Department of Surgery Division of Chest Surgery, Breast and Endocrinology Surgery

Toshiaki Morikawa, *Professor* Tadashi Akiba, *Professor* Shuji Sato, *Assistant Professor* Makoto Odaka, *Assistant Professor* Hiroshi Takeyama, Associate Professor Satoki Kinoshita, Associate Professor Yasuo Toriumi, Associate Professor Kazumi Kawase, Assistant Professor Isao Tabei, Assistant Professor Hiroko Nogi, Assistant Professor

General Summary

The Divisions of Chest Surgery and of Breast and Endocrinology Surgery were established in June 2005. Since then, all staff members have been active in surgical practice, research, and education. Many studies are in progress.

Research Activities

Chest Surgery

Thoracoscopic surgery is the focus of our clinical activity. This minimally invasive surgery produces fewer postoperative complications and sequelae and is especially beneficial for elderly, high-risk patients. Thoracoscopic surgery requires advanced skills, and we have independently developed total thoracoscopic surgery, which uses only a thoracoscope and video monitors to provide intraoperative views. Our method of thoracoscopic surgery can be used to treat many chest conditions, such as juvenile pneumothorax, peripheral lung nodules, mediastinal tumors, and lung cancer.

Thoracoscopic surgery is also indicated for higher-risk patients with such complications as advanced pulmonary emphysema, impaired pulmonary function, and extremely high age who are not candidates for conventional open surgery.

Operative procedures, including wedge resection, segmentectomy, lobectomy, and pneumonectomy of the lung, are all safely performed, in addition to resection of mediastinal tumors or the thymus. Surgery for lung cancer requires much more advanced skills and oncological considerations, which have also been independently developed. Of the mediastinal procedures, thymectomy is usually performed via thoracoscopy rather than via a conventional median sternotomy. In our department the percentage of the chest operations performed via thoracoscopy is more than 90%, which we assume to be the highest rate in the world.

The minimally invasive thoracoscopic surgery is being investigated with prospective clinical studies. These studies include a comparative study of open surgery and video-assisted surgery for lung cancer and evaluations of video-assisted surgery for bullous lung diseases in elderly patients with impaired lung function, of video-assisted surgery for thymic tumors, and of video-assisted thymectomy for myasthenia gravis.

Our clinical studies are also evaluating new devices and methods, such as narrow-band

imaging for the thoracoscopic diagnosis of benign and malignant lung diseases, and LaparoSonic coagulating shears (Ethicon Endo-Surgery, Inc., Cincinnati, OH, USA) for small thoracotomy. Three-dimensional diagnosis with computed tomography is used to make thoracoscopic surgery safer. The diagnosis and treatment of ground glass opacity of the lung, which is considered to indicate early adenocarcinoma, are being evaluated.

Many basic research studies are also underway. In the morphological expression-related advancement of the molecular genetic analysis of lung cancer, we are investigating whether CA19-9 activity is an important marker of de novo carcinogenesis. The biological and genetic characteristics of peripheral adenocarcinoma of the lung are being investigated to establish the most appropriate surgical procedures. The correlation of the detection of blood circulating tumor cells and the prognosis of patients with lung cancer is being examined.

The oncogenes of lung cancer are being analyzed with a next-generation sequencer. A system for viewing videos on the Internet is now being developed which will help improve surgical training and research.

Breast

- 1. Clinical study
- 1) The evaluation of sentinel lymph-node biopsy after neoadjuvant chemotherapy The disease status of the axillary lymph nodes is the most important prognostic factor for breast cancer. However, axillary lymph-node dissection is associated with postoperative morbidities, such as upper extremity edema, pain, paresthesia, and restriction of the shoulder girdle. The minimally invasive technique of sentinel lymph-node biopsy produces less morbidity and yet allows accurate pathologic staging of the axilla. Experience with sentinel lymph-node biopsy after neoadjuvant chemotherapy is limited. The purpose of our clinical study is to evaluate the feasibility, accuracy, and safety of this procedure in patients who have breast cancer treated with neoadjuvant chemotherapy.
- 2) Evaluation of the usefulness of Sonazoid for detecting breast tumors We performed phase II and III studies of the ultrasonographic imaging of the breast with the microbubble contrast medium Sonazoid (Daiichi Sankyo Co., Ltd., Tokyo) in collaboration with the Department of Radiology. With Sonazoid the sensitivity of ultrasonography for detecting small cancers of the breast equals that of magnetic resonance imaging.
- 3) Evaluation of psychiatric illnesses of patients with breast cancer Many women experience emotional distress, depression, and anxiety after a diagnosis of breast cancer. We have prospectively analyzed patients with breast cancer who have undergone surgery.
- 4) Evaluation of the effectiveness of exercise for psychiatric illnesses in patients after surgery for breast cancer

We prospectively investigated the effects of exercise on psychological health

5) Evaluation of the beneficial effects of cryotherapy for small cancers of the breast (Kashiwa)

Minimally invasive cryoablation techniques are being included in research protocols to treat small cancers of the breast. These techniques offer the advantage of improved cosmesis.

- 2. Basic research
- 1) Studies of the early development of breast cancer

As screening mammography has become more common in Japan, the prevalence of ductal carcinoma in situ has increased to account for 20% of breast cancers in Japan. We have used immunohistochemical techniques to study biological factors involved in the progression of ductal carcinoma in situ to invasive breast cancer.

- 2) The evaluation of clinically useful biomarkers for triple-negative breast cancer Triple-negative breast cancer (TNBC) tumors do not express estrogen receptor or progesterone receptor and do not overexpress human epidermal growth factor receptor 2. Historically, TNBC has responded well in the neoadjuvant setting, with rates of pathologic complete response commonly higher than for other types of breast tumor. However, more than half of patients with TNBC do not achieve a pathologic complete response and have an extremely poor prognosis. Gene-expression profiling has demonstrated that TNBC is a highly heterogeneous disease, including 2 basal-like, immunomodulatory, mesenchymal, mesenchymal stem-like, and luminal androgen receptor subtypes. By analyzing biological markers, we have attempted to identify chemosensitivity factors in TNBC.
- 3) The detection of circulating tumor cells in the bone marrow
 The presence of circulating tumor cells in the peripheral blood and the bone marrow of
 patients with breast cancer is an independent prognostic factor. We are studying the
 prognostic value of the presence of circulating tumor cells in the bone marrow of patients
 receiving chemotherapy.

Endocrine

- 1. Basic research
- 1) The detection of antigens of thyroid carcinoma in serum or urine

A monoclonal antibody, designated JT-95, was made against a thyroid papillary carcinoma obtained by our Department of Breast and Endocrine Surgery. We are attempting to measure the antigen recognized by JT-95 in the serum or urine of patients with papillary carcinoma, in collaboration with the Division of Molecular Cell Biology of The Jikei University. The quantity of antigen of JT-95 is higher in patients with papillary carcinoma, especially those with metastasis to lung or bone, than in patients with breast carcinoma.

2) Research regarding the metastasis of thyroid carcinoma to the lymph nodes Thyroid papillary carcinoma tends to metastasize to lymph nodes. On the other hand, follicular carcinoma tends to metastasize hematogenously to the lungs and bone. We co-cultured a papillary carcinoma cell line (SW1736) and a lymphoma cell line (Daudi) with or without the JT-95 antibody to examine changes in cell attachment. We found that the adhesion between cells was inhibited in proportion to the quantity of JT-95 added. We are investigating the mechanism of cell-to-cell inhibition.

Publications

Takeyama H, Manome Y, Fujioka K, Tabei I, Nogi H, Toriumi Y, Kato K, Kamio M, Imawari Y, Kinoshita S, Akiba N, Uchida K, Morikawa T. An extracellular matrix molecule, secreted by the epithelial-mesenchymal transition is associated with lymph node metastasis of thyroid papillary carcinoma. Int J Endocrinol Metab. 2014; 12: e10748.

Kinoshita S, Kyoda S, Hirano A, Akiba T, Nojima K, Uchida K, Takeyama H, Morikawa T. Clinical comparison of four types of skin incisions for skin-sparing mastectomy and immediate breast reconstruction. Surg Today. 2014; 44: 1470-5. Epub 2013 Sep 17.

Nakada T, Akiba T, Inagaki T, Morikawa T, Ohki T. A rare case of primary intercostal leiomyoma: complete resection followed by reconstruction using a Gore-Tex® Dual Mesh. Ann Thorac Cardiovasc Surg. 2013 Aug 30. Epub ahead of print.

Mori S, Odaka M, Asano H, Marushima H, Yamashita M, Kamiya N, Morikawa T. Anomalous systemic arterial supply to the Basal segments of the lung: feasible thoracoscopic surgery. Ann Thorac Surg. 2013; 96: 990-4.

Kawase K, Kwong Å, Yorozuya K, Tomizawa Y, Numann PJ, Sanfey H. The attitude and perceptions of work-life balance: a comparison among women surgeons in Japan, USA, and Hong Kong China. World J Surg. 2013; 37: 2-11.

Akiba T, Morikawa T, Inagaki T, Nakada T, Ohki T. A new classification for right top pulmonary vein. Ann Thorac Surg. 2013; 95: 1227-30. Odaka M, Akiba T, Mori S, Asano H, Marushima H, Yamashita M, Kamiya N, Morikawa T. Oncological outcomes of thoracoscopic thymectomy for the treatment of stages I-III thymomas. Interact Cardiovasc Thorac Surg. 2013; 17: 285-90.