELCs less than 1 cm in diameter showed a favorable cure rate by PDT, thus this is a good indication for PDT. The relatively newer photosensitizer NPe6, which has a stronger antitumor effect than Photofrin, showed similar treatment outcome even for large tumors >1.0 cm in diameter. Furthermore, comprehensive management including photodynamic diagnosis before and after PDT should be effective to minimize the possibility of local recurrence after PDT.

Conclusion: The present guidelines of PDT for CELC were established based on the data obtained from studies in the 1980's. We postulate that comprehensive diagnosis and the new generation of photosensitizers may increase the CR rate and expand the indications of PDT for larger tumors. Lasers Surg. Med. 43:749–754, 2011.

Key words: autofluorescence bronchoscopy; central type early stage lung cancer; endobronchial ultrasonography; photodynamic therapy

INTRODUCTION

Lung cancer, the leading cause of cancer-related death worldwide, is divided into four major histological types, each of which has distinct biological characteristics. It is also classified into two categories based on its location; central type, and peripheral type. The former originates from large bronchi, while the latter originates from lung parenchyma.

It is generally assumed that squamous cell carcinoma originating in the bronchial tree develops in a gradual and stepwise process where the epithelial changes from normal to preneoplastic lesions, then carcinoma *in situ* and microinvasive squamous cell carcinoma [1,2]. The histological classification by the World Health Organization includes precise guidelines for grading of preneoplastic lesions: grading squamous dysplasia as mild, moderate, and severe dysplasia, and defining carcinoma *in situ*. These precise criteria allowed better interobserver reproductibility [3]. Breuer et al. [1] reported that 9% of squamous metaplasia, 9% of mild/moderate dysplasia, and 32% of severe dysplasia progressed to carcinoma *in situ* or squamous cell carcinoma. Also, the progression rate of carcinoma *in situ* to invasive cancer (87%) is reported to be significantly higher than that of severe dysplasia (37%; $P < 0.05$) [4].

As smoking is by far the greatest cause of central type lung cancer, most patients with this disease also suffer from poor cardio-pulmonary function due to chronic

There was no financial support for the authors nor does any author have a financial relationship with a commercial entity that has an interest in this manuscript.
Contract grant sponsor: Ministry of Health, Labor, and Welfare, Japan.
*Corresponding to: Norihiko Ikeda, MD, PhD, Department of Surgery, Tokyo Medical University, 6-7-1, Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan.
E-mail: ikeda-n@tokyo-med.ac.jp
Accepted 6 June 2011
Published online 15 August 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/lsm.21091