Total thyroidectomy has a great advantage in that thyroglobulin (Tg) can be used as a tumor marker. Also, the postoperative Tg doubling time is a useful parameter for predicting patients' cause-specific survival (CSS) [17]. Moreover, recurrence (especially distant recurrence) is easily detected, and immediate RAI therapy can be performed. However, if total thyroidectomy is performed by a nonexpert severe complications may occur, such as bilateral recurrent laryngeal nerve paralysis and persistent hypoparathyroidism. Our guidelines were not established for experts in thyroid surgery, and the balance between the merits and demerits of a given therapy must be considered when CQs are to be addressed.

Thus, the indications for total thyroidectomy described in the 2010 JSTS/JAES guidelines are appropriate at least in Japan, an iodine-rich country. The indications may also be applicable for Western countries, although more data accumulation is necessary among western patients before any conclusion can be drawn.

Is prophylactic central node dissection beneficial? (CQ18)

The most useful tool for detecting lymph node metastasis preoperatively is ultrasound, but the diagnostic accuracy of ultrasonography for central node metastasis is not high: The reported negative predictive value and sensitivity were 37 and 12 %, respectively [18], indicating that ultrasonography frequently overlooks small and latent central node metastasis. In addition, when the recurrence manifests clinically, reoperation of the central compartment may result in severe complications such as recurrent laryngeal nerve injury and persistent hypoparathyroidism. For such cases, the 2010 JSTS/JAES guidelines recommend routine bilateral central node dissection (CND) in patients who undergo total thyroidectomy. Ito et al. [19] showed that on multivariate a tumor size >2 cm was the strongest predictor of micro-lymph node metastasis and recurrence of N0 PTC, indicating that careful prophylactic CND is preferable, especially for large PTCs.

There are pros and cons for routine prophylactic CND for PTC patients. The present ATA guideline does not recommend routine CND. Its indication is limited to T3 or T4 patients based on expert opinion [9]. Conzo et al. [20] also proposed that the indication of CND might be limited to high-risk patients in whom nodal recurrence is more frequent because only 3.75 % of N0 patients showed lymph node recurrence even though they did not undergo prophylactic CND. Monchik et al. [21] demonstrated that failure to conduct prophylactic CND in low-risk PTC cases resulted in a very low incidence (1.8 %) of persistent nodal disease and elevated Tg levels 4–6 months after surgery, but they did not report the disease-free survival (DFS) or CSS rates over a long-term follow-up. Yoo et al. [22] showed that CND did not reduce the uptake of ^{131}I, and the preablation Tg level did not depend on whether CND was performed (0.93 vs. 1.2 %; $p = 0.17$). According to a study by Lang et al [23]., CND offers a more complete initial tumor resection than total thyroidectomy alone by evaluating the stimulated Tg ($p = 0.020$), but the difference becomes less noticeable 6 months after ablation ($p = 0.292$). Moreno et al. [24] performed a retrospective chart review and showed that prophylactic CND did not improve overall survival ($p = 0.32$), disease-specific survival ($p = 0.49$), or recurrence-free survival ($p = 0.32$) regardless of the histopathologic status of the lymph node retrieved.

In contrast, routine CND has been recommended by several studies, mainly because it is useful for accurate staging and for choosing the appropriate dose of ^{131}I for ablation. Prophylactic CND and lateral node dissection were recommended by Hartl et al. [25] because patients staged pN0 received less ^{131}I than those staged pN1 (median 30 vs. 100 mCi, $p < 0.0001$). Following a series of patients who underwent prophylactic bilateral CND, Laird et al. reported that the pathologically node-positive patients were more likely to show detectable Tg levels and require a higher dose of ^{131}I (150 vs. 30 mCi, $p < 0.001$) [26]. Similar findings were reported by others [27, 28]. Bonnet et al. [28] demonstrated that after pathological examination 30 % of the tumors initially staged as T1N0 were considered for RAI ablation. Using univariate and multivariate analyses for PTCs $\leq$ 2 cm, Perrino et al. [29] demonstrated that performing CND prevents persisting/relapsing disease in pateints with a PTC measuring $\leq$2 cm. Ryu et al. [30] indicated that the lymph node ratio of the central compartment is a significant predictor ($p < 0.001$) according to a multivariate analysis of locoregional recurrence for patients who underwent total thyroidectomy with bilateral prophylactic CND.

There are two strategies for CND: unilateral and bilateral. Complication rates, especially for persistent hypoparathyroidism, increase in the order of no CND, unilateral CND, and bilateral CND [31–34]. The incidence of contralateral CND metastasis is not low [35, 36]. It was shown that ipsilateral lymph node metastasis significantly predicted contralateral node metastasis [37, 38]. Chae et al. [39] thus proposed routine ipsilateral CND with intraoperative reading of the frozen section to decide whether contralateral CND is also to be performed.

In 2012, the ATA investigated the design and feasibility of a prospective randomized controlled trial of prophylactic CND for PTC [40]. It concluded that this trial is not readily feasible in light of the number of patients needed and the cost. For the time being, therefore, we cannot expect any

Table 3 Merits and demerits of prophylactic central node dissection

Merits	Demerits
May reduce the local recurrence rate	Complications of initial surgery may be increased
Precise staging useful for the decision of 131I dose for ablation plus prediction of the prognosis are available	No evidence of improved patient cause-specific survival
Severe complications of re-operation of this compartment can be avoided	

confirmative data about the utility of prophylactic CND for PTC [40]. Table 3 summarizes the merits and demerits of prophylactic CND.

Does dissection of the lateral compartment improve the prognosis of PTC patients? (CQ19)

In contrast to prophylactic CND, few studies have been published about whether dissection of the lateral compartment improves the prognosis of PTC patients. No guidelines, including the 2010 JSTS/JAES guidelines, actively recommend prophylactic lateral compartment dissection. However, there were some reports that recommended prophylactic lateral compartment dissection. In 2007, Ito et al. [41] demonstrated that the incidence of lateral node metastasis increased with tumor size. Also, in the subset of PTC patients who underwent prophylactic lateral node dissection, tumor size > 3 cm and significant extrathyroid extension were risk factors for lymph node recurrence. If these patients did not undergo lateral node dissection, their lymph node recurrence rates would be even poorer. In 2008, Sugitani et al. [42] conducted a multivariate analysis on patients who had no lateral node metastasis detectable by ultrasonography and who underwent CND only. These authors discovered that the presence of distant metastasis at diagnosis and tumor size ≥ 4 cm were independent prognostic factors of lymph node recurrence. Therefore, they recommended prophylactic lateral node dissection for such patients. In 2011, after the publication of our guidelines, Ito et al. [43] demonstrated that in the subset of patients with PTC who did not show ultrasonographically detectable lateral node metastasis and whose lesions measured 1.1–3.0 cm, N1a tumors were more likely to be associated with lymph node recurrence than N0 tumors, indicating that they may be candidates for prophylactic lateral node dissection. All of theses studies were retrospective. Nevertheless, patients with large or N1a tumors and with distant metastasis at diagnosis might be candidates for prophylactic lateral node dissection.

When is completion total thyroidectomy recommended as a second surgery for patients who underwent hemithyroidectomy and were classified as having follicular thyroid carcinoma? (CQ23)

In many Western institutions, completion total thyroidectomy is almost routinely performed in patients who underwent a hemithyroidectomy for the diagnosis of a follicular neoplasm or adenomatous nodule and were diagnosed as having follicular thyroid carcinoma (FTC). The 2010 JSTS/JAES guidelines recommend completion total thyroidectomy when the primary lesions are widely invasive FTC or have poorly differentiated components (especially insular carcinoma). However, no recommendation of completion total thyroidectomy is made for minimally invasive FTC.

Although the indications for completion total thyroidectomy for FTC still vary among the institutions in Japan, two relevant studies were recently published (Table 4) [44, 45]. Sugino et al. [44] demonstrated that patients aged <45 years showed an excellent prognosis, and completion total thyroidectomy might thus not be mandatory. The authors also showed that not only capsular but vascular invasion was unrelated to the prognosis of patients with minimally invasive FTC [44].

More recently, Ito et al. [45] showed that although the presence of vascular invasion did not affect the prognosis of their patients the recurrence rate for the patients with extensive vascular invasion (four or more lesions in total in all available H&E sections) was rather poor (20 % during a 10-year follow-up). They proposed that such patients may be candidates for completion total thyroidectomy. Both the Sugino et al. and Ito et al. studies indicated that tumor size (>4 cm) and patient age (≥45 years) are also significant

Table 4 Proposals for the management of minimally invasive FTC without distant metastasis: Sugino et al. [44] and Ito et al. [6, 19, 45]

Study	Proposals
Sugino [44]	Age ≥ 45 years and tumor size > 4 cm are significant prognostic factors for DFS
	In a multivariate analysis, age was the most powerful prognostic factor, and routine completion total thyroidectomy (with radioactive iodine ablation) is thus thought unnecessary for patients < 45 years
Ito [45]	Extensive vascular invasion (four or more total lesions in all available H&E-stained sections), age ≥ 45 years, and size > 4 cm were predictors of carcinoma recurrence
	The DFS of patients with extensive vascular invasion was especially poor, and they might be candidates for completion total thyroidectomy

FTC follicular thyroid cancer, *DFS* disease-free survival, *H&E* hematoxylin and eosin

prognostic factors, and they noted that physicians should decide how to treat patients with minimally invasive FTC in consideration of these factors.

One study investigated the timing of completion total thyroidectomy [46]. The results indicated that it should be performed either within 3 days of or >3 months after the primary surgery because persistent hypocalcemia was significantly decreased at these time points compared to other times. Because it takes some time to diagnose the degree of vascular invasion by pathology examination, it seems better to perform the second surgery ≥3 months after the initial surgery.

In 2002, Randolph and Daniels proposed that ablation of the remnant lobe be performed instead of completion thyroidectomy in patients who undergone previous limited thyroidectomy [47]. In 2012, Barbesino et al. [48] demonstrated that in FTC patients remnant thyroid lobe ablation with RAI resulted in outcomes similar to those of patients who underwent completion total thyroidectomy. This protocol eliminated the potential complications of a second surgery, such as hypoparathyroidism and recurrent laryngeal nerve paralysis or injury. In Japan, however, because legal restrictions regarding the use of RAI are still in place this strategy remains unrealistic.

What is the application and role of ablation? (CQ40)

Since publication of the 2010 JSTS/JAES guidelines, RAI ablation using 30 mCi (1.1 GBq) is permitted at outpatient clinics in Japan. Caglar et al. [49] showed that this dose is adequate at least for low-risk well-differentiated carcinoma [50]. The availability of rhTSH has also made ablation easier to perform in Japan, although it is costly. The issue of how to use 30 mCi RAI ablation in Japan needs to be addressed.

In Western countries, the indications for RAI ablation are broad, including tumor size > 1.5 cm, persistent disease, age ≥ 45 years, multifocality, and extrathyroid extension. Vascular invasion and lymph node metastasis are considered indications for RAI ablation [51], but these cases include many "non-high-risk" patients. In Japan, the legal restrictions and the lack of capacity make the use of RAI ablation for vascular invasion or lymph node metastasis not feasible.

Thus, a relatively new issue is whether RAI ablation is truly necessary for most patients. In a study of low-risk DTC patients, Schwartz et al. [52] reported that they failed to observe any survival benefit of RAI after surgery. Durante et al. [53] demonstrated that serum Tg values naturally dropped to undetectable levels within 5–7 years after thyroidectomy in low-risk patients. In a systematic analysis of the literature, Sacks et al. [54] concluded that postoperative RAI is not necessary.

Many endocrine surgeons in Japan have encountered patients with persistent disease (Tg detectable after total thyroidectomy), but most of these patients survived without RAI administration if their Tg levels were stable. Traditionally in Japan, RAI ablation has not been actively performed, but we do know that most DTC patients in Japan display an excellent prognosis. For example, at Kuma Hospital, the mortality rate of M0 PTC patients was slightly over 1 %, although most of these patients did not undergo RAI ablation (our unpublished data).

Iyer et al. [55] investigated the Surveillance and Epidemiology and End Results (SEER) database (http://seer.cancer.gov/) and demonstrated the rising incidence of second cancers among low-risk thyroid cancer patients who underwent RAI therapy. Hay et al. [56] showed that in patients who underwent RAI administration after surgery for PTC during childhood, 68 % of the patients who died thereafter died from nonthyroid malignancies. Taken together, these findings suggest that the indications for RAI ablation could be narrowed down: that is, to only high-risk patients, such as those with severe extrathyroid extension, a large lesion and many lymph node metastases, and aggressive histology.

Higher and therapeutic doses of RAI are preferable when a patient is classified as at high risk and when a poor CSS is predicted. For M1 patients, immediate administration of a therapeutic dose of RAI is mandatory. Miyauchi et al. [17] demonstrated that short (<2 years) Tg doubling times strongly predicted the carcinoma death of Tg antibody-negative PTC patients who underwent total thyroidectomy, regardless of preoperative and intraoperative clinicopathologic features. Thus, administration of a high dose of RAI when a patient's Tg starts rising during the follow-up is an alternative.

Discussion

In this review, we revisited the 2010 JSTS/JAES guidelines. In doing so, we found that most of the DTC treatment strategies described in the guidelines are reasonable, although some revisions based on new findings are necessary. In addition, the appearance of novel agents should be added to the guidelines. Extensive revisions might even be mandatory in such cases.

During the past few years, the strategies used in Western countries and those used in Japan for treating DTC have become more similar. The complete body of data suggests that immediate surgery for incidentally detected PMC is overtreatment. Endocrinologists and endocrine surgeons in Western countries are thus facing or will encounter a dilemma as numerous microcarcinomas are incidentally

detected with the increasing use of ultrasonography and ultrasonography-guided aspiration biopsy. The excellent prognosis for low-risk patients who underwent limited thyroidectomy raises issues concerning whether routine total thyroidectomy is truly beneficial for patients.

There is a U.S. report that patients with pT1/T2N0, well-DTCs were safely managed by thyroid lobectomy only [57]. Similarly, as indicated above, recent reports from Western countries display negative data for routine RAI ablation for low-risk patients. Unfortunately, the ATA concluded that a prospective randomized study for prophylactic CND is not feasible. Thus, we cannot expect any informative data about prophylactic CND in a large series of patients for the time being. At present, its indication may depend on institutional policy and surgeons' skill levels.

The production of molecularly targeted agents and their applications for thyroid carcinoma have recently been initiated. For example, the effectiveness of vandetanib for medullary thyroid carcinoma was demonstrated in a Phase III study [58]. Thus, the U.S. Food and Drug Administration approved the use of vandetanib for this purpose. Vandetanib will be available in Japan in the near future. A Phase III study of vandetanib for DTC is in progress on a worldwide scale.

The effectiveness of sorafenib for advanced or metastatic (and progressive) RAI-refractory DTC was reported at the 2013 American Society for Clinical Oncology meeting [59]. At present, many other molecularly targeted agents are in Phase I–III trials, and new agents can also be expected. We do not know whether the use of these agents will bring about major changes in the therapeutic strategies for DTC, but their positive and negative data will be considered in future revisions of the JSTS/JAES guidelines.

Conclusions

Taken together, the strategies for treating DTC in Western countries and Japan are moving toward a consensus. The issue of how to treat DTC itself may change because of the prevalence of molecularly target agents. The JSTS/JAES guidelines will be revised again within a few years, and the corresponding guidelines in other countries may also be updated in the near future. However, the policies and ultimate goal is not change. That is, the starting point of the guidelines is identifying the best treatment for patients with thyroid carcinoma worldwide.

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References

1. Takami H, Ito Y, Noguchi H et al (eds) (2013) Treatment of thyroid tumor. Springer, New York
2. Takami H, Ito Y, Okamoto T et al (2011) Therapeutic strategy for differentiated thyroid carcinoma in Japan based on a newly established guideline managed by Japanese Society of Thyroid Surgeons and Japanese Association of Endocrine Surgeons. World J Surg 35:111–121
3. Sugitani I, Toda K, Yamada K et al (2010) Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. World J Surg 34:1222–1231
4. Ito Y, Miyauchi A, Inoue H et al (2010) An observation trial for papillary thyroid microcarcinoma in Japanese patients. World J Surg 34:28–35
5. Sugitani I, Fujimoto Y, Yamada K (2013) Association between serum thyrotropin concentration and growth of asymptomatic papillary thyroid microcarcinoma. World J Surg Nov 14. [Epub ahead of print]
6. Ito Y, Miyauchi A, Kihara M et al (2013) Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid 24:27–34
7. Ito Y, Kudo T, Kobayashi K et al (2012) Prognostic factors for recurrence of papillary thyroid carcinoma in the lymph node, lung, and bone: analysis of 5,768 patients with average 10-year follow-up. World J Surg 36:1274–1278
8. Takebe K, Date M, Yamamoto Y et al (1994) Mass screening for thyroid cancer with ultrasonography. KARKINOS 7:309–317 (in Japanese)
9. Cooper DS, Doherty GM, Haugen BR et al (2009) Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 19:1167–1214
10. Anonymous (2007) Guidelines for the management of thyroid cancer second edition. http://www.british-thyroid-association.org/news/Docs/Thyroid_cancer_guidelines_2007.pdf
11. Thyroid Carcinoma Task Force (2001) AACE/AAES medical/surgical guidelines for clinical practice management of thyroid carcinoma. Endocr Pract 7:202–220
12. National Comprehensive Cancer Network (2013) NCCN clinical practice guidelines in Oncology. Thyroid Carcinoma. Version 2
13. Dralle H, Musholt TJ, Schabram J et al (2013) German Association of Endocrine Surgeons practice guideline for the surgical management of malignant thyroid tumors. Langenbecks Arch Surg 398:347–375
14. Ito Y, Masuoka H, Fukushima M et al (2010) Excellent prognosis of patients with solitary T1N0M0 papillary thyroid carcinoma who underwent thyroidectomy and elective lymph node dissection without radioiodine therapy. World J Surg 34:1285–1290
15. Ito Y, Fukushima M, Kihara M et al (2012) Investigation of the prognosis of patient age with papillary thyroid carcinoma by size. Endocr J 59:457–464
16. Matsuzu K, Sugino K, Kasthikot M et al (2014) Thyroid lobectomy for papillary thyroid cancer: long-term follow-up study of 1088 patients. World J Surg 38:68–79
17. Miyauchi A, Kudo T, Miya A et al (2011) Prognostic impact of serum thyroglobulin doubling-time under thyrotropin suppression in patients with papillary thyroid carcinoma who underwent total thyroidectomy. Thyroid 21:707–716
18. Ito Y, Miyauchi A (2009) Prognostic factors and therapeutic strategies for differentiated carcinoma of the thyroid. Endocr J 58:177–192
19. Ito Y, Fukushima M, Higashiyama T et al (2013) Tumor size is the strongest predictor of microscopic lymph node metastasis and

lymph node recurrence of N0 papillary thyroid carcinoma. Endocr J 60:113–117
20. Conzo G, Docirro G, Ruggiero R et al (2012) Surgical treatment of papillary thyroid carcinoma without lymph nodal involvement. G Chir 33:339–342
21. Monchik JM, Simon CJ, Caragacianu DL et al (2009) Does failure to perform prophylactic level VI node dissection leave persistent disease detectable by ultrasonography in patients with low-risk papillary carcinoma of the thyroid? Surgery 146:1182–1187
22. Yoo D, Ajmal S, Gowda S et al (2012) Level VI lymph node dissection does not decrease radioiodine uptake in patients undergoing radioiodine ablation for differentiated thyroid cancer. World J Surg 36:1255–1261
23. Lang BH, Wong KP, Wan KY et al (2012) Impact of routine unilateral central neck dissection on preablative and postablative stimulated thyroglobulin levels after total thyroidectomy in papillary thyroid carcinoma. Ann Surg Oncol 19:60–67
24. Moreno MA, Edeiken-Monroe BS, Siegel ER et al (2012) In papillary thyroid cancer, preoperative central neck ultrasound detects only macroscopic surgical disease, but negative findings predict excellent long-term regional control and survival. Thyroid 22:347–355
25. Hartl DM, Leboulleux S, Al Ghuzlan A et al (2012) Optimization of staging of the neck with prophylactic central and lateral neck dissection for papillary thyroid carcinoma. Ann Surg 255:777–783
26. Laird AM, Gauger PG, Miller BS et al (2012) Evaluation of postoperative radioactive iodine scans in patients who underwent prophylactic central lymph node dissection. World J Surg 36:1268–1275
27. Moo TA, McGill J, Allendorf J et al (2010) Impact of prophylactic central neck lymph node dissection on early recurrence in papillary thyroid carcinoma. World J Surg 34:1187–1191
28. Bonnet S, Hartl D, Leboulleux S et al (2009) Prophylactic lymph node dissection for papillary thyroid cancer less than 2 cm: implications for radioiodine treatment. J Clin Endocrinol Metab 94:1162–1167
29. Perrino M, Vannucchi G, Vicentini L et al (2009) Outcome predictors and impact of central node dissection and radiometabolic treatments in papillary thyroid cancers $\leq$2 cm. Endocr Relat Cancer 16:201–210
30. Ryu IS, Song C, Choi SH et al (2013) Lymph node ratio of the central compartment is a significant predictor for locoregional recurrence after prophylactic central neck dissection in patients with thyroid papillary carcinoma. Ann Surg Oncol 21:277–283
31. Kwan WY, Chow TL, Choi CY et al (2013) Complication rates of central compartment dissection in papillary thyroid cancer. ANZ J Surg Jul 26. [Epub ahead of print]
32. Giordano D, Valcavi R, Thompson GB et al (2012) Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1087 patients and review of the literature. Thyroid 22:911–917
33. Khatib ZE, Lamblin J, Augert S et al (2010) Is thymectomy worthwhile in central lymph node dissection for differentiated thyroid cancer? World J Surg 34:1181–1186
34. Raffaelli M, De Crea C, Sessa L et al (2012) Prospective evaluation of total thyroidectomy versus ipsilateral versus bilateral central neck dissection in patients with clinically node-negative papillary thyroid carcinoma. Surgery 152:957–964
35. Ito Y, Jikuzono T, Higashiyama T et al (2006) Clinical significance of lymph node metastasis of thyroid papillary carcinoma located in one lobe. World J Surg 30:1821–1826
36. Sadowski BM, Snyder SK, Laimore TC (2009) Routine bilateral central lymph node clearance for papillary thyroid cancer. Surgery 146:696–703
37. Lee KE, Chung IY, Kagn E et al (2013) Ipsilateral and contralateral central lymph node metastasis in papillary thyroid cancer: patterns and predictive factors of nodal metastasis. Head Neck 35:672–676
38. Kim WW, Park HY, Jung JH (2013) Surgical extent of central lymph node dissection in clinically node-negative papillary thyroid cancer. Head Neck Jan 16 [Epub ahead of print]
39. Chae BJ, Jung CK, Lim DJ et al (2011) Performing contralateral central lymph node dissection in papillary thyroid carcinoma: a decision approach. Thyroid 21:873–877
40. Carling T, Carty SE, Clarlegio MM et al (2012) American Thyroid Association design and feasibility of a prospective randomized controlled trial of prophylactic central lymph node dissection for papillary thyroid carcinoma. Thyroid 22:237–244
41. Ito Y, Higashiyama T, Takamura Y et al (2007) Risk factors for recurrence to the lymph node in papillary thyroid carcinoma patients without preoperatively detectable lateral node metastasis: validity of prophylactic modified radical neck dissection. World J Surg 31:2085–2091
42. Sugitani I, Fujimoto Y, Yamada K et al (2008) Prospective outcomes of selective lymph node dissection for papillary thyroid carcinoma based on preoperative ultrasonography. World J Surg 32:2494–2502
43. Ito Y, Tsushima Y, Masuoka H et al (2011) Significance of prophylactic modified radical neck dissection for patients with low-risk papillary thyroid carcinoma measuring 1.1–3.0 cm: first report of a trial at Kuma Hospital. Surg Today 41:1486–1491
44. Sugino K, Kameyama K, Ito K et al (2012) Outcomes and prognostic factors of 251 patients with minimally invasive follicular thyroid carcinoma. Thyroid 22:798–804
45. Ito Y, Hirokawa M, Masuoka H et al (2013) Prognostic factors of minimally invasive follicular thyroid carcinoma: extensive vascular invasion significantly affects patient prognosis. Endocr J 60:637–642
46. Glockzin G, Hronung M, Klaus K et al (2013) Completion thyroidectomy: effect of timing on clinical complications and oncologic outcome in patients with differentiated thyroid cancer. World J Surg 36:1168–1173
47. Randolph GW, Daniels GH (2002) Radioactive iodine lobe ablation as an alternative to completion thyroidectomy for follicular carcinoma of the thyroid. Thyroid 12:989–996
48. Barbesino G, Goldfarb M, Parangi S et al (2012) Thyroid lobe ablation with radioactive iodine as an alternative to completion thyroidectomy after hemithyoridectomy in patients with follicular thyroid carcinoma: long-term follow-up. Thyroid 22:369–376
49. Caglar M, Bozkurt FM, Akca CK et al (2012) Complication of 800 and 3700 MBQ iodine-131 for the postoperative ablation of thyroid remnant in patients with low-risk differentiated thyroid cancer. Nucl Med Commun 33:268–274
50. Schlumberger M, Catargi B, Borget I et al (2012) Strategies of radioiodine ablation in patients with low-risk thyroid cancer. N Engl J Med 366:1663–1673
51. Robbins RJ, Schlumberger MJ (2005) The evolving role of ^{131}I for the treatment of differentiated thyroid carcinoma. J Nucl Med 46(Suppl 1):28S–37S
52. Schwartz C, Bonnetain F, Dabakuyo S et al (2012) Impact on overall survival of radioactive iodine in low-risk differentiated thyroid cancer patients. J Clin Endocrinol Metab 97:1526–1535
53. Durante C, Montesano T, Attard M et al (2012) Long-term surveillance of papillary thyroid cancer patients who do not undergo postoperative radioiodine remnant ablation: is there a role for serum thyroglobulin measurement? J Clin Endocrinol Metab 57:2748–2753
54. Sacks W, Fung CH, Chang JT et al (2010) The effectiveness of radioactive iodine for treatment of low-risk thyroid cancer: a

systematic analysis of the peer-reviewed literature from 1966 to April 2008. Thyroid 20:1235–1245
55. Iyer NG, Morris LGT, Tuttle RM et al (2011) Rising incidence of second cancers in patients with low-risk (T1N0) thyroid cancer who receive radioactive iodine therapy. Cancer 117:4439–4446
56. Hay ID, Gonzalez-Losada T, Reinalda MS et al (2010) Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. World J Surg 34:1192–1202
57. Nixon IJ, Banly I, Patel SG et al (2012) Thyroid lobectomy for treatment of well differentiated intrathyroid malignancy. Surgery 151:571–579
58. Wells SA, Robinson BG, Gagel RF et al (2012) Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol 30:134–141
59. Brose MS, Nutting C, Jarzab B et al (2013) Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer: the phase III DECISION trial. Presented at the 49th annual meeting of the American Society of Clinical Oncology (ASCO) plenary session. Abstract #4

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ORIGINAL ARTICLE

Differences in the prognosis of resected lung adenocarcinoma according to the histological subtype: a retrospective analysis of Japanese lung cancer registry data

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Abstract

OBJECTIVES: This study intended to assess the clinicopathological features of the histological subtypes of adenocarcinoma of the lung in a large registry population.

METHODS: The Japanese Joint Committee of Lung Cancer Registry performed a nationwide retrospective registry study on the prognosis and clinicopathological profiles of 11 663 patients who underwent resection for primary lung neoplasm in 2004. The registry data of 7921 (62.5%) patients with adenocarcinoma were analysed regarding the prognosis and clinicopathological features according to the histological subtype of adenocarcinoma. The histological subtypes were defined according to the 1999 World Health Organization classification (third edition), where bronchioloalveolar carcinoma (BAC) is defined as adenocarcinoma with a pure bronchioloalveolar growth pattern without invasion.

RESULTS: The distribution of the histological subtype was acinar in 471 patients (7.5%), papillary in 2004 (32.2%), BAC in 1385 (22.3%), solid adenocarcinoma with mucin in 103 (1.7%) and adenocarcinoma with mixed subtypes (AMS) in 2257 (36.3%). The 5-year overall survival rates according to histological subtype were 63.4% for acinar, 72.9% for papillary, 90.3% for BAC, 54.4% for solid adenocarcinoma with mucin and 73.7% for AMS. While the survival rate in patients with BAC was significantly better than those for the other histological subtypes, acinar and solid adenocarcinoma with mucin had significantly worse prognoses than the other histological subtypes. The histological subtype was an independent predictor of survival in a multivariate analysis ($P < 0.001$). Regarding BAC, the pathological stage included not only Stage IA/IB ($n = 1275$; 92.1%), but also Stage II–IV ($n = 110$; 7.9%). One hundred twenty-five patients (9.0%) with BAC had recurrence, including both local and distant recurrence.

CONCLUSIONS: The histological subtype in adenocarcinoma significantly correlated with the prognosis. In BACs with recurrence or pathological stage II–IV, these tumours might have been classified as invasive adenocarcinoma rather than as BAC. The need for the rigorous pathological evaluation of adenocarcinomas that are considered to be a preinvasive or minimally invasive tumour should be addressed in the new lung adenocarcinoma classification to be proposed by the International Association for the Study of Lung Cancer, the American Thoracic Society and the European Respiratory Society.

Keywords: Database • Histology • Lung cancer surgery • Lung pathology • Outcomes

INTRODUCTION

Adenocarcinoma of the lung is the most common histology of lung cancer in Japan, and the proportion of adenocarcinoma has been increasing in many countries [1, 2]. Adenocarcinomas frequently exhibit a heterogeneous histology, while combining bronchioloalveolar (lepidic), papillary, acinar and solid growth patterns [1]. The histological subtyping of lung adenocarcinoma has

developed over the past several decades as reflected in the World Health Organization (WHO) classification. The most significant change was introduced in the third edition of the latter in 1999 [3]. In the third edition, the histological subtype of adenocarcinoma consisted of five subtypes based on the histological growth pattern, i.e. four pure forms [acinar, papillary, bronchioloalveolar carcinoma (BAC) and solid adenocarcinoma with mucin] and one heterogeneous form [adenocarcinoma with mixed subtypes (AMS), which shows a variable admixture of more than one histological subtype pattern]. In particular, BAC was strictly defined as a noninvasive tumour with a pure lepidic growth pattern [3].

Several important prognostic factors have been identified, such as tumour-node-metastasis (TNM) stage, performance status, gender, age, histology and so forth [4, 5]. Although it has been speculated that the particular biological behaviour likely influences the presence of specific histological growth patterns of adenocarcinoma [6], the relationship between the histological subtype of adenocarcinoma and prognosis has not been clearly demonstrated in a large cohort. For BACs, an excellent prognosis should be expected based on the definition of BAC as a non-invasive tumour. Nevertheless, in previous reports based on the 1999 WHO classification, resected BACs were not necessarily associated with satisfactory prognosis even if they were in stage I [6–8].

In Japan, the task force committee of the Japanese Joint Committee of Lung Cancer Registry has periodically performed nationwide registry studies on the prognosis and clinicopathological profiles of lung neoplasms [2, 4]. Recently, the committee reported a retrospective registry study that focused on 11 663 cases of lung cancer resected in 2004 after a 5-year follow-up period [2]. The present study deals with this retrospective registry for patients with lung cancer resected in 2004. This registry data has been used in other publications previously without direct overlap with the present study [9].

The aim of this study was to evaluate the clinicopathological characteristics and prognostic implications according to the histological subtypes of lung adenocarcinoma based on the 1999 third edition of the WHO classification [3], and furthermore to investigate the pattern of recurrence in BAC, which has been defined as a noninvasive adenocarcinoma.

PATIENTS AND METHODS

Registry

In 2010, the Japanese Joint Committee of Lung Cancer Registry performed a nationwide retrospective registry study on the prognosis and clinicopathological profiles of resected lung neoplasms in Japan. The committee received the registries of 11 663 patients from 253 teaching hospitals. The registered data included the clinicopathological and prognostic items, which had been described previously [2]. Recurrent or multiple lung cancers were not included in this registry. Cancer recurrence was divided into three categories according to the site of the initial relapse: loco-regional, distant and at both sites simultaneously. Loco-regional recurrence was defined as any recurrent disease within the ipsilateral hemithorax, mediastinum or supraclavicular lymph nodes. All other sites of recurrence were considered distant recurrence. The cause of death was recorded as either lung-cancer-related, other disease or unknown. The data relating to survival time, recurrence, and cause of death were collected from a medical chart or a national death registry in the respective teaching hospitals. Although the method of data collection for the postoperative follow-up was not standardized because of a retrospective study, the postoperative follow-up was regularly scheduled in the respective teaching hospitals. All patients were staged on the basis of the seventh edition of the Union for International Cancer Control TNM Classification of the malignant tumour staging system published in 2009 [10]. Tumour histology was described according to the third edition of the WHO classification published in 1999 [3], where lung adenocarcinomas were subclassified into the following five histological subtypes: acinar, papillary, BAC, solid adenocarcinoma with mucin and AMS, and variants such as well-differentiated foetal adenocarcinoma, colloid adenocarcinoma, mucinous cystadenocarcinoma, signet-ring adenocarcinoma or clear cell adenocarcinoma. In addition, BAC was cytologically subdivided into three groups: non-mucinous, mucinous and mixed mucinous and non-mucinous or indeterminate.

Patients

The study focused on patients with an adenocarcinoma histology. Of the 11 663 registered patients, 7921 (62.5%) had adenocarcinoma. Patients with variants such as well-differentiated foetal adenocarcinoma ($n = 3$), colloid adenocarcinoma ($n = 4$), mucinous cystadenocarcinoma ($n = 3$), signet-ring adenocarcinoma ($n = 9$) or clear cell adenocarcinoma ($n = 11$) and those ($n = 1671$) with incomplete data regarding the histological subtype of adenocarcinoma were excluded. The remaining 6220 patients were analysed in terms of prognosis and clinicopathological characteristics according to the histological subtype of adenocarcinoma.

Statistical analysis

The χ^2 test and one-way analysis of variance were used to evaluate the differences in categorical variables and continuous variables, respectively. The survival time was defined as the time between the date of surgery and the last follow-up date. The survival curves were estimated by the Kaplan–Meier method, and differences in survival were assessed by the log-rank test. Overall survival was defined as the time between the operation and death from any cause. Disease-free survival was defined as the time between the operation and disease recurrence, lung cancer-related death or the last follow-up. A multivariate analysis by a Cox proportional hazards model was used to test the significance of prognostic factors, including gender, age, smoking status, operative mode, surgical curability, histological subtype of adenocarcinoma, tumour size, p-T status and p-N status. Significance was defined as a P-value of <0.05. All statistical analyses were performed with the SAS version 9.1.3 (SAS Institute, Inc., Cary, NC, USA) or with IBM SPSS version 19 (IBM Corporation, NY, USA).

RESULTS

Clinicopathological features

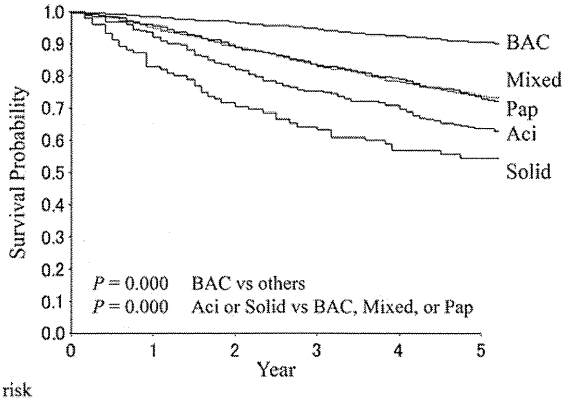
The distribution of histological subtypes in adenocarcinoma is as follows. The most common subtype was AMS ($n = 2257$; 36.3%), followed by papillary ($n = 2004$; 32.2%), BAC ($n = 1385$; 22.3%), acinar ($n = 471$; 7.5%) and solid adenocarcinoma ($n = 103$; 1.7%). Of the 1385 patients with BAC, 1110 (80.1%) had non-mucinous

type, 102 (7.4%) had mucinous type and 173 (12.5%) had mixed mucinous and non-mucinous or indeterminate type. The clinicopathological features according to the histological subtype are summarized in Table 1. The mean age at surgical resection for patients with solid adenocarcinoma was significantly younger than that for patients with other subtypes. With regard to gender, the proportion of females in BAC was significantly greater than that in other subtypes, whereas the proportion of males in solid adenocarcinoma was significantly greater than that in other subtypes. The proportion of smokers was significantly higher in those with acinar and solid adenocarcinoma than in those with other subtypes, whereas it was significantly lower in patients with BAC than in those with other subtypes. One hundred fifty-seven patients (2.5%) of all the 6220 patients received neoadjuvant therapy. The neoadjuvant therapy included chemotherapy ($n = 111$; 1.8%), radiotherapy ($n = 4$; 0.1%), chemoradiotherapy ($n = 34$; 0.5%) and others ($n = 8$; 0.1%). The proportion of patients who received neoadjuvant therapy was significantly higher in patients with solid adenocarcinoma than in those with other subtypes, whereas it was significantly lower in patients with BAC than in those with other subtypes. With regard to the operative mode, the proportion of pneumonectomy was higher in patients with solid adenocarcinoma than in those with other subtypes, whereas the proportion of segmentectomy/wedge resection was higher in patients with BAC than in those with other subtypes. Regarding tumour size, BAC was significantly smaller and solid

Table 1: Clinicopathological features of patients with resected adenocarcinoma of the lung according to the histological subtype

Characteristic	BAC ($n = 1385$)	Acinar ($n = 471$)	Papillary ($n = 2004$)	Solid ($n = 103$)	AMS ($n = 2257$)	*P*
Age (year)						
Mean	65.1 ± 10.3	66.0 ± 10.0	66.6 ± 9.7	63.9 ± 9.7	65.9 ± 9.7	<0.001
Sex						
Male	551 (39.8%)	309 (65.6%)	1024 (51.1%)	76 (73.8%)	1186 (52.5%)	<0.001
Female	834 (60.2%)	162 (34.4%)	980 (48.9%)	27 (26.2%)	1071 (47.5%)	
Smoking status						
Non-smoker	834 (65.3%)	158 (36.8%)	964 (51.7%)	23 (22.8%)	1093 (50.8%)	<0.001
Ex-smoker	223 (17.4%)	93 (21.7%)	341 (18.3%)	21 (20.8%)	456 (21.2%)	
Current smoker	221 (17.3%)	178 (41.5%)	560 (30.0%)	57 (56.4%)	602 (28.0%)	
Serum CEA level						
Normal	1217 (87.9%)	308 (65.4%)	1488 (74.3%)	59 (57.3%)	1616 (71.6%)	<0.001
High	168 (12.1%)	163 (34.6%)	516 (25.7%)	44 (42.7%)	641 (28.4%)	
Clinical stage						
IA	1189 (85.8%)	248 (52.7%)	1226 (61.2%)	40 (38.8%)	1374 (60.9%)	<0.001
IB	150 (10.8%)	113 (24.0%)	494 (24.7%)	28 (27.2%)	545 (24.1%)	
IIA	4 (0.3%)	5 (1.1%)	30 (1.5%)	6 (5.8%)	48 (2.1%)	
IIB	12 (0.9%)	39 (8.3%)	81 (4.0%)	10 (9.7%)	108 (4.8%)	
IIIA	13 (0.9%)	41 (8.7%)	96 (4.8%)	12 (11.7%)	113 (5.0%)	
IIIB/IV	17 (1.2%)	25 (5.2%)	77 (3.8%)	7 (6.8%)	69 (3.1%)	
Neoadjuvant therapy						
No	1374 (99.2%)	450 (95.5%)	1952 (97.4%)	93 (90.3%)	2194 (97.2%)	<0.001
Yes	11 (0.8%)	21 (4.5%)	52 (2.6%)	10 (9.7%)	63 (2.8%)	
Operative mode						
Pneumonectomy	2 (0.1%)	8 (1.7%)	27 (1.4%)	8 (7.9%)	31 (1.4%)	<0.001
Lobectomy	844 (61.2%)	382 (82.4%)	1680 (84.6%)	74 (73.3%)	1900 (85.4%)	
Segmentectomy/wedge resection	533 (38.6%)	74 (16.0%)	279 (14.1%)	19 (18.8%)	295 (13.2%)	
Curability						
R0	1364 (99.3%)	482 (92.0%)	1887 (94.8%)	98 (95.1%)	2134 (95.5%)	<0.001
R1	4 (0.3%)	15 (3.2%)	56 (2.8%)	3 (2.9%)	45 (2.0%)	
R2	6 (0.4%)	22 (4.7%)	48 (2.4%)	2 (1.9%)	56 (2.5%)	
Tumour size						
Mean	1.9 ± 1.6	3.0 ± 1.6	2.7 ± 1.5	3.5 ± 2.0	2.8 ± 1.7	<0.001
Pleural invasion						
pl0	1297 (93.8%)	286 (61.4%)	1328 (66.6%)	62 (60.2%)	1588 (71.0%)	<0.001
pl1/pl2	82 (5.9%)	139 (29.8%)	559 (28.0%)	29 (28.2%)	512 (22.9%)	
pl3	4 (0.2%)	41 (8.8%)	107 (5.4%)	12 (11.6%)	138 (6.2%)	
Pathological stage						
IA	1143 (82.5%)	165 (35.0%)	883(44.1%)	31 (30.1%)	1046 (46.4%)	<0.001
IB	132 (9.5%)	118 (25.1%)	502 (25.1%)	18 (17.5%)	489 (21.7%)	
IIA	25 (1.8%)	42 (8.9%)	135 (6.7%)	11 (10.6%)	142 (6.3%)	
IIB	32 (2.3%)	36 (7.7%)	83 (4.1%)	14 (13.6%)	106 (4.7%)	
IIIA	40 (2.9%)	84 (17.8%)	297 (14.8%)	25 (24.3%)	367 (16.2%)	
IIIB/IV	13 (1.0%)	26 (5.5%)	104 (5.2%)	4 (3.9%)	107 (4.7%)	
Adjuvant chemotherapy						
No	1235 (91.4%)	295 (65.0%)	1403 (72.3%)	61 (61.0%)	1604 (74.0%)	<0.001
Yes	116 (8.6%)	159 (35.0%)	538 (27.7%)	39 (39.0%)	565 (26.0%)	

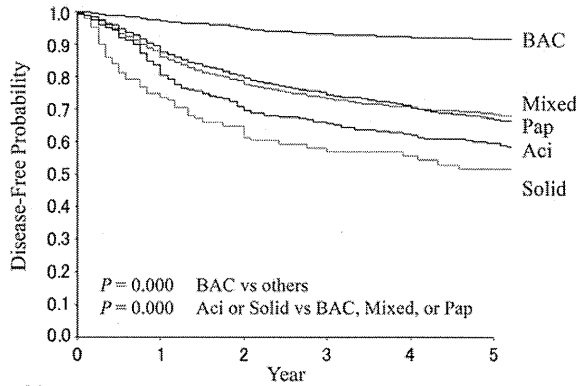
BAC: bronchioloalveolar carcinoma; Solid: solid adenocarcinoma with mucin; AMS: adenocarcinoma with mixed subtypes.



No. at risk

BAC	1385	1321	1269	1220	1131	922
Mixed	2257	2099	1921	1729	1543	1278
Pap	2004	1856	1686	1505	1347	1121
Aci	471	424	363	318	282	223
Solid	103	81	69	60	53	45

Figure 1: Overall survival curves based on the histological subtype of adenocarcinoma. There is a significant difference in survival between BAC and the other subtypes ($P < 0.001$) and between acinar or solid and BAC, mixed subtypes or papillary ($P < 0.001$). BAC: bronchioloalveolar carcinoma; Mixed: adenocarcinoma with mixed subtypes; Aci: acinar; Pap: papillary; Solid: solid adenocarcinoma with mucin.



No. at risk

BAC	1385	1283	1217	1160	1073	886
Mixed	2257	1847	1601	1436	1295	1099
Pap	2004	1646	1419	1266	1127	930
Aci	471	354	286	251	221	187
Solid	103	68	57	48	45	37

Figure 2: Disease-free survival curves based on the histological subtype of adenocarcinoma. There is a significant difference in survival between BAC and the other subtypes ($P < 0.001$) and between acinar or solid and BAC, mixed subtypes or papillary ($P < 0.001$). BAC: bronchioloalveolar carcinoma; Mixed: adenocarcinoma with mixed subtypes; Aci: acinar; Pap: papillary; Solid: solid adenocarcinoma with mucin.

adenocarcinoma was significantly larger, compared with the other subtypes. Pleural invasion was significantly infrequent in BAC compared with the other subtypes. With regard to the pathological stage, BAC had significantly more cases in Stage IA and solid adenocarcinoma had more cases in Stage IIIA, compared with the other subtypes.

Survival according to the histological subtype of adenocarcinoma

The postoperative follow-up was complete in 87% of all the patients. The overall 5-year survival rates according to the histological subtype of adenocarcinoma were 90.3% in BAC, 73.7% in AMS, 72.9% in papillary, 63.4% in acinar and 54.4% in solid adenocarcinoma. The survival curves are shown in Fig. 1. Patients with BAC had significantly better overall survival than those with other subtypes ($P < 0.001$). Patients with acinar or solid adenocarcinoma had significantly worse overall survival than those with BAC, AMS or papillary subtype ($P < 0.001$). Disease-free 5-year survival rates according to the histological subtype in adenocarcinoma were 91.4% in BAC, 68.3% in mixed subtypes, 66.6% in papillary, 59.4% in acinar and 51.5% in solid adenocarcinoma with mucin (Fig. 2). Patients with BAC had significantly better disease-free survival than those with other subtypes ($P < 0.001$). Patients with acinar or solid adenocarcinoma with mucin had significantly worse disease-free survival than those with BAC, mixed subtypes or papillary subtype ($P < 0.001$).

In a Cox proportional hazards model to predict overall survival, the following factors persisted as important prognostic factors: gender, age, operative mode, histological subtype of adenocarcinoma, surgical curability, tumour size, p-T status and p-N status (Table 2). With regard to histological subtype of adenocarcinoma, BAC had a significantly better prognosis, whereas solid adenocarcinoma and acinar subtype had significantly worse prognoses.

The prognosis among histological subtypes was further examined with regard to each pathological stage. In patients with pathological stage IA, BAC had significantly better overall survival than other subtypes ($P < 0.001$) (Fig. 3A). In patients with pathological stage IB, BAC had significantly better survival than acinar or solid adenocarcinoma (Fig. 3B). In patients with pathological stage II, solid adenocarcinoma had significantly worse survival than BAC, AMS or papillary subtype (Fig. 3C). In patients with pathological stage IIIA, there were no significant differences among histological subtypes (Fig. 3D).

Death was observed in 139 (10.0%) of the 1385 patients with BAC, 168 (35.7%) of the 471 patients with acinar, 538 (26.8%) of the 2004 patients with papillary, 44 (42.7%) of the 103 patients with solid adenocarcinoma and 597 (26.5%) of the 2257 patients with AMS in their clinical course. The distribution of cause of death in patients with adenocarcinoma according to the histological subtype is given in Table 3. With regard to cause of death, patients with BAC significantly had more death from diseases other than lung cancer ($P < 0.001$) more frequently.

The recurrence was observed in 125 (9.0%) of the 1385 patients with BAC, 198 (42.0%) of the 471 patients with acinar, 658 (32.8%) of the 2004 patients with papillary, 46 (44.7%) of the 103 patients with solid adenocarcinoma and 738 (32.7%) of the 2257 patients with AMS in their clinical course. The distribution of mode of recurrence in patients with adenocarcinoma according to the histological subtype is given in Table 4. There were no significant differences in mode of recurrence among the histological subtypes ($P = 0.089$).

Prognosis of bronchioloalveolar carcinoma

Regarding the mode of recurrence, 71 (56.8%) were distant, 38 (30.4%) were loco-regional and 7 (5.6%) were both simultaneously as given in Table 4. The distribution of pathological stage in BAC patients with recurrence was 40 patients in Stage IA, 19 in Stage IB, 25 in Stage II and 41 in Stage III/IV. The recurrence in BACs in

Table 2: Multivariate analysis of overall survival for resected cases of adenocarcinoma of the lung: Cox proportional hazard model ($n = 6220$)

Variable	HR	95% CI	P
Gender			
Men	1.000		
Women	0.665	0.568–0.778	<0.001
Age (year)			<0.001
<50	1.000		
50–70	1.177	0.902–1.537	0.230
>70	2.000	1.562–2.620	<0.001
Smoking status			0.052
Non-smoker	1.000		
Ex-smoker	1.151	0.962–1.376	0.124
Current smoker	1.227	1.040–1.446	0.015
Operative mode			<0.001
Pneumonectomy	1.000		
Lobectomy	0.633	0.461–0.868	0.005
Segmentectomy	0.951	0.653–1.386	0.795
Wedge resection	1.160	0.804–1.674	0.427
Surgical curability			
Complete	1.000		
Incomplete	1.772	1.449–2.166	<0.001
Histological subtype			<0.001
Acinar	1.000		
Papillary	0.844	0.697–1.023	0.084
BAC	0.508	0.393–0.656	<0.001
Solid with mucin	1.146	0.808–1.625	0.445
Mixed subtypes	0.817	0.676–0.988	0.037
Tumour size	1.099	1.064–1.134	<0.001
p-T status			<0.001
T1a	1.000		
T1b	1.445	1.204–1.734	<0.001
T2a	1.895	1.605–2.237	<0.001
T2b	1.701	1.228–2.355	0.001
T3	2.757	2.210–3.439	<0.001
T4	2.431	1.716–3.444	<0.001
p-N status			<0.001
N0	1.000		
N1	2.251	1.883–2.691	<0.001
N2	3.462	3.058–3.919	<0.001
N3	6.166	3.805–9.990	<0.001

HR: hazard ratio; CI: confidence interval; BAC: bronchioloalveolar carcinoma.

Stage I accounted for 3.5% of all BACs in Stage IA and 14.4% of those in Stage IB.

DISCUSSION

In this Japanese Lung Cancer Registry Study of 6,220 patients with resected lung adenocarcinoma, we showed that the histological subtype was a significant predictor of prognosis, independent of T- or N-factor in staging for lung cancer. In the WHO classification, the histological subtype of lung adenocarcinoma is classified according to the histological growth pattern. In our study, BAC had a significantly better prognosis, whereas solid adenocarcinoma and acinar subtype had significantly worse prognoses. In addition, the proportion of patients with advanced stage (Stage II–III) was higher in solid subtype than in other subtypes. We supposed that this could be the reason why the proportion of patients with pneumonectomy or patients who received neoadjuvant therapy was higher in patients with solid subtype than those with other subtypes.

In the present study, we investigated the clinicopathological features of histological subtypes of lung adenocarcinoma based on the 1999 WHO histological classification [3]. AMS is likely to be the most common histological subtype of lung adenocarcinoma because most lung adenocarcinomas are histologically heterogeneous and consist of more than one subtype even if they are small [1, 11, 12]. According to recent reports [12, 13], >80–90% of adenocarcinomas were classified as AMS when qualified expert pathologists re-reviewed the tumour histology in surgically resected adenocarcinoma using the 1999 WHO classification. However, AMS accounted for only 36.3% of adenocarcinomas in the present study. This may expose potential problems in the reproducibility of diagnosis with regard to the histological subtyping of lung adenocarcinoma among pathologists. Poor interobserver concordance regarding interpretation of the histological pattern in lung adenocarcinoma has been pointed out for some time [14].

BAC was once considered a well-differentiated adenocarcinoma that grew along the alveolar wall or underwent aerogenous spread [1]. The clinical manifestations varied, such as a single pulmonary nodule, multiple pulmonary nodules, localized infiltrates and diffuse pulmonary involvement (pneumonic-type) [1, 6]. In the 1999 WHO classification, the term BAC was newly defined as adenocarcinoma that showed the lepidic growth without evidence of stromal, vascular or pleural invasion. Thus, there should be no evidence of invasion for a diagnosis of BAC. If an invasive component is identified, the tumour is classified as AMS rather than BAC. Naturally, patients with BAC might be expected to have early stage without lymph node metastasis, and thus would have an excellent prognosis without recurrence. However, of the 1385 patients with BAC in the present study, 7.9% were in pathological stage II–IV and 9.0% had recurrence, including both local and distant recurrence. This recurrence was seen even in Stage I BACs. Consequently, the disease-free 5-year survival rate in BAC reached no further than 91.4%. Perhaps these BACs with recurrence or a positive-node should have been classified as invasive adenocarcinoma, i.e. AMS, rather than as BAC, although it is not possible to perform a detailed histological review to confirm the diagnosis in each case with such a large number of BAC patients from a variety of hospitals. In past reports on BAC as determined based on the 1999 WHO classification, resected BACs were not necessarily associated with excellent survival, as given in Table 5 [6–8, 11, 15–22]. In addition, these reports on BAC also included patients with distant as well as loco-regional recurrence. Surprisingly, reports that refer to BAC with N1 and N2 disease are still being published [23]. The issue of a strict pathological evaluation of 'invasion' must be clarified. The increasing importance of the precise definition and education on interpretation of pathological 'invasion' is also advocated in the recent report [24].

On the other hand, despite recent remarkable advances in our understanding of lung adenocarcinoma in the fields of medical oncology, molecular biology and radiology, there remains a need for a universally accepted classification of adenocarcinoma subtypes. Many reports have demonstrated a correlation between the predominant histological growth pattern of adenocarcinoma and survival [6, 13]. Tumours with a predominant lepidic growth pattern are associated with a better prognosis [6, 13], while those with a predominantly solid pattern or papillary pattern are more aggressive [5, 13]. Molecular markers such as epidermal growth factor receptor (EGFR) mutation, K-ras mutation or fusion of anaplastic lymphoma kinase (ALK) rearrangement are likely to be

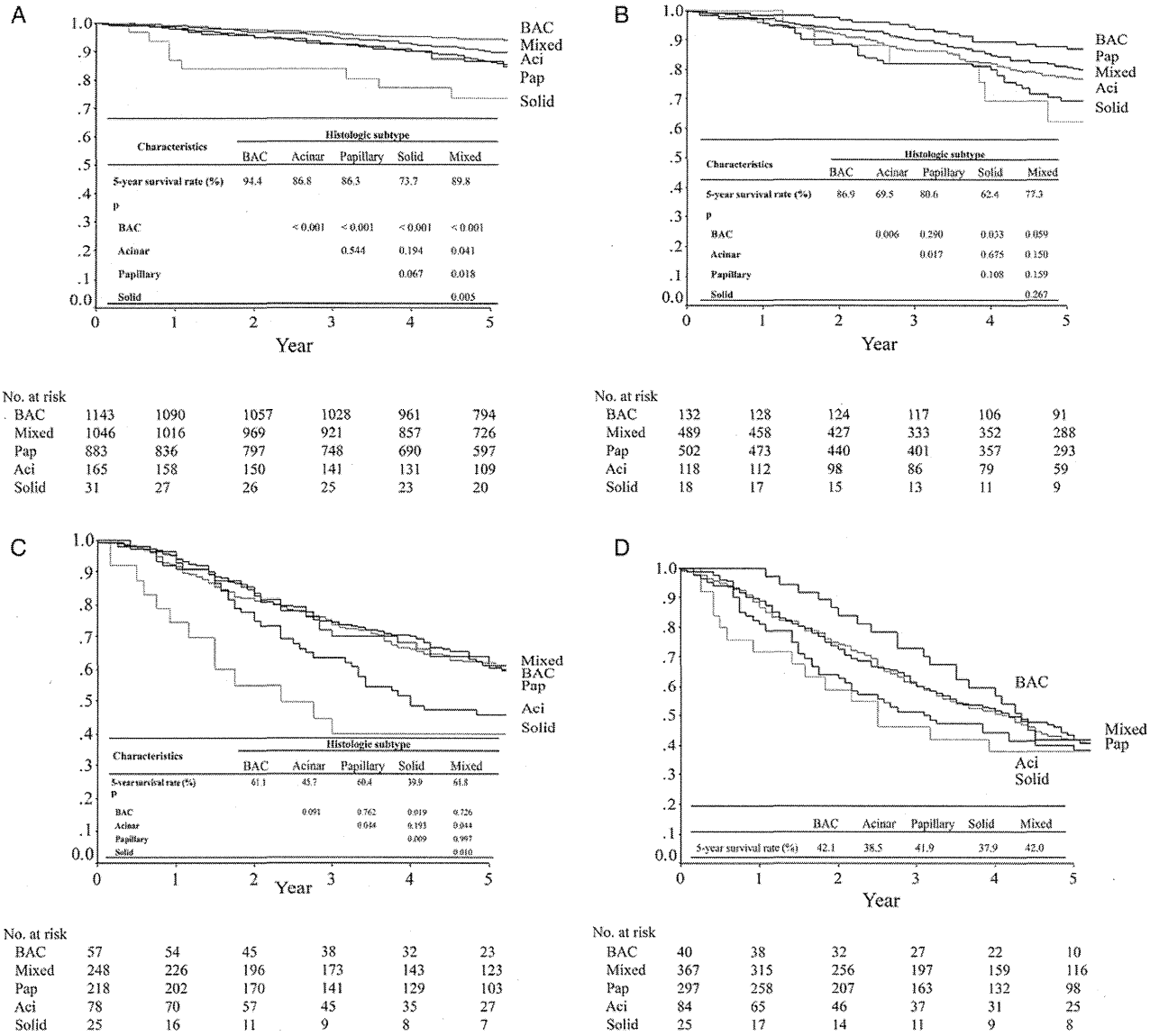


Figure 3: (**A**) Overall survival curves based on the histological subtype of pathological stage IA in adenocarcinoma. The 5-year survival rates according to the histological subtype and *P* values in survival differences among histological subtypes are shown in the cross-table. BAC: bronchioloalveolar carcinoma; Mixed: adenocarcinoma with mixed subtypes; Aci: acinar; Pap: papillary; Solid: solid adenocarcinoma with mucin. (**B**) Overall survival curves based on the histological subtype of pathological stage IB in adenocarcinoma. The 5-year survival rates according to the histological subtype and *P* values in survival differences among histological subtypes are shown in the cross-table. (**C**) Overall survival curves based on the histological subtype of pathological stage II in adenocarcinoma. The 5-year survival rates according to the histological subtype and *P* values in survival differences among histological subtypes are shown in the cross-table. (**D**) Overall survival curves based on the histological subtype of pathological stage IIIA in adenocarcinoma. The 5-year survival rates according to the histological subtype and *P* values in survival differences among histological subtypes are shown in the cross-table.

Table 3: Cause of death in patients with resected adenocarcinoma according to the histological subtype

Cause of death	BAC	Acinar	Papillary	Solid	AMS
Lung-cancer-related	69 (49.6%)	132 (78.6%)	418 (77.7%)	34 (77.3%)	467 (78.2%)
Other disease	67 (48.2%)	34 (20.2%)	115 (21.4%)	10 (22.7%)	117 (19.6%)
Unknown	3 (2.2%)	2 (1.2%)	5 (0.9%)	0 (0%)	13 (2.2%)
Total number of death	139	168	538	44	597

BAC: bronchioloalveolar carcinoma; Solid: solid adenocarcinoma with mucin; AMS: adenocarcinoma with mixed subtypes.

Table 4: Mode of recurrence in patients with resected adenocarcinoma according to the histological subtype

Mode of recurrence	BAC	Acinar	Papillary	Solid	AMS
Loco-regional	38 (30.4%)	53 (26.8%)	202 (30.7%)	14 (30.4%)	210 (28.5%)
Distant	71 (56.8%)	112 (56.6%)	328 (49.8%)	29 (63.0%)	384 (52.0%)
Both simultaneously	7 (5.6%)	21 (10.6%)	98 (14.9%)	2 (4.3%)	105 (14.2%)
Unknown	9 (7.2%)	12 (6.1%)	30 (4.6%)	1 (2.2%)	39 (5.3%)
Total number of recurrence	125	198	658	46	738

BAC: bronchioloalveolar carcinoma; Solid: solid adenocarcinoma with mucin; AMS: adenocarcinoma with mixed subtypes.
No statistical significant difference in mode of recurrence among the histological subtypes ($P = 0.089$).

Table 5: Postoperative 5-year survival rates for patients with BAC diagnosed according to the 1999 WHO classification

Author (year)	Number of patients	Pathological stage	5-year survival rate
Breathnach and colleagues (2001)	33	I	74%/83%, DFS/OS
Volpino and colleagues (2001)	34	IA	74.9%, OS
Ebright and colleagues (2002)	47	I	83.3%, OS
Rena and colleagues (2003)	28	I	81%, DFS
Furak and colleagues (2003)	67	All (IA/IB)	61.9%, OS (71%/77%, OS)
Sakurai and colleagues (2004)	85	IA (≤2 cm)	100%, DFS
Campione and colleagues (2004)	54	IA	88%, OS
Zell and colleagues (2007)	627	I	65%, OS
Koike and colleagues (2009)	46	I	93%, DFS
Casali and colleagues (2010)	40	All (I)	51%/64%, DFS/OS (69%/79%, DFS/OS)
Ebbert and colleagues (2010)	78	All	83.5%, OS
Whitson and colleagues (2012)	5532	All (lobectomy cases)	59.5%, OS
Present study	1385	All	91.4%/90.3%, DFS/OS

BAC: bronchioloalveolar carcinoma; WHO: World Health Organization; DFS: disease-free survival; OS: overall survival.

associated with a particular histological growth pattern of adenocarcinoma [1]. Moreover, these molecular markers can be used to predict the response to targeted therapy, particularly after the discovery of EGFR mutations and their association with sensitivity to EGFR tyrosine kinase inhibitors (EGFR TKIs) such as gefitinib [1]. It has been reported that EGFR mutations are more prevalent in the lepidic growth predominant subtype and ALK rearrangement in the acinar predominant subtype [1]. According to radiological-pathological studies, tumours that show ground-glass opacity on high-resolution computed tomography seem to be BACs or adenocarcinomas like BAC with a lepidic growth pattern accompanied by minimal invasion [1]. However, most of these adenocarcinomas will be classified as 'AMS' based on the 1999 WHO classification despite having such widely varied clinical behaviours. Therefore, the 1999 WHO classification has limited clinical utility. Ultimately, AMS includes tumours that are minimally invasive to overtly invasive. Additionally, with regard to BAC tumours, a discrepancy still exists between the rigorous pathological definition of BAC according to the 1999 WHO classification and the clinical use of the term. To address these issues, a new adenocarcinoma classification has recently been proposed by international multidisciplinary lung cancer experts including medical oncologists, respiratory physicians, pathologists, surgeons, molecular biologists and radiologists, who are sponsored by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) [1]. This was published as the new IASLC/ATS/ERS International Multidisciplinary Lung Adenocarcinoma Classification in 2011. Although we had too much incomplete data on histological subtype in adenocarcinoma in the present study, detailed pathological evaluation of histological subtype is becoming more important for clinical practice in the future. Pathologists need to put the focus on identifying the histological subtype of adenocarcinoma.

Regarding EGFR mutations in lung adenocarcinoma for a matter peculiar to a Japanese, EGFR TKIs have been developed as a targeted therapy in this disorder. East-Asians and patients with bronchioloalveolar pathological subtype have been shown to be significantly associated with a favourable response to EGFR TKIs [1]. Although the proportion of BAC in adenocarcinoma was ~20% in this Japanese registry data, it was reportedly lower in Western countries. Actually, the proportion of BAC in adenocarcinoma, even if it includes bronchioloalveolar-growth predominant subtype, has been reported to be only ~8% in Western countries [12, 13]. The distribution of the histological subtype in adenocarcinoma could be quite different among countries. The difference might affect the future drug development of targeted therapy among countries.

In the new proposed classification [1], the terms BAC and AMS were made obsolete. A BAC is called 'adenocarcinoma *in situ*' as a preinvasive lesion and the category of 'minimally invasive adenocarcinoma' was added, whereas invasive tumours other than minimally invasive adenocarcinoma are classified according to their

predominant growth pattern, i.e. lepidic predominant, acinar predominant, papillary predominant, micropapillary predominant and solid predominant with mucin production. Hereafter, the issue of interobserver concordance in the pathological diagnosis of adenocarcinoma subtypes will become increasingly important [25], although the new classification is currently being verified by several researchers [13, 24]. Unless the histological subtyping of adenocarcinoma can be accurately determined, the true clinicopathological characteristics will still be equivocal regardless of the revision of the histological classification.

In conclusion, we found a significant correlation between the prognosis and histological subtype of adenocarcinoma based on the 1999 WHO classification. In particular, BACs were significantly associated with a better prognosis compared with the other subtypes. On the other hand, even though BAC is defined as non-invasive adenocarcinoma in the 1999 WHO classification, some of the patients in our registry with BAC had lymph node metastasis, pleural invasion or recurrence. The reproducible pathological evaluation of preinvasive or minimally invasive findings or the growth pattern of adenocarcinoma should be discussed in the forthcoming WHO classification of lung adenocarcinoma to be proposed by IASLC/ATS/ERS.

Conflict of interest: none declared.

REFERENCES

[1] Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y *et al.* International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6: 244–58.

[2] Sawabata N, Miyaoka E, Asamura H, Nakanishi Y, Eguchi K, Mori M *et al.* Japanese Lung Cancer Registry Study of 11,663 surgical cases in 2004. Demographic and prognosis changes over decade. J Thorac Oncol 2011;6: 1229–35.

[3] Travis WD, Colby TV, Corrin B, Shimosato Y, Brambilla E. Histological Typing of Lung and Pleural Tumours, World Health Organization International Histological Classification of Tumors. Berlin, Germany: Springer, 1999.

[4] Asamura H, Goya T, Koshiishi Y, Sohara Y, Eguchi K, Mori M *et al.* A Japanese Lung Cancer Registry Study. Prognosis of 13,010 resected lung cancers. J Thorac Oncol 2008;3:46–52.

[5] Noguchi M, Morikawa A, Kawasaki M, Matsuno Y, Yamada T, Hirohashi S *et al.* Small adenocarcinoma of the lung. Histologic characteristics and prognosis. Cancer 1995;75:2844–52.

[6] Breathnach OS, Kwiatkowski DJ, Finkelstein DM, Godleski J, Sugarbaker DJ, Johnson BE *et al.* Bronchioloalveolar carcinoma of the lung: recurrences and survival in patients with stage I disease. J Thorac Cardiovasc Surg 2001;121:42–7.

[7] Volpino P, D'Andrea N, Cangemi R, Mingazzini P, Cangemi B, Cangemi V. Bronchioloalveolar carcinoma: clinical, radiographic and pathological findings. Surgical results. J Cardiovasc Surg 2001;42:261–7.

[8] Rena O, Papalia E, Ruffini E, Casadio C, Filosso PL, Oliaro A *et al.* Stage I pure bronchioloalveolar carcinoma: recurrences, survival and comparison with adenocarcinoma of the lung. Eur J Cardiothorac Surg 2003;23: 409–14.

[9] Yoshino I, Yoshida S, Miyaoka E, Asamura H, Nomori H, Fujii Y *et al.* Surgical outcome of stage IIIA-cN2/pN2 non-small-cell lung cancer patients in Japanese Lung Cancer Registry Study in 2004. J Thorac Oncol 2012;7:850–55.

[10] International Union Against Cancer. Lung and pleural tumours. In: Sobin LHGospodarowicz M (eds). TNM Classification of Malignant Tumours, 7th edn. New York, NY: Wiley-Blackwell, 2009, 138–46.

[11] Sakurai H, Maeshima A, Watanabe S, Suzuki K, Tsuchiya R, Maeshima AM *et al.* Grade of stromal invasion in small adenocarcinoma of the lung. Histopathological minimal invasion and prognosis. Am J Surg Pathol 2004; 28:198–206.

[12] Motoi N, Szoke J, Riely GJ, Seshan VE, Kris MG, Rusch VW *et al.* Lung adenocarcinoma: modification of the 2004 WHO mixed subtype to include the major histologic subtype suggests correlations between papillary and micropapillary adenocarcinoma subtypes, EGFR mutations and gene expression analysis. Am J Surg Pathol 2008;32:810–27.

[13] Russell PA, Wainer Z, Wright GM, Daniels M, Conron M, Williams RA. Does lung adencarcinoma subtype predict patient survival? A clinicopathologic study based on the new International Association for the Study of Lung Cancer/ American Thoracic Society/ European Respiratory Society international multidisciplinary lung adenocarcinoma classification. J Thorac Oncol 2011;6:1496–504.

[14] Roggli VL, Vollmer RT, Greenberg SD, McGavran M, Spjut HJ, Yesner R. Lung cancer heterogeneity: a blinded and randomized study of 100 consecutive cases. Hum Pathol 1985;16:569–79.

[15] Ebright MI, Zakowski MF, Martin J, Venkatraman ES, Miller VA, Bains MS *et al.* Clinical pattern and pathologic stage but not histologic features predict outcome for bronchioloalveolar carcinoma. Ann Thorac Surg 2002;74:1640–7.

[16] Furak J, Trojan I, Szoke T, Tiszlavicz L, Morvay Z, Eller J *et al.* Bronchioloalveolar lung cancer: occurrence, surgical treatment and survival. Eur J Cardiothorac Surg 2003;23:818–23.

[17] Campione A, Ligabue T, Luzzi L, Ghiribelli C, Paladini P, Voltolini L *et al.* Impact of size, histology, and gender on stage IA non-small cell lung cancer. Asian Cardiovasc Thorac Ann 2004;12:149–53.

[18] Zell JA, Ignatius Ou SH, Ziogas A, Anton-Culver H. Validation of the proposed International Association for the Study of Lung Cancer non-small cell lung cancer staging system revisions for advanced bronchioloalveolar carcinoma using data from the California Cancer registry. J Thorac Oncol 2007;2:1078–85.

[19] Koike T, Togashi K, Shirato T, Sato S, Hirahara H, Sugawara M *et al.* Limited resection for noninvasive bronchioloalveolar carcinoma diagnosed by intraoperative pathologic examination. Ann Thorac Surg 2009;88:1106–11.

[20] Casali C, Rossi G, Marchioni A, Sartori G, Maselli F, Longo L *et al.* A single institution-based retrospective study of surgically treated bronchioloalveolar adenocarcinoma of the lung. Clinicopathologic analysis, molecular features, and possible pitfalls in routine practice. J Thorac Oncol 2010;5: 830–6.

[21] Ebbert JO, Chhatwani L, Aubry MC, Wampfler J, Stoddard S, Zhang F *et al.* Clinical features of bronchioloalveolar carcinoma with new histologic and staging definitions. J Thorac Oncol 2010;5:1213–20.

[22] Whitson BA, Groth SS, Andrade RS, Mitiek MO, Maddaus MA, D'Cunha J. Invasive adenocarcinoma with bronchoalveolar features: a population-based evaluation of the extent of resection in bronchoalveolar cell carcinoma. J Thorac Cardiovasc Surg 2012;143:591–600.

[23] Varlotto JM, Flickinger JC, Recht A, Nikolov MC, Decamp MM. A comparison of survival and disease-specific survival in surgically resected, lymph node-positive bronchioloalveolar carcinoma versus nonsmall cell lung cancer. Implication for adjuvant therapy. Cancer 2008;112: 1547–54.

[24] Thunnissen E, Beasley MB, Borczuk AC, Brambilla E, Chirieac LR, Dacic S *et al.* Reproducibility of histopathological subtypes and invasion in pulmonary adenocarcinoma. An international interobserver study. Mod Pathol 2012;25:1574–83.

[25] Franklin WA, Aisner DL, Varella-Garcia M. Prognostic patterns in the histopathology of pulmonary adenocarcinoma. J Clin Oncol 2012;30: 1401–3.

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Clinicopathological characteristics and surgical results of lung cancer patients aged up to 50 years: The Japanese Lung Cancer Registry Study 2004

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ABSTRACT

Objective: The clinicopathological characteristics and surgical results of young lung cancer patients were investigated.
Materials and methods: Seven hundred and four (6.0%) patients with lung cancer, aged up to 50 years, were enrolled from among the 11,663 patients registered in the Japanese Lung Cancer Registry Study 2004, and their clinical data were compared with those of 10,959 patients older than 50 years. This epidemiological study is based on the single year registration of surgically treated patients in the major institutes in Japan.
Results: The 5-year overall survival rate (5Y-OS) and the 5-year lung cancer-related survival rate was 79.2%/69.0% ($p < 0.001$) and 81.3%/76.6% ($p = 0.005$) in the young/old groups, respectively. In the young/old groups, lobectomy and pneumonectomy was performed in 76.9%/78.0% and 5.7%/3.2%, respectively; adjuvant therapies were given preoperatively in 10.4%/4.7% ($p < 0.001$) and postoperatively in 31.4%/24.5% ($p < 0.001$). The proportions of patients with p-stage IIIA (18.2%) and adenocarcinoma histology (78.7%) were higher in the young group. The 5Y-OS was 94.8%/86.2% for p-stage IA ($p < 0.001$), 87.0%/73.2% for p-stage IB ($p = 0.001$), 61.0%/61.6% for p-stage IIA ($p = 0.595$), 71.0%/48.4% for p-stage IIB ($p = 0.003$), 49.6%/39.4% for p-stage IIIA ($p = 0.020$), and 80.0%/24.8% for p-stage IIIB ($p = 0.012$); it was 83.5%/80.7% for females ($p = 0.106$) and 75.1%/62.3% for males ($p < 0.001$) in the young/old groups. The postoperative survival was significantly better with all operative procedures in the young group. The 5Y-OS after recurrence was 17.9%/13.4% in the young/old groups ($p = 0.016$). In the young group, the 5Y-OS was better in females (83.5%) than in males (75.1%, $p = 0.002$), and for patients with adenocarcinoma (80.3%) than for those with squamous cell carcinoma (68.5%, $p = 0.013$). Age up to 50 years was identified as an independent better prognostic factor on multivariate analysis.
Conclusions: The postoperative survival in lung cancer patients aged up to 50 years was better than that in patients older than 50 years.

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1. Introduction

Lung cancer is a leading cause of malignancy-related death. The American Cancer Society estimates that 226,160 people will be diagnosed and 160,340 patients will die of lung cancer in the United States in 2012 [1]. Lung cancer occurs mainly in older people, and fewer than 2% of all cases are found in people younger than 45 years in the USA [1]. The Ministry of Health, Labor, and Welfare, Japan, reported that 69,813 people died of lung cancer in 2010 in Japan, and the number is still increasing. According to the Japanese Lung Cancer Registry Study, the number of patients younger than 50 years ranged from 5.0% to 8.2% of all resected cases since 1994 [2]. Because of the small size of the young population, the clinical features of young lung cancer patients remain unclear.

Better survival of lung cancer patients in the middle-aged group (45–60 years) as compared to the young (<45 years) or old group (>60 years) was reported by a multicenter study [3]. Several previous studies also revealed better postoperative survival rate in the young lung cancer patients [4–6], while other reports showed equivalent survival outcome to the old patients [7,8]. So, the survival superiority of the young patients is still controversial in lung cancer. Active treatment with multiple modalities was recommended in young patients in association with these results, while the study cohort included all lung cancer patients treated with surgery, chemotherapy, and irradiation [3]. However, the clinicopathological characteristics and surgical results of young patients with lung cancer have not yet been identified. Recent developments in chemotherapy and molecular targeted therapy might contribute to prolonged survival and improvement of results with multimodality management, especially in young patients, who are expected to be able to tolerate active treatments.

Patients aged up to 50 years extracted from the Japanese Lung Cancer Registry Study 2004 who underwent surgical resection were evaluated in order to clarify their clinicopathological characteristics and the results of surgical intervention in the present study [2].

2. Materials and methods

2.1. Patients

A total of 704 lung cancer patients aged up to 50 years were extracted from among the 11,663 patients listed in the Japanese Lung Cancer Registry Study 2004, which was conducted as a multicenter surveillance study of patients who underwent surgery by the Japanese Joint Committee of the Lung Cancer Registry (JJCLCR) [2]. JJCLCR is officially authorized by The Japan Lung Cancer Society, The Japanese Association for Chest Surgery, The Japanese Respiration Society, and The Japan Society for Respiratory Endoscopy. Of the 605 teaching hospitals certified by the Japanese Board of General Thoracic Surgery, 253 participated in this registry. All patients analyzed in the present study underwent surgery in 2004 and the single year registration included the following data: (1) demographic background (age and sex), (2) preoperative status (Eastern Cooperative Oncology Group performance status (ECOG PS), preoperative comorbidity, smoking status, tumor markers), (3) clinical TNM, (4) induction therapy, (5) operative procedure, (6) postoperative morbidity, (7) tumor histology, (8) adjuvant therapy, (9) pathological TNM. The clinicopathological characteristics and the results of surgical intervention in patients aged up to 50 years were analyzed in detail and compared to those of 10,959 patients older than 50 years. The data collected using the UICC-TNM staging system (version 6) were converted to the UICC-TNM staging system (version 7) to assess the extent of lung cancer [9].

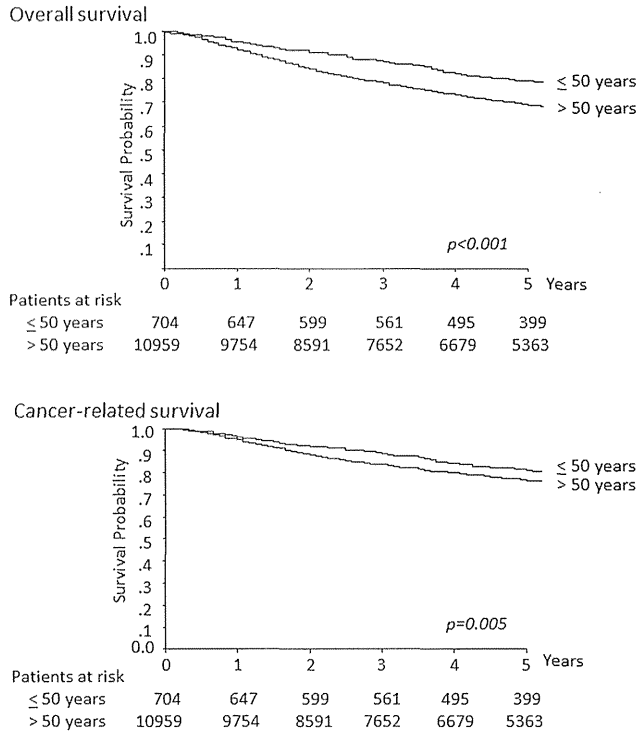

Fig. 1. The overall and lung-cancer related survival rates for patients aged up to and older than 50 years with surgical intervention. The postoperative survival rate was significantly better in the young group.

2.2. Statistical analyses

All data were extracted and analyzed by a JJCLCR member biostatistician (EM). Survival after pulmonary resection was estimated according to the Kaplan–Meier method, and survival differences were tested using the log-rank test. The prognostic effect of variables on survival was analyzed using the multivariate Cox regression model with variables of sex, ECOG-PS, smoking history, comorbidity, operative procedure, p-stage, histology, adjuvant chemotherapy. The χ^2-test was used to compare the rates between groups. A p value less than 0.05 was considered significant.

3. Results

Patients' characteristics, with a comparison of patients aged up to 50 years and older than 50 years, are shown in Table 1. The proportion of females was significantly higher in the young group than in the old group ($p < 0.001$). Performance status (ECOG) was significantly better in the young group ($p < 0.001$). Smoking history and preoperative comorbidity were significantly more frequent in the old group ($p < 0.001$). The operative procedure was significantly different ($p = 0.013$) and the rate of pneumonectomy was higher in the young group. The distribution of p-stage showed the significant difference, and the proportion of p-stage IB and IIA was lower and that of locally advanced disease with p-stage IIIA was higher in the young group as compared to the old group. The proportion of histopathology was significantly different ($p < 0.001$) and the rate of adenocarcinoma was higher in the young group. Young patients received both preoperative and postoperative adjuvant therapy more frequently than old patients.

The 5-year overall survival rate (5Y-OS) was 79.2% and 69.0% in the young and old groups, respectively ($p < 0.001$), as shown in Fig. 1. The 30-days mortality was 1/704 (0.1%) and 47/10959 (0.4%), and the hospital mortality was 2/704 (0.3%) and 134/10959 (1.2%) in the young and old groups, respectively. The morbidity was

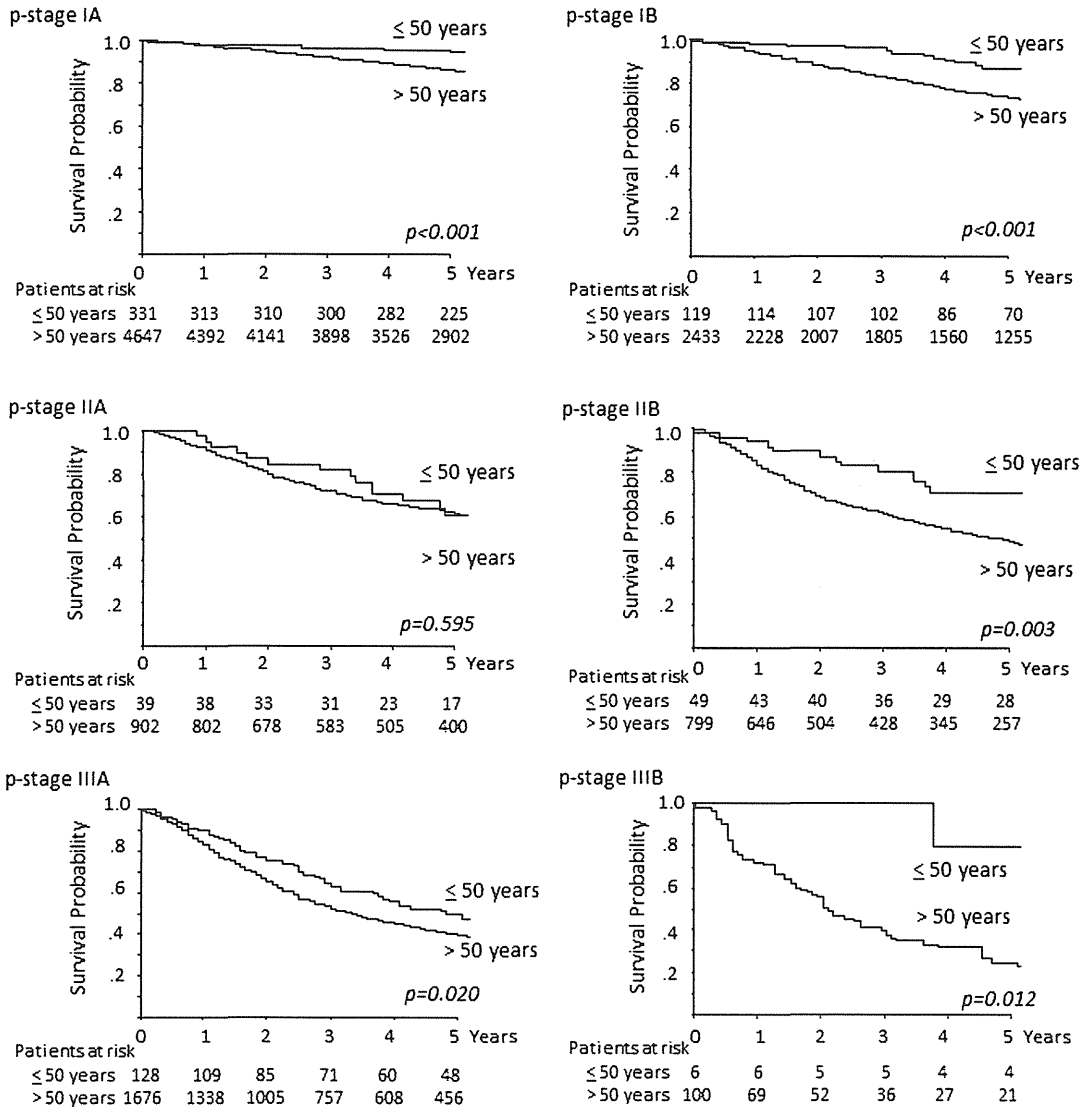

Fig. 2. The survival curves of patients aged up to and older than 50 years with surgery according to p-stage using UICC version 7. The postoperative survival was significantly better in the young group for each p-stage IA – IIIB except stage IIA.

58/704 (8.2%) and 1921/10959 (17.5%) in the young and old groups, respectively ($p < 0.001$). When analyzing disease-specific outcome, the 5-year lung cancer-related survival rate was 81.3% and 76.6% in the young and old groups, respectively ($p = 0.005$), as shown in Fig. 1. According to p-stage, the 5Y-OS was 94.8% and 86.2% for IA ($p < 0.001$), 87.0% and 73.2% for IB ($p < 0.001$), 61.0% and 61.6% for IIA ($p = 0.595$), 71.0% and 48.4% for IIB ($p = 0.003$), 49.6% and 39.4% for IIIA ($p = 0.020$), and 80.0% and 24.8% for IIIB ($p = 0.012$), in the young and old groups, respectively, as shown in Fig. 2.

Among male patients, the 5Y-OS was 75.1% and 62.3% in the young and old groups, respectively ($p < 0.001$), although there was no significant difference among female patients and the 5Y-OS was 83.5% and 80.7%, respectively (Fig. 3). The cause of death, preoperative comorbidities, smoking history, and adjuvant therapy were examined by age and sex. Lung cancer-unrelated death was higher (25.3%) in the old group than that in the young group (6.8%) in males ($p < 0.001$), while no significant difference was observed in females. Preoperative comorbidities were frequent in the old group in both male and female patients. Smoking history was significantly more frequent in the old group in males, while it was less frequent in females. Male patients in the young group more frequently had both preoperative and postoperative adjuvant therapies as compared to the old group, while no significant difference was found in female patients.

According to operative procedure, the 5Y-OS was better in the young group than in the old group for all procedures: 59.1% and 42.0% for pneumonectomy ($p = 0.050$), 79.9% and 71.7% for lobectomy ($p < 0.001$), 87.3% and 73.1% for segmentectomy ($p = 0.034$), and 93.5% and 65.9% for wedge resection ($p < 0.001$), in the young and old groups, respectively (Fig. 4). According to histological type, the 5Y-OS for adenocarcinoma was 80.3% in the young group which was significantly better than 74.5% in the old group, though no significant survival difference was observed for squamous cell carcinoma. The 5Y-OS after recurrence was 17.9% and 13.4% in the young and old groups, respectively ($p = 0.016$). In the young group, the 5Y-OS was significantly better for female patients (83.5%) than for male patients (75.1%, $p = 0.002$). 5Y-OS was better for the histology of adenocarcinoma (80.3%) than for squamous cell carcinoma (68.5%, $p = 0.013$).

Since the comparison of survival difference between young and old patients might be affected by patients older than 70 years, who are expected to have poor long-term survival, another comparison of survival difference between patients aged up to 50 years ($n = 704$) and those 50–70 years ($n = 6152$), which was a young elderly cohort,

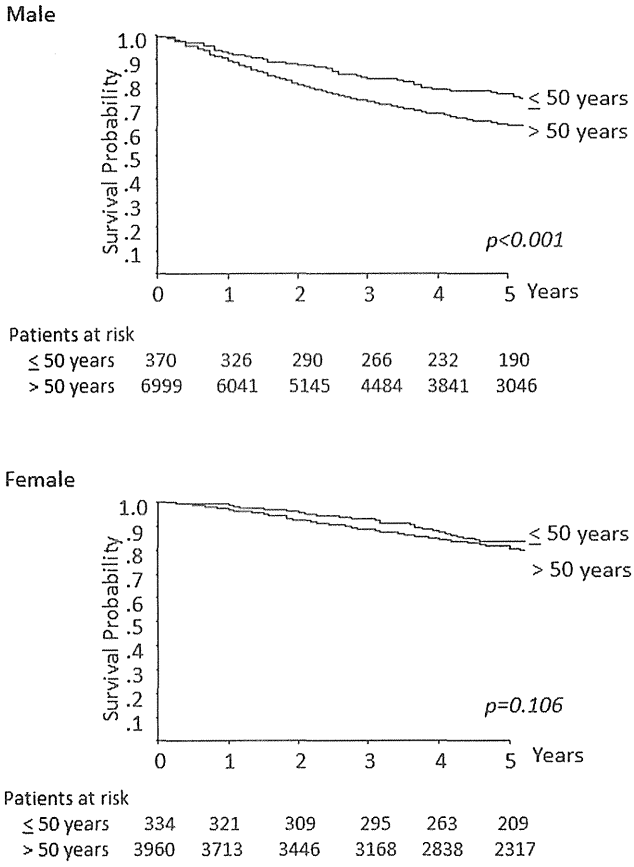

Fig. 3. The survival curves of patients aged up to and older than 50 years with surgery according to sex. Among male patients, the overall survival in patients aged up to 50 years was significantly better than that in patients older than 50 years. No significant difference was found in female patients.

were also performed. The 5Y-OS was 79.2% and 73.7% in the young and young elderly groups, respectively ($p = 0.002$). According to p-stage, the 5Y-OS was 94.8% and 90.6% for IA ($p = 0.022$), 87.0% and 79.0% for IB ($p = 0.027$), 61.0% and 66.9% for IIA, 71.0% and 54.7% for IIB ($p = 0.027$), 49.6% and 44.7% for IIIA, and 80.0% and 27.7% for IIIB ($p = 0.023$), in the young and young elderly groups, respectively. These differences showed a similar tendency to have a better survival rate in the young group as seen with the comparative results between those aged up to and those older than 50 years shown above. However, survival after postoperative recurrence did not show a significant difference between the young and young elderly groups.

The prognostic factors were tested by multivariate analyses using the variables of age, sex, ECOG-PS, smoking history, comorbidity, operative procedure, p-stage, histology, adjuvant therapy (Table 2). Age up to 50 years was identified to be an independent prognostic factor with a hazard ratio of 1.451. Female, good ECOG-PS, no smoking history, no comorbidity, early p-stage, and no preoperative adjuvant therapy were also identified as predictors of a better prognosis. When analyzing age as continuous variable in multivariate analysis, age was identified as an independent prognostic factor with the hazard ratio 1.026 (CI: 1.022–1.030).

4. Discussion

The postoperative survival of young lung cancer patients remains unclear due to their low numbers, though several studies have been reported so far [3–10]. Radzikowska et al. and Minami et al. investigated patients younger than 50 years and showed significantly better survival as compared to old patients [4,6]. Among several studies with definition of the young group as up to 40 years, Tian et al. reported higher 5Y-OS in young patients, though no superior survival was shown in the study by Hanagiri et al. or by Maruyama et al. [5,7,8]. In the present epidemiological study, cancer patients aged up to 50 years who underwent surgery were extracted from the Japanese Lung Cancer Registry Study 2004 [2],

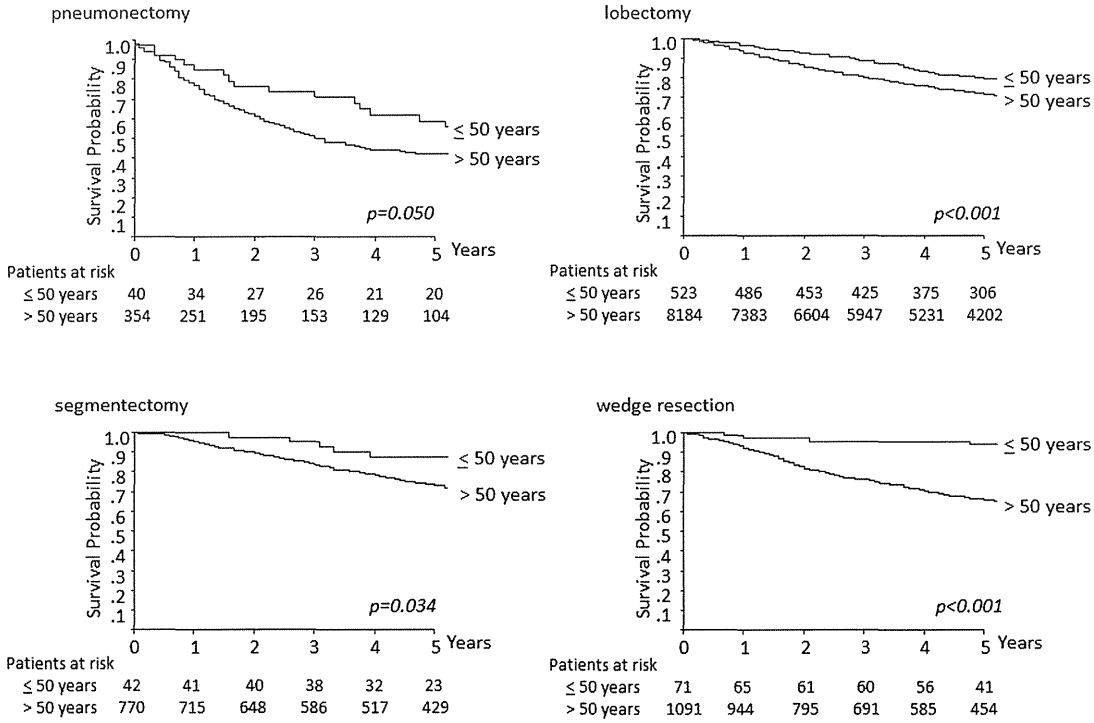

Fig. 4. The survival curves of patients aged up to and older than 50 years with surgery according to operative procedure. The postoperative survival was significantly better in the young group for each procedure.

Table 1
Patients' characteristics.

	Age ≤ 50 years	Age > 50years	p value
Sex			p < 0.001
Male	370(52.6%)	6999(63.2%)	
Female	334(47.4%)	3960(36.8%)	
PS			p < 0.001
0	665(94.5%)	8943(81.6%)	
1	27(3.8%)	1661(15.1%)	
Others	12(1.7%)	355(3.3%)	
Smoking history			p < 0.001
No	308(43.8%)	3777(34.5%)	
Yes	334(47.4%)	6290(57.4%)	
Unknown	62(8.8%)	892(8.1%)	
Comorbidity			p < 0.001
No	562(79.8%)	7151(65.3%)	
Yes	79(11.2%)	3048(27.8%)	
Unknown	63(8.9%)	760(6.9%)	
c-stage			p < 0.001
Stage IA	420(59.7%)	5875(53.6%)	
Stage IB	88(12.5%)	2700(24.6%)	
Stage IIA	36(5.1%)	167(1.5%)	
Stage IIB	45(6.4%)	854(7.8%)	
Stage IIIA	84(11.9%)	856(7.8%)	
Stage IIIB	13(1.8%)	394(3.6%)	
Stage IV	18(2.6%)	113(1.0%)	
Operative procedure			p < 0.001
Pneumonectomy	40(5.7%)	354(3.2%)	
Bilobectomy	18(2.6%)	357(3.3%)	
Lobectomy	523(74.3%)	8184(74.7%)	
Segmentectomy	42(6.0%)	770(7.0%)	
Wedge resection	71(10.1%)	1091(10.0%)	
Others	10(1.3%)	203(1.9%)	
p-stage			p < 0.001
Stage IA	331(47.0%)	4647(42.4%)	
Stage IB	119(16.9%)	2433(22.2%)	
Stage IIA	39(5.5%)	902(8.2%)	
Stage IIB	49(7.0%)	799(7.3%)	
Stage IIIA	128(18.2%)	1676(15.3%)	
Stage IIIB	6(0.9%)	100(0.9%)	
Stage IV	32(4.5%)	402(3.7%)	
Histology			p < 0.001
Adenocarcinoma	554(78.7%)	7367(67.2%)	
Squamous cell carcinoma	52(7.4%)	2548(23.3%)	
Large cell carcinoma	30(4.3%)	357(3.3%)	
Small cell carcinoma	11(1.6%)	232(2.1%)	
Others	57(8.0%)	455(4.1%)	
Preoperative adjuvant therapy			p < 0.001
Yes	73(10.4%)	520(4.7%)	
No	631(89.6%)	10,439(95.3%)	
Postoperative adjuvant therapy			p < 0.001
Yes	221(31.4%)	2682(24.5%)	
No	483(68.6%)	8277(75.5%)	
Total	704(100%)	10,959(100%)	

PS, Eastern Cooperative Oncology Group performance status; Smoking history, including both current and ex-smokers; Comorbidity, including current smoking history, obesity with BMI > 30 kg/m^2, cerebrovascular disease, chronic obstructive pulmonary disease, interstitial pneumonia, ischemic heart disease, renal dysfunction with creatinine> 2.0 g/dL, liver cirrhosis with Child-Turcotte classification > B, diabetes mellitus with HbA1c > 8%, anemia with Hb < 8 g/dL, and treatment for other malignancy within a year.

Table 2
Results of multivariate analysis in lung cancer patients with surgical resection.

Variables		Hazard ratio	95% Confidence Interval	p value
Age				
≤50 years		1.000		
>50 years		1.451	1.211–1.739	<0.001
Sex				
Male		1.000		
Female		0.664	0.593–0.744	<0.001
ECOG PS				
PS 0		1.000		
PS 1		1.582	1.441–1.736	<0.001
PS 2		2.041	1.600–2.604	<0.001
PS 3		2.706	1.717–4.266	<0.001
Smoking history				
No		1.000		
Yes		1.150	1.026–1.289	0.016
Comorbidity				
No		1.000		
Yes		1.232	1.135–1.338	<0.001
Operative procedure				
Pneumonectomy		1.000		
Bilobectomy		1.089	0.873–1.358	0.450
Lobectomy		0.782	0.665–0.920	0.003
Segmentectomy		0.978	0.786–1.218	0.844
p-stage				
IA		1.000		
IB		1.958	1.741–2.203	<0.001
IIA		2.878	2.488–3.329	<0.001
IIB		4.031	3.505–4.637	<0.001
IIIA		6.940	5.288–9.108	<0.001
Histology				
Pre-invasive lesion		1.000		
Squamous cell carcinoma		1.280	0.318–5.151	0.728
Small cell carcinoma		1.961	0.481–7.994	0.348
Adenocarcinoma		1.166	0.291–4.682	0.828
Large cell carcinoma		1.721	0.425–6.978	0.447
Adjuvant therapy				
Preoperative	No	1.000		
	Yes	1.169	1.018–1.342	0.027
Postoperative	No	1.000		
	Yes	0.923	0.850–1.002	0.055

ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; Adjuvant therapy includes systemic chemotherapy and radiation therapy.

and better postoperative survival was observed in these young lung cancer patients, although the proportion of advance disease was higher as compared to the old group. It was also found that, among young patients, women and those with adenocarcinoma had a better survival, which was similar to the results of all-generation analyses [2].

The higher proportion of young patients who underwent pneumonectomy could imply that they were better able to tolerate surgery, as a previous report showed similar results [5]. Pneumonectomy was, however, reported to increase the perioperative morbidity in elderly patients in a case-control study [11], and sleeve lobectomy, if possible, is recommended as an alternative procedure to pneumonectomy, with lower mortality and better survivals [12].

The results of the present study might indicate the importance given to curative intention over the preservation of pulmonary function in young patients. The superior 5Y-OS in young group treated with a pneumonectomy in the present study could suggest that pneumonectomy is still a considerable option for resectable locally advanced disease in the young patients.

Higher rates of both preoperative and postoperative adjuvant therapy in the young group could reflect the higher proportion of stage IIIA advanced disease, which is a prime indication for induction therapy [13], in addition to the ability of young patients to tolerate such treatment. Radzikowska et al. also reported similar results with more aggressive treatment in young patients [4]. The rate of preoperative adjuvant therapy in the young group was more than 2-fold that in those old group (Table 1). These results indicate a planned active multimodal strategy in young patients with good performance status, while the clinical effect to the survival is unclear. Since postoperative adjuvant chemotherapy was adopted as an evidence-based treatment in a practice guideline for lung cancer treatment in 2005 in Japan, quoting several meta-analyses and randomized studies [14–17], only a proportion of patients with stage IB-IIIA analyzed in the present study had received adjuvant therapy. Thus, it might be expected that postoperative survival in patients with locally advanced disease has potentially become better with postoperative chemotherapy, though further investigation is necessary to identify the issue.

The overall survival rates for patients with stages IA, IB, IIB, IIIA, and IIIB were better for patients aged up to 50 years than for

patients older than 50 years. We added another comparison of survival between patients aged up to 50 years and those 50–70 years, because it is expected that patients older than 70 years could have more frequent lung cancer-unrelated death. The similar results to the comparison between patients aged up to and older than 50 years might suggest other factors in addition to the natural aging bias. Though we could not analyze the treatment after recurrence in the present study, young patients with good performance status might have more chance to receive second and third lines of chemotherapy. Further investigation is required to clarify the clinical impact on survival of the aggressive multimodality therapy in young patients with postoperative recurrence using recent cases.

The worse postoperative survival in males older than 50 years was probably due to the greater number of lung cancer-unrelated deaths in that group. This cohort with more comorbidities and smoking history could have cardiopulmonary diseases or second primary malignancies related to tobacco exposure. The poor general status of the old patients might also be related to the less frequent use of adjuvant therapies. As a result, the young male patients without comorbidity or smoking history might improve the survival of the entire patient group. The death rate of male is reported to be twice higher than that of female in 30–84 year-old population by Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labor and Welfare, Japan. Thus, such natural biological bias might also influence to the results.

The tendency for favorable survival in female patients and in patients with adenocarcinoma histology was the same as that seen with all-generation analyses [2]. Bronchioloalveolar carcinoma (BAC) showing ground glass opacity on CT scanning, which is currently classified as adenocarcinoma in situ or minimally invasive adenocarcinoma [18], is generally recognized to be a slow growing, low-grade adenocarcinoma and a unique subtype related to a never-smoking history, female sex, and Asian race [19]. Though CT findings were not analyzed in the present study cohort, higher proportions of adenocarcinoma and females in the Japanese young patients' group might change the patients' characteristics, with a higher rate of BAC and low-grade malignant behavior. Further investigations including CT findings are necessary to resolve these issues.

The present epidemiological study has several limitation and speculation for the results. The retrospective study cannot clarify the prognostic effect of multimodal therapy in young patients due to the lack of data for chemotherapy regimens or molecular target therapy. Younger age is well-known better prognostic predictor in other malignancies and the influence of other factors except the variables analyzed in this study cannot be completely denied. Further prospective analyses using high volume surgically and non-surgically treated lung cancer patients are required to clarify the cause for the better prognosis of young patients treated surgically.

5. Conclusion

In conclusion, surgically treated young lung cancer patients showed the highest rate of locally advanced disease and received active multimodality therapies. Their postoperative survival was better than that of patients older than 50 years, and age was identified as an independent better prognostic factor. Even when comparing cancer-related survival, the outcome was significantly better in young lung cancer patients.

Conflict of interest statement

All authors contributing to this work have no other conflict of interest to declare.

References

[1] Lung Cancer. American Cancer Society; 2013. Available at: http://www.cancer.org/Cancer/ [accessed 22.01.13].
[2] Sawabata N, Miyaoka E, Asamura H, Nakanishi Y, Eguchi K, Mori M, et al. Japanese lung cancer registry study of 11,663 surgical cases in 2004: demographic and prognosis changes over decade. J Thorac Oncol 2011;6:1229–35.
[3] Zhang J, Chen S, Zhen Y, Xiang J, Wu C, Bao P, et al. Multicenter study of lung cancer patients younger than 45 years in Shanghai. Cancer 2010;116:3656–62.
[4] Radzikowska E, Roszkowski K, Glaz P. Lung cancer in patients under 50 years old. Lung Cancer 2001;33:203–11.
[5] Tian DL, Liu HX, Zhang L, Yin HN, Hu YX, Zhao HR, et al. Surgery for young patients with lung cancer. Lung Cancer 2003;42:215–20.
[6] Minami H, Yoshimura M, Matsuoka H, Toshihiko S, Tsubota N. Lung cancer treated surgically in patients <50 years of age. Chest 2001;120:32–6.
[7] Hanagiri T, Sugio K, Uramoto H, Sugaya M, Ono K, So T, et al. Results of surgical treatment for lung cancer in young adults. Int Surg 2008;93:50–4.
[8] Maruyama R, Yoshino I, Yohena T, Uehara T, Kanematsu T, Kitajima M, et al. Lung cancer in patients younger than 40 years of age. J Surg Oncol 2001;77:208–12.
[9] International Union against Cancer, Sobin LH, Gospodarowicz MK, Wittekind C, editors. TNM classification of malignant tumours. 7th ed. New York, NY: Wiley-Liss; 2009.
[10] Mauri D, Pentheroudakis G, Bafaloukos D, Pectasides D, Samantas E, Efstathiou E, et al. Non-small cell lung cancer in the young: a retrospective analysis of diagnosis, management and outcome data. Anticancer Res 2006;26:3175–81.
[11] Leo F, Scanagatta P, Baglio P, Radice D, Veronesi G, Solli P, et al. The risk of pneumonectomy over the age of 70. A case-control study. Eur J Cardiothorac Surg 2007;31:780–2.
[12] Park JS, Yang HC, Kim HK, Kim K, Shim YM, Choi YS, et al. Sleeve lobectomy as an alternative procedure to pneumonectomy for non-small cell lung cancer. J Thorac Oncol 2010;5:517–20.
[13] Non-Small Cell Lung Cancer. http://www.nccn.org/index.asp
[14] Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004;350:351–60.
[15] Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M, Tanimoto M. Role of adjuvant chemotherapy in patients with resected non-small-cell lung cancer: reappraisal with a meta-analysis of randomized controlled trials. J Clin Oncol 2004;22:3860–7.
[16] Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005;352:2589–97.
[17] Hamada C, Tanaka F, Ohta M, Fujimura S, Kodama K, Imaizumi M, et al. Meta-analysis of postoperative adjuvant chemotherapy with tegafur-uracil in non-small-cell lung cancer. J Clin Oncol 2005;23:4999–5006.
[18] Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International association for the study of lung cancer/American thoracic society/European respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244–85.
[19] Raz DJ, Jablons DM. Bronchioloalveolar carcinoma is not associated with younger age at diagnosis: an analysis of the SEER database. J Thorac Oncol 2006;1:339–43.