agreement, our results also showed no association between ABCB1 expression and clinical features.

Among ABC transporters, ABCC11 is at relatively early stages of investigation. ABCC11 is lipophilic anion pump that can confer resistance to chemotherapeutic agents such as methotrexate and 5-FU [17]. We previously reported that a SNP in *ABCC11* is associated with the risk of developing breast cancer among Japanese women [12], although the association of *ABCC11* with breast cancer risk is unclear in Caucasian and European women [13, 14]. These reports mentioned host factors that might differ among races and thus modify the impact of this gene on breast cancer risk. *ABCC11* mRNA is reportedly over-expressed in breast tumors and breast cancer cell lines [9, 21, 22], but few studies discuss expression of the ABCC11 protein in human tumors [23]. Although the breast cancer risk conferred by the SNP in *ABCC11* is not within the scope of this study, we did not see significant differences in breast cancer prognosis by SNP genotype in our samples.

Core-basal and HER2-enriched subtypes are associated with poor clinical outcome [5]. In our series, high expressions of ABCC1 and ABCG2 were more common in aggressive subtypes such as core-basal. Strikingly, high expression of ABCC11 was more frequent and intense in both the HER2-enriched and core-basal subtypes, which implies that ABCC11 may promote the aggressive behavior of these subtypes. Indeed, ABCC11 has been shown to export not only drugs but also other factors that affect cancer biology. In agreement, our results show that patients with high tumor expression of ABCC11 have worse outcomes, particularly among the HER2-enriched and core-basal subtypes. This is the first study to show such an association.

Reportedly, ABCC11 expression is related to sensitivity and resistance to chemotherapy [17, 24–26]. In our data, only ABCC11, but not other transporters, tended to correlate with neoadjuvant chemotherapy response. Interestingly, this was true of chemotherapy regimens that both did and did not include 5-FU, which suggests that ABCC11 possesses unidentified supportive functions for drug resistance other than simple drug efflux. For example, we reported that ABCC1 and ABCG2 in breast cancer cells export sphingosine-1-phosphate [27], a bioactive lipid mediator known to affect drug resistance; we cannot exclude the possibility that ABCC11 possesses such a function. In that case, ABCC11 could become a new target in suppressing drug resistance.

Interestingly, it has been suggested that ABCB1 and ABCG2 may affect the role of cancer stem cells in drug resistance [8]. Although we do not currently have data on this relationship, it is intriguing to speculate that the worse prognosis of ABCC11-expressing tumors may be related to cancer stem cells.

Our study is limited in that it is a retrospective analysis of prospectively collected breast tumor samples, and that it shows only association of these transporters with breast cancer prognosis. To evaluate adequately the role of ABCC11 in breast cancer drug resistance, further studies of the mechanism of resistance are needed.

In conclusion, this is the first demonstration that ABCC11 expression in breast cancer is associated with aggressive subtypes and poor disease-free survival.

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Ethical standards This study was approved by the Institutional Review Board of Yokohama City University, Kanagawa, Japan.

Conflicts of interest The authors declare that they have no conflict of interest.

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Optical Coherence Tomography

15

Norihiko Ikeda and Stephen Lam

Introduction

Optical coherence tomography (OCT) is a promising technique for clinical diagnosis of various types of tissue, because high-resolution tomography is easily obtained by its compact imaging optics.

The fundamental principles of OCT evolved from optical one-dimensional low-coherence reflectometry, which uses a Michelson interferometer and a broadband light source.

Due to the additional transverse scanning (B-scan), two-dimensional imaging was obtained, and this technique was named OCT by Fujimoto and rapidly expanded to numerous biomedical and clinical applications [1, 2].

The mechanism is similar to ultrasound imaging but uses light rather based on the low-coherence interferometry. In ultrasound, the imaging is accomplished by measuring the delay time (echo delay) for an incident ultrasonic pulse to be reflected back from structures within tissue. Because the velocity of sound is relatively slow, this delay time can be measured electronically. However, since the velocity of light is 200,000 times that of sound, measurements of delay cannot be performed directly by electronic techniques. Therefore, a technique known as low-coherence interferometry is used [1, 3–5]. Tomographic images are produced in a manner similar to radar, by scanning the optical beam across the sample, and represent a cross-sectional image of the optical reflectance properties within tissue.

Thus, the resolution of OCT, in both the axial and the lateral dimensions, is more than an order of magnitude higher than that of ultrasonic examination; therefore, OCT can be used to obtain the high-resolution cross-sectional images of microstructure of biological tissues which is comparable to histology [3–5].

Figure 15.1a shows a schematic diagram of the time domain OCT (TD-OCT). Low-coherence light, or light containing many different wavelengths, is generated from the source. The light is split evenly, toward the sample and toward a moving mirror; thus, the reflected light comes from both within the sample and from the mirror. If the distance traveled by light from both directions is nearly identical, interference will occur when the light reflected from the sample and the light reflected from the reference arm mirror recombine at the beam splitter. The coherence length is analogous to the pulse length in ultrasonic imaging systems. The position of the moving reference mirror is precisely controlled electronically. Moving the mirror allows interference (back reflection) information to be obtained from different depths within the sample, because the distance traveled by light in the reference

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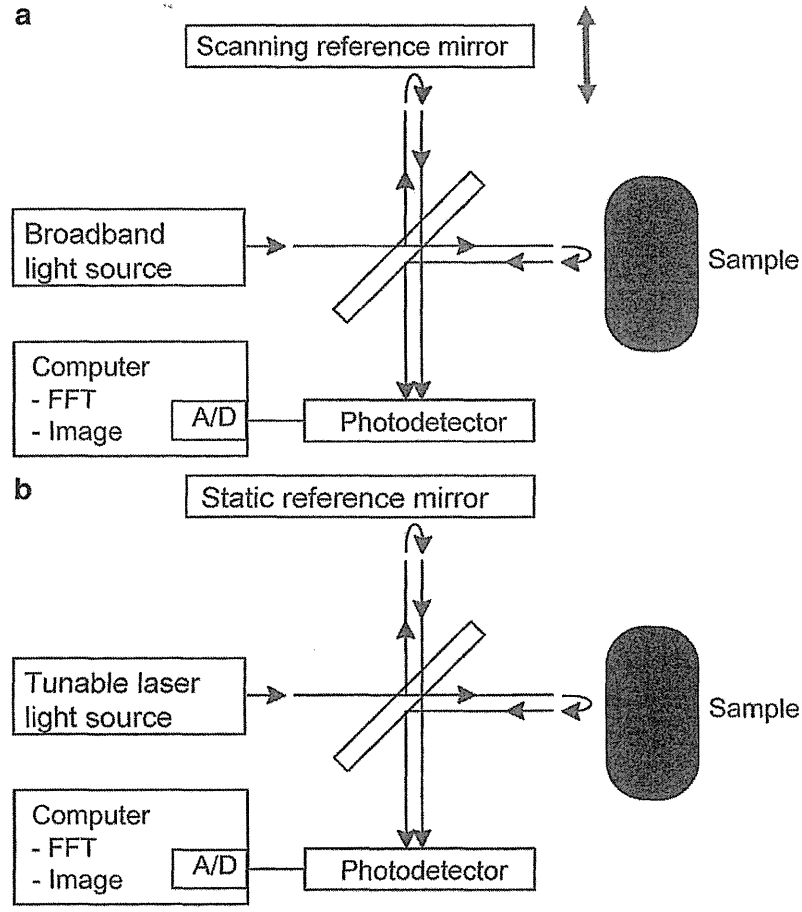

Fig. 15.1 (a) TD-OCT. (b) FD-OCT

mirror arm changes. In A-mode ultrasound, the intensity of back reflection is displayed on a gray scale map as a function of depth.

As the different layers of the tissue have different optical properties, they produce different image patterns on OCT [3, 4].

In recent years, Fourier-domain OCT (FD-OCT) (Fig. 15.1b) has been extensively employed due to its significantly higher imaging speed. FD-OCT has much higher A-scan rates because it requires no mechanical scanning of the reference path length. The spectral response of the interferometer measured is then encoded as an interferogram in optical frequency space. A Fourier transform of this interferogram reveals the reflectivity profile of the sample [5]. The application of FD-OCT to endoscopic OCT requires the use of a Swept-source OCT (SS-OCT). With a tunable narrow-band light source, a sweep over a broad range of optical frequencies is performed [5].

Historical Perspective

In ophthalmology, the first application of OCT involved imaging the transparent structures in the eye [6]. Recent clinical studies have shown that OCT provides tomographic images of the retina with 10-μm resolution and can be used to diagnose a wide range of retinal macular diseases [7]. OCT is accepted as a clinical standard for diagnosing and monitoring the treatment of a number of retinal diseases.

In dermatology, OCT has been employed for monitoring inflammatory diseases. It is useful in visualizing subsurface structures of normal skin, including the epidermis, dermoepidermal junction, dermis, hair follicles, blood vessels, and sweat ducts. Therefore OCT has been employed to diagnose vascular skin lesions, skin malignancy, psoriasis, keratosis, and so on [8].

As OCT is based on sophisticated technology used in optical communication, it can be constructed with common optical fiber components; thus, it is well suited for intralumenal diagnosis.

A key technology that is necessary for the application of OCT for endoscopy is a catheter–endoscope that is capable of delivering, focusing, scanning, and collecting a single spatial-mode optical beam. In addition, the catheter must be flexible and have a smaller diameter than the working channel of the endoscope [9, 10].

Numerous other possible applications of OCT in the field of medicine have been investigated to evaluate their potential in the clinical environment.

OCT is endoscope-compatible and is thus well suited to examining hollow organs like the gastrointestinal tract, the bronchi, and the coronary artery. Gastroenterologists have found that in vivo OCT scanning accurately detected disease features of ulcerative and cancerous lesions in gastrointestinal tract as well as colon segments with high sensitivity [11–13].

In the field of cardiovascular disease, diagnostic assessment of coronary atherosclerosis under OCT-guided coronary intervention has been performed. OCT provides the clear image of the stenotic lumen of the coronary artery caused by the atherosclerosis, which can support interventional procedures [14, 15].

Equipment

Figure 15.2 shows the OCT system developed in collaboration between LightLab Imaging (Boston, USA) and Pentax (Tokyo, Japan).

The catheter is part of the sample arm and is attached externally to the probe interface unit (PIU). The axial resolution of the OCT system is proportional to the coherence length, which is inversely proportional to the bandwidth (wavelength distribution) of the source. In this study, the source used had a bandwidth of 70 nm and power output of 10 nW.

The lateral or transverse resolution is determined by the diffraction limit of the OCT endoscopic catheter [4].

Application to Pulmonary Disease

Endoscopic OCT examination provides high-resolution images of the bronchial surface enabling detailed examination of intraepithelial lesions. Figure 15.3 shows an OCT image of squamous cell carcinoma located in the left upper lobe. Due to the limitation of light penetration, the normal structures observed in the current OCT system are the boundaries of layers between the epithelium, basement membrane, and cartilage. As most bronchial lesions originate from this area, this method is extremely

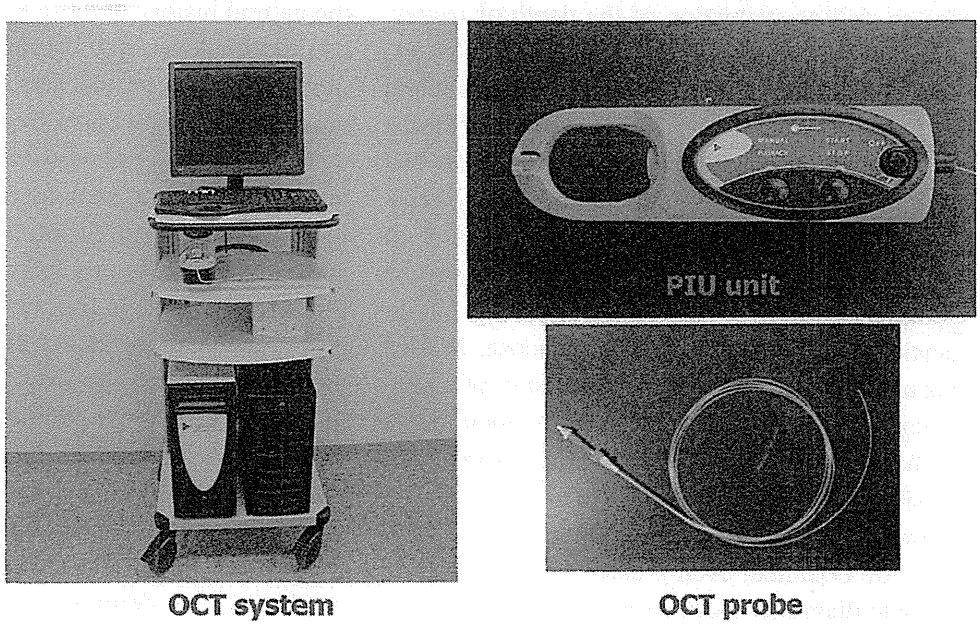

Fig. 15.2 OCT unit

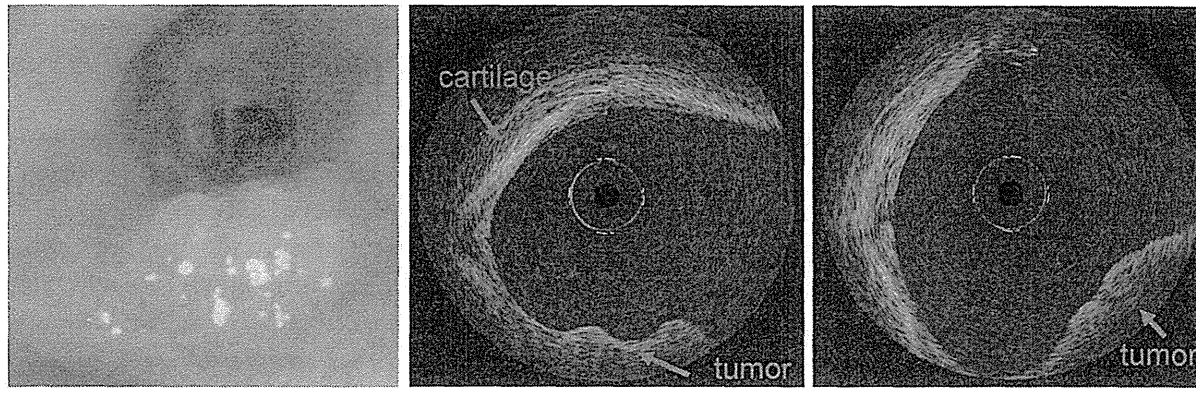

Fig. 15.3 Bronchoscopic and OCT images of squamous cell carcinoma in the left upper lobe (Tokyo Medical University)

useful in capturing the loss of normal structures of the bronchial surface due to tumor invasion by OCT (Fig. 15.3). Also OCT is helpful in evaluating the depth of invasion of bronchial tumors, which is especially useful in selecting the optimal treatment of endobronchial malignancies [3, 4, 16]. Endobronchial ultrasonography (EBUS) is often employed for the same purpose; however, the resolution of the EBUS image is not as good as that of the OCT. Also, the requirement of a transducing medium can make ultrasound difficult and often impractical for routine integration with endoscopy. Furthermore, because OCT is based on light, imaging is possible through air and does not require a transducing medium or direct contact with the object.

OCT is presently used for only investigational purposes, but improvement of this device will enable diagnosis of lesions without invasive biopsies as well as evaluation of the depth of lesions [16]. In a recent study by Lam, using radial scanning endobronchial OCT imaging, the bronchial epithelial thickness of invasive lung carcinoma was reported to be significantly greater than that of carcinoma in situ [16]. Although increased epithelial thickness can be an important feature of lung malignancies, other OCT features may be equally important in distinguishing lung malignancies from normal bronchial mucosa. Michel postulated that some OCT characteristics of malignancy included the loss of normal, identifiable epithelial and subepithelial microstructures, and possibly subepithelial optical fracture [17].

In the future, when cellular-level OCT resolutions are obtained, even greater uses for OCT in thoracic diagnostics can be envisioned. However, at present, the depth of penetration of OCT is relatively shallow (1–2 mm) and is likely to remain limited due to the degree of scattering inherent in complex biologic tissues of the lung and thorax, and thus, major advances in depth of penetration are unlikely, unless more advanced intratissue focusing devices can be developed [18].

OCT might be particularly useful in malignancies such as adenoid cystic carcinomas in which tumor spread tends to occur in the submucosal plane well beyond the observed lumenal component of the tumor. Application of OCT in this and similar settings would allow for possible detection of indistinct margins that might otherwise be overlooked in gross examination and could assist in the accurate determination of resection margins, as well as assessing operability [18]. Autofluorescence bronchoscopy (AFB) aids in screening and localizing preneoplastic and neoplastic lesions; AFB alone cannot be used to study the natural history of these lesions without biopsy confirmation. A combination of multiple imaging modalities can provide an increased and more accurate diagnostic yield from bronchoscopy.

OCT can be applied to evaluate the degree of airway remodeling such as occurring COPD, and there is a strong correlation between CT and OCT measurements of lumen and wall area [19]. In addition to an increase in airway wall thickness, differences in the subepithelial matrix and number of alveoli attached to the airway wall can be shown. OCT can capture the real-time changes in airway lumen diameter between maximal inspiration and tidal breathing which may correlate with the degree of COPD, and the wall measurement of airway relates to the value of forced expiratory volume [20].

Figure 15.4 demonstrates the 3D image of a terminal bronchiole from a smoker without COPD (Fig. 15.4a) and that with adjacent

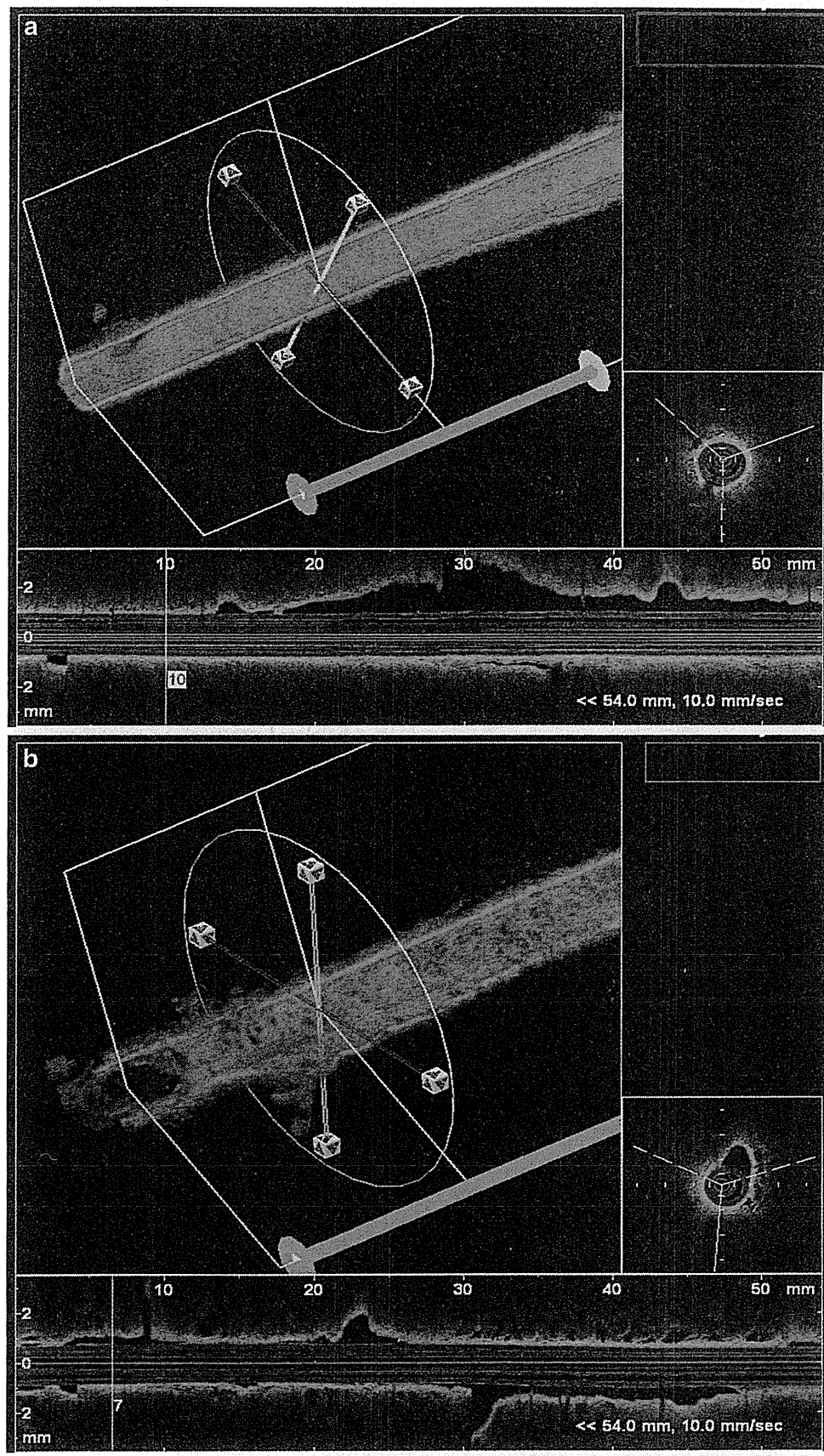

Fig. 15.4 (**a**) 3D image of a terminal bronchiole from a smoker without COPD (British Columbia Cancer Agency). (**b**) 3D image of a terminal bronchiole with adjacent pulmonary emphysema with destroyed alveolar walls in a smoker with COPD (British Columbia Cancer Agency)

pulmonary emphysema with destroyed alveolar walls in a smoker with COPD (Fig. 15.4b). The difference of alveolar structure is precisely demonstrated by OCT.

Summary and Recommendation

OCT imaging is likely to become a powerful tool in diagnostic pulmonary medicine, not only in the early detection of lung cancer but also in the evaluation and monitoring of bronchial microstructures that are affected by other inflammatory or invasive disease processes. It could potentially be used in conjunction with endobronchial ultrasound, autofluorescence bronchoscopy, or narrow band imaging to determine the location of biopsies.

The discrimination of carcinoma in situ, dysplasia, and chronic inflammation should become possible by OCT image soon, although at present, these cannot be definitively diagnosed without biopsy. With further improvement in resolution, contrast, acquisition, display, and processing and the development of specific thoracic probes, OCT might offer a significant advance for the diagnosis and treatment of patients with thoracic diseases.

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最新肺癌学

—基礎と臨床の最新研究動向—

X　肺癌の治療戦略

外科治療

III期肺癌の外科治療

多田弘人

X 肺癌の治療戦略

外科治療

III期肺癌の外科治療

Surgical treatment for stage III non-small cell lung cancer

多田弘人

Key words：III期非小細胞肺癌，縦隔リンパ節，ガイドライン

はじめに

III期非小細胞肺癌は，非小細胞肺癌全体の1/3を占めるといわれる．そのほかの病期と比較して非常に広い対象集団から成り立っているため，その治療戦略は非常に難しく議論の大きいところである．そのため，III期の定義は病期分類の改訂のたび少しずつ改訂されており，少しずつ変化している．

III期は更にIII A期とIII B期に分けられ，TNM分類の第7版からはIIIBでは全く手術を行うことが許容されない分類に定義されるようになった．すなわちTNM分類の第6版まではIIIBはT4anyNM0が含まれていたため，切除可能なT4N0が含まれていた．今回の改訂でT4N0+1がstage IIIAに移行されたことによって，IIIBの中で手術の対象となる集団は消滅したことになる．そのため，本稿のタイトルはIIIA期肺癌の外科治療と読み替えた方が正しい．

n2肺癌の診断と予後

n2肺癌について考察するにあたり，n2の診断が問題となる．画像的にn2と診断されることと病理組織学的にn2と診断されることには大きな違いがある．2004年の我が国の肺がん登録事業のデータでは画像的にn2と診断されたが手術が行われた1,111例の5年生存率は9.6％であり，切除された後で病理学的にn2と診断された1,775例の5年生存率は15.2％であった[1]．これは，画像的にn0と診断していたが実際に切除をしてみるとn2であった集団の方が術前にn2と診断し実際にもn2であった症例よりも予後が良いことを示している．一方で，画像的にも病理学的にもn2であった症例の予後は5％であったという報告もあり，そういった集団に手術単独での治療を行うことは許容されないと考えられている[2]．そのために，術前画像診断で縦隔リンパ節転移が疑われる場合には手術を回避する目的で組織学的診断をすることが勧められる．

n2肺癌の分類

日本のガイドラインでは，縦隔リンパ節の転移の程度についての記載が成されていないが，欧米ではn2をRuckdeschelら[3]が分類したものがガイドラインで用いられている(表1)．

ただし，IIIA2とIIIA3(および一部のIIIA1とIIIA4)は医師による介入によるものであり，この両者は施設・症例によって変化する．今日ではPETによる縦隔リンパ節の診断が普及し，

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表1 Subsets of stage IIIA(n2)

IIIA1 incidental nodal metastases found on final pathological examination of resection specimen.
術後の病理診断で縦隔リンパ節転移があると判断されたもの.
IIIA2 Nodal (single station) metastases recognized intra-operatively.
単一ステーションでの縦隔リンパ節転移が術中に認められたもの.
IIIA3 Nodal metastases (single or multiple station) recognized by pre-thoracotomy staging.
術前に縦隔リンパ節転移があることが証明されたもの.
IIIA4 Bulky or fixed multi-station n2 disease.
画像で明らかに縦隔リンパ節転移があり節外進展を伴っており,病理学的診断をする必要がないもの.

EBUSによる病理学的診断が増えてきている.

ACCPのガイドラインでは,術前のstagingで発見できなかった縦隔リンパ節転移(stage IIIA1-2)が手術中に発見された場合は,試験開胸にせず切除することが望ましいと述べられている[4]. ただし,術中所見で節外浸潤があるとか複数の部位にわたる縦隔リンパ節転移を認めた場合は切除を断念することが望ましいとしている. 肺門部に転移が見つからなくても,縦隔リンパ節にスキップ転移が認められることがあるので縦隔リンパ節を十分にサンプリングする必要があると考えられている. しかし,縦隔リンパ節の郭清まで必要かどうかについてははっきりとした証拠は見いだされていない.

③ n2と診断された完全切除症例の補助療法

手術中,もしくは術後にn2と判定された切除後の症例に対して,考えられる追加治療法は術後補助放射線治療と術後補助化学療法の2つがある.

まず,術後補助放射線治療については幾つかの比較試験が行われた. すなわち,術後放射線治療が局所再発を抑制することによって予後を改善することができるかどうかが問われた. The Lung Cancer Study Groupは1986年に扁平上皮癌だけを対象にn1ないしn2の扁平上皮癌症例を対象に術後50 Gyの縦隔照射を行う群と観察のみの群を比較した試験を報告した[5]. 局所再発率は放射線治療群で大幅に減少させることができたが全体としての予後の改善には繋がらなかった. 同様の比較試験が幾つか出されたがいずれも同様の傾向であり予後の改善に繋がったものはなく,症例数の不足による可能性は否定できなかった. そのため,PORT meta-analysisと呼ばれる212例を包含したメタ解析が行われた. その結果は,早期症例ではむしろ放射線治療は有害であり行うべきではないと結論された.

術後補助化学療法について長年検討されてきた. 1995年のNon-small Cell Lung Cancer Collaborative Groupが行ったメタ解析で,シスプラチンベースの化学療法がハザード比で0.87,5年生存率を5%改善することが示されたが統計学的有意差には届かなかった.

その後,IALT study[6], JBR-10[7], ANITA study[8]が報告され,CDDPにnaverbineなどの併用を4コース行うことで切除単独に比べ予後の改善が得られることが証明された. この効果はstage II-IIIAで認められるがstage IBに関しては観察されなかった. これらによって術後stage II-IIIAの非小細胞肺癌に関してはcisplatin doubletを術後補助化学療法として行うことが標準治療として認められている.

④ 治療前に切除可能n2と判断された症例の治療法

術前に局所進行肺癌と考えられる症例を対象に手術前に導入化学療法±放射線治療を行った後に切除を行うというphase II試験が多く行われた. 比較的良好な結果が得られたため,幾つかのstage IIIを含んだ症例を対象とした導入化

学療法と手術単独の比較試験が行われた．ただし，これらの試験のほとんどが対象の選択基準が明確でなく，やや若い病期が含まれていたり，症例数がそれほど多くないことが問題視されている．比較的サンプルサイズの大きな試験が2つ報告されているので紹介する．ただし，いずれも術前のstagingについては画像のみであり病理学的病期診断はついてはいない．

Depierreら[9]は，術前にifomide，CDDP+mitomycinを術前術後に行う群と手術単独を比較する試験行った．試験全体では予後に統計学的有意差を認めなかったが，subset analysisの結果pn0−1の症例で導入化学療法の効果があったが，pn2の集団では手術単独と変わらなかったという結果であった．

Scagliottiら[10]は，術前にCDDP+gemcitabineと切除単独を比較した試験を行った．この試験は，途中で手術単独群を作っていることが倫理的に許容されなくなったため途中で中止された．結果としてはstage IIB/IIIAのみで術前化学療法が有効であったが，stage IB/IIAでは有効ではなかった．その結果，術前化学療法は術後化学療法の効果とほぼ同等であると考えられ，これ以降術前化学療法に対する興味は薄れている．術前の化学療法に対しては，臨床試験以外で実地医療として行うことは許容できないとされている．

5 切除困難なn2症例に対する治療

最後に，marginally resectable n2(IIIA3)を対象とした比較試験が幾つか行われているので紹介する(**表2**)．

1番目の試験は縦隔鏡で証明されたn2症例を対象に導入化学療法に続いて手術をする群と放射線64 Gyをする群を比較する試験であったが，残念ながら4年間で75例の症例集積しかなく，更にrandomizeされたのはわずかに45例であったため途中で中止され，両群間に差はほとんどみられなかった[11]．

2番目の報告はMD Anderson Cancer Centerで治療された107例の症例で(組織学的に縦隔リンパ節転移を証明したのはそのうち47例のみ)を後方視的に検討し，化学療法後に手術をしたものと，放射線化学療法の同時併用を比較したものである．使用された薬剤と放射線の方法は一定ではなく，これも両群間に予後の差を認めることはなかった[12]．

3番目の試験は前向き試験であり，縦隔リンパ節転移が証明されている症例を対象に(IIIA3, unresectableと称している)，導入化学療法が奏効した症例を対象に，手術を行うか放射線を行うかをrandomizeする試験である．化学療法剤はプラチナを含んだ多剤併用療法を3コース行った．579例が登録され332例にrandome割り付けが行われた．放射線治療は60−62 Gyが照射された(治療薬剤の取り決めが緩やかなのはヨーロッパの各国共同試験のため薬剤を厳密に取り決めることが不可能であったものと考えられる)．手術群の約40％に術後放射線治療が追加されていたが，両群の5年生存は15.7％，14％，両群のMSTは16.4カ月，17.5カ月で変わりはなかった[13]．

4番目の試験は米国で行われた試験である．縦隔リンパ節転移が証明された症例を対象にinduction concurrent chemo−radiation therapyを行った後にrandomizeして，手術をするかbooster radiationをするかを比較した試験である[14]．この試験も統計学的有意差を証明できなかったが，手術群の中で全摘になった54症例中26％にあたる14例が治療関連死亡しており，葉切除が行われた98例では治療関連死亡が1例しか発生していなかったことより，症例選択上問題があったものと評価されている．そのため，肺全摘症例を省けば手術群の予後が良好であり，症例を選択することで手術の意義はあるかもしれないという玉虫色の結論にしている．ただし，この高い治療関連死亡はほかの試験では報告されておらず，真相は不明瞭なままである．

最後の試験は，縦隔リンパ節転移を証明された集団を対象に術前化学療法後に無作為割り付けを行い，放射線化学療法同時併用後に手術をするか，手術後に放射線治療を加えるかを比較したものである[15]．化学療法に対して手術と放

表2　切除困難なn2症例に対する臨床試験

author	year	patients No.	chemo/radiation/surgery	chemo-radiotherapy	median survival, mo.	survival, %
Johnstone, et al.	2002	75	Cis/Vb/Mito, no XRT then surgery	Cis/Vb/Mito+64 Gy XRT	19.4 vs 17.4	70 vs 66 at 1 yr (p=NS)
Taylor, et al.	2004	107	Cis-based, no XRT then surgery	Cis-based 3 cycle+69.9 Gy concurrent XRT	31 vs 27	33 vs 30 at 5yr (p=NS)
van Meerbeeck, et al.	2005	332	Cis-based, no XRT then surgery	Cis-based 3 cycle+60 Gy concurrent XRT	16.4 vs 17.5	16 vs 13 at 5 yr (p=NS)
Albain, et al.	2005	396	Cis/Et+45 Gy XRT then surgery	Cis/Et+45 Gy XRT then 16 Gy XRT	12.8 vs 10.5 (PFS, p=0.017)	27.2 vs 20.3 at 5 yr (p=0.10)
Thomas, et al.	2008	558	Cis/Et 2 cycles, Carbo+vindesine+concurent 45 Gy XRT then surgery	Cis/Et 2 cycle then surgery postoperative 54 Gy XRT	9.5 vs 10.0 (PFS p=NS)	39 vs 34 at 5 yr (p=NS)

Cis: cisplatin, Vb: vinbrastine, Mito: mitomycin, XRT: chest radiotherapy, Et: etoposide, Carbo: carboplatin.

射線の追加の順番を変えたものを比較したものであるが，両群間に差はみられなかった．

おわりに

術前に証明された縦隔リンパ節転移症例で技術的に切除可能と考えられるときは手術単独は奨励されず，放射線化学療法の併用療法(できれば同時併用)が推奨されている．また，術前に放射線化学療法を行ってから手術をする場合には臨床試験として行うべきであり，その際も肺全摘になる症例は除外すべきであると述べている．今後n2に対する治療法については，臨床試験で明らかにされるべきではあるがその前途は多難である．

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