THE SECOND BRAZIL-JAPAN CANCER MEETING

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Introduction

Shoichiro Tsugane[1]

The second Brazil-Japan Cancer Meeting was held from February 13 to 14, 1995 in east campus of National Cancer Center, located in Kashiwa city, Japan. Nearly 50 scientists including 5 Brazilians, participated in the meeting from National Cancer Center and other institutes in Japan. The aim of meeting was to stimulate the collaborative studies in the field of basic, clinical and epidemiological research through the information exchange. The topics of the second meeting were: 1 - *Clinical aspects of lung cancer in Brasil and Japan* (February 13) and 2 - *Clinical aspects of head and neck in Brazil and Japan* (February 14), both of them were composed of epidemiological, basic and clinical presentations. The results of the collaborative studies between Brazil and Japan were presented in the area of epidemiology and this kind of collaborations were proposed in the area of basic and clinical studies. This 2 day meeting were very informative for both Brazilian and Japanese participants and the outcome of the Brazil-Japan collaborative studies are expected to be presented in the future meeting.

Program

Date: February 13 (Mon), 1995

CLINICAL ASPECTS OF LUNG CANCER IN BRASIL AND JAPAN

Opening remark

- Welcome address (Dr. S. Tsugane)

Epidemiology (Chairman: Dr. S. Tsugane, NCCRI, East)

- Lung cancer among brazilian, japanese and japanese-brazilian (Dr. S. Tsugane)
- Case-control study of lung cancer in Rio de Janeiro, Brazil (Dr. G. S. Hamada)

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Basic research (Chairman: Dr. R. Brentani)
- Genetic susceptibility of lung cancer (Dr. H. Sugimura)
- Problems in pathological diagnosis of small cell carcinoma (Dr. K. Mukai)
- The correlation between P53 gene mutation and postoperative recurrence of lung cancer (Dr. G. Shao)

Coffee break

Clinical research - Brazil (Chairman: Dr. T. Kodama)
- Results of the treatment of lung cancer: a prospective study at ACCH (Dr. R. N. Younes)
- Prognostic factors in lung cancer: role of morphometric histology (Dr. R. N. Younes)

Clinical research - Japan (Chairman: Dr. T. Kodama)
- Combined modality treatment of chemotherapy and radiotherapy for inoperable stage III non-small cell lung cancer (Dr. K. Kubota)
- Alternating radiotherapy and chemotherapy in locally advanced non-small cell lung cancer - pilot study - (Dr. I. Sekine)
- Indication of video assisted thoracoscopic biopsy in diagnosis of lung cancer (Dr. M. Nishimura)

Date: February 14 (Tue), 1995

CLINICAL ASPECTS OF HEAD & NECK CANCER IN BRAZIL AND JAPAN

Epidemiology (Chairman: Dr. L. P. Kowalski)
- Epidemiology of head & neck cancer in Brazil
  Risk factors for laryngeal cancer in Brazil: a case-control study (Dr. G.S. Hamada)

Basic research (Chairman: Dr. K. Mukai)
- Genetic alterations in head and neck cancers (Dr. R. R. Brentani)

Coffee break

Clinical research - Brazil (Chairman: Dr. S. Ebihara)
- Multi-institutional prospective trials on head and neck dissection in oral and laryngeal carcinomas (Dr. L. P. Kowalski)
  Changing concepts on the treatment of advanced tongue cancer (Dr. Luiz P. Kowalski)

Clinical research - Japan (Chairman: Dr. S. Ebihara)
- Multiple primary carcinomas in patients with head and neck cancer (Dr. M. Saikawa)
- Surgical treatment for hypopharynx and cervical esophagus (Dr. T. Yoshizumi)

Closing Remark
- Conclusion and closing address (Dr. R. R. Brentani)

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LUNG CANCER AMONG BRAZILIAN, JAPANESE AND JAPANESE BRAZILIAN

Shoichiro Tsugane

A total of 42,000 japanese died of lung cancer in Japan in 1993; the most frequent cancer death in men and the second most in women. The available mortality data in my hand showed that the age-adjusted mortality rates of lung cancer in 1980 were almost same between Brazil (Sao Paulo) and Japan both in men and women. The figures from incidence data around 1973 revealed the same tendency.

The incidence and mortality rates of lung cancer among japanese brazilian were lower than those among japanese in Japan. The lower rate of male smoker among japanese brazilian (43%) may be attributable to these decrease in lung cancer occurrence. The rate of female smoker among japanese brazilian (9%) was as low as that among japanese in Japan. However, the association with smoking was not clear if brazilian population was included. Genetic factors should be considered for explaning lung cancer risk.

Age - adjusted rates (to the world population) of lung cancer

	Brazilian	*Japanese-Brazilian*	*Japanese*
Mortality (around 1980)			
Males	*25.6*	*18.7*	*24.3*
Females	*6.5*	*3.3*	*7.1*
Incidence (around 1973)			
Males	*31.1*	*22.5*	*29.4*
Females	*6.4*	*7.2*	*8.5*

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EPIDEMIOLOGY OF LUNG CANCER IN BRAZIL

Gerson S. Hamada

Despite the regional differences in disease occurrence in Brazil, lung cancer mortality and incidence rates have shown an increasing trend in Southern and Southeast regions. In order to know the risk factors associated with of lung cancer in Brazil, we carried out a case-control study in the city of Rio de Janeiro where the mortality rate for lung cancer is one of the highest in the country.

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We examined the association between the risk of lung cancer and tobacco smoking, dietary factors and occupational exposures.

This study revealed that smoking is the strongest predictor of lung cancer in our population. The risk increased significantly with the amount of tobacco smoked per day and with the duration of smoking. On the other hand, a striking reduction of risk was observed after cessation of smoking. The mean age of initiation was 16.9 much younger then the smokers of two prospective studies from Japan and the United Kingdom. An expressive number of cases start smoking before the age of 10.

We did not detect any significant protective effect of yellow and green vegetables, or fruit consumption. However, meat consumption was positively associated, mainly in the highest frequency category after adjustment for smoking and other risk factors.

The examination of occupational factors was performed to gain a preliminary insight into the problem. We were not able to detect any significant increase in risk for those who were possibly exposed to respiratory carcinogens, even among heavily exposed groups or those exposed for a long period to harmful agents.

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GENETIC SUSCEPTIBILITY OF LUNG CANCER

Haruhiko Sugimura

Recent advances in molecular markers for lung cancer risk are reviewed and its applications for lung cancer case-control studies in several populations including the ones of Rio de Janeiro are presented.

The practical value of many putative "high risk alleles" for cancer is confounded by ethnic differences in its distribution whereas different distribution of these in different populations may possibly be one of the mechanistic basis for ethnic difference in cancer prevalence.

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PROBLEMS IN PATHOLOGICAL DIAGNOSIS OF LUNG CANCER

Kiyoshi Mukai

Pathology diagnosis is an important part of clinical oncology practice. It provides a large amount of information necessary for the care of cancer patients. Differentiation of benign and malignant neoplastic lesion is an example. Accuracy of pathology diagnosis depends on knowledge and experience of pathologists. There are certain discrepancies in diagnostic criteria among institutions and among individual pathologists. In daily practice, accuracy of pathology diagnosis is seldom questioned. However, in multi-institutional protocol study, discrepancy in diagnostic criteria among institutions may be large enough to cause an inclusion of a certain number of ineligible cases.

In order to see how much discrepancy exists among pathologists, agreement rate of three pathologists for diagnosis of lung cancer was examined using 30 cases of lung cancer of various histology. All three pathologists reached to an agreement in 70% of cases for histological types and 17% for subclassification. Disagreement is most apparent for diagnosis of small cell carcinoma. From this data, it appears necessary to unify diagnostic criteria among pathologists through mutual communication. Additionally, incorporation of immunohistochemistry is expected to increase the agreement rate. At present it is recommended to have a central pathology review for cases registered for protocol studies.

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THE CORRELATIONS BETWEEN P53 GENE MUTATION AND POSTOPERATIVE RUCURRENCE OF LUNG CANCER

G. Shao • T. Ogura • N. Yokosaki • I. Sekine • K. Nagai • T. Kodama • H. Esumi

Abstract

DNA samples from 112 cases of surgically treated lung cancer patients were analysed by fluorescence based method for polymerase chain reaction-single-strand conformation polymorphism (PCR-F-SSCP) analysis. 37,5% (42/112) mutations were detected, including 33.7% (26/77) in adenocarcinoma, 48% (12/25) in squamous cell carcinoma, 25% (1/4) in large cell carcinoma, 50% (1/2) in adenosquamous carcinoma, 100% (2/2) in small cell carcinoma and 0% (0/2) in carcinoid. The mean recurrence time in P53 mutation positive group was 9.14 months and 13.36 months in P53 mutation negative group in which there has been no statistical significance was observed so far. Much longer follow-up time was needed.

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TREATMENT OF NON-SMALL CELL LUNG CANCER AT HOSPITAL A. C. CAMARGO: A PROSPECTIVE STUDY

Riad N. Younes

The presentation will show the standard treatment of NSCLC at our institution, with a multivariate analysis to determine prognostic factors for survival. Our current research protocols will be shown. We will present also results of a study on stereological characteristics of lung cancer that could increase the predictibility of survival staging procedures.

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COMBINED MODALITY TREATMENT OF RADIOTHERAPY AND CHEMOTHERAPY FOR INOPERABLE STAGE III NON-SMALL CELL LUNG CANCER

Kaoru Kubota

Treatment policy for inoperable stage III non-small cell lung cancer (NSCLC) were evaluated. Radiotherapy (RT) has been widely used in the treatment of inoperable stage III NSCLC.

However, the results are poor, with median survival times of less than 1 year and a 15% 2-year survival rate and approximately 5% 5-year survival rate. There were 2 historic randomized studies to compare thoracic irradiation with placebo or delayed irradiation, with one showing marginal benefit and the other no survival benefit. The only prospective randomized study to evaluate the efficacy of megavoltage, high-dose RT showed that immediate RT was no better than vindesine alone or the combination of the same RT and vindesine. To evaluate the role of radiotherapy in combined modality treatment of stage III NSCLC, we conducted a randomized trial using three cisplatin-based chemotherapy (CT) regimens with or without RT in patients with stage III NSCLC. Sixty-three patients were included in the second randomization. The survival rate in the CT/RT group was 58% at 1 year, 36% at 2 years, and 29% at 3 years, as compared with 66%, 9%, and 3% at 1, 2 and 3 years, respectively, in the CT-alone group. This study showed that P-based combination CT followed by chest RT significantly increases the number of long-term survivors. Based on the results, we started a phase II study of concurrent RT and CT with cisplatin, MMC, and VDS. Of 61 eligible patients, 53 (86.9%) had a partial response (PR). The median survival time was 16 months and the 2-year survival rate was 36.7%. The major toxicity was leukopenia ($\geq$ grade 2, 95%). Non-hematological toxicities of $\geq$ grade 3 included nausea/vomiting (16%), fever (11%), and esophagitis (6%). Treatment related death occurred in 2 patients. We concluded that concurrent RT and CT can be safely administered to patients with stage III NSCLC, with excellent response rates and 2-year survival rates. Randomized trial comparing concurrent CT and RT with sequential CT followed by RT started at 1992.

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ALTERNATING RADIOTHERAPY AND CHEMOTHERAPY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - PILOT STUDY

I. Sekine • Y. Nishiwaki • R. Kakinuna • K. Kubota • H. Hojo • T. Matsumoto • N. Ohmatsu • M. Yokosaki • K. Goto • H. Ogino • W. Shimizu • T. Kodama

Unresectable locally advanced non-small cell lung cancer (NSCLC), which accounts for about one-forth of all lung cancer in Japan, has poor prognosis with 5 years survival rate of 5% to 10%. Recently a combination of radiotherapy (RT) and chemotherapy (CT) has been the treatment of choice for the disease. There are three modes of combining RT and CT: sequential, concurrent, and alternating. Although a therapeutic benefit of the alternating strategy is fully expected from the results of experimental and theoretical studies, only a few studies of this combined modality are reported.

We conducted a pilot study to evaluate the safety and feasibility of alternating RT and CT in unresectable stage IIIA or IIIB NSCLC. Patients must have a tumor within an irradiation field no larger than a half of the hemithorax, age of 75 years or less, ECOG performance status of 0 or 1, $Pa0_2$ of 70 Torr or more. Informed consent was obtained from all patients.

Between June and December 1993, 12 patients were treated with hyperfractionated RT (1.5 Gy twice daily, 5 days per week) on weeks 1 and 2, 5 and 6, and 9, to a total dose of 66 to 72 Gy, alternating whith CT (cisplatin 80mg/m2 on day 1 and vindesine 3mg/m2 on days 1 and 8, repeated every 4 weeks for 2 or 3 courses) beginning on week 3. The median age was 60 (range 39-75), 8 were male and 4 female. Seven and 5 were adeno and squamous cell carcinomas, and 1 and 11 were stage IIIA and IIIB, respectively. The median total dose of RT was 72 Gy (range 55.5-72.0). A delay of RT was observed in 10 patients, and the median total duration of irradiation was 67 days (range 42-113). Nine patients received 3 courses of CT, and 3 received 2 courses. Although grade 3 or 4 leukopenia was observed in 11 patients, all of them recovered within 4 days with G-CSF administration. Grade 4 thrombocytopenia was observed in one patient, Grade 1, 2 or 3 esophagitis was observed in 3, 5, 4 patients, respectively. RT was discontinued in 2 patients because of severe esophagitis at the dose of 55.5 Gy or 64.5 Gy. The other non-hematologic toxicities were mild and acceptable. Eleven partial responses were obtained. In conclusion, the regimen of alternating hyperfractionated RT and CT with cisplatin and vindesine was feasible for the most of the patients, and encouraging response rate was achieved.

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INDICATION OF VIDEO ASSISTED THORACOSCOPIC BIOPSY (VATB) IN DIAGNOSIS OF LUNG CANCER

Mitsuyo Nishimura

We evaluated the clinical usefulness of VATB in comparison with trans-bronchial biopsy (TBB), and needle biopsy (NB) in the diagnosis of lung cancer. Between June 1992 and December 1993, 651 patients were suspected lung cancer. 632 patients were examined by TBB. Lung cancer

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patients were diagnosed in 328 cases. Peripheral lesions were 261 cases. We diagnosed 206 (78%) in 261 peripheral cases by TBB. 45 (84%) patients of remaining 55 were obtain the diagnosis by fine needle biopsy (FNB). FNB was done in 159 cases through that time. Video assisted thoracoscopic biopsy (VATB) was done in 8 cases. Only 2 cases were done open lung biopsy. Between June 1992 and December 1994, surgical resections were performed in 259 primary lung cancer. We get diagnosis of 194 (74%) cases by TBB, and obtained diagnosis of 47 (18%) cases by FNB. Remaining 18 cases were diagnosed either VATB (16 cases) and open lung biopsy (2 cases). Those could not diagnose by TBB were mostly patients with tumor located in the peripheral regions and tumor size less than 1.5cm in diameter. In 29 patients with tumor size less than 1.5cm in diameter, TBB could diagnose 11/29 (38%), FNB 5/18 (28%) and VATB 11/13 (85%). Bronchoscopic complications were rare. Complications of FNB were pneumothorax 13 (8.2%), hemosputa 5 (3.1%) and shock 2 (1.2%). In VATB, air leakage was 2 (7.7%) cases. In the case of tumor of less than 1.5cm in diameter, located peripheral region. VATB is indicated to obtain the final diagnosis and can be applied the patients without BFS examination.

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EPIDEMIOLOGY OF HEAD AND NECK CANCERS IN BRAZIL

Gerson S. Hamada

The incidence of oral and laryngeal cancers in men in Southern Brazil is among the highest in the world. The risk of oral cancer is second only to those observed in selected areas of India and France.

Oral cancer case-control study: smoking and alcohol consumption were the most important risk factors for oral cancer in Brazil. Risk levels generally decreased to those of never smokers after 10 years had elapsed since stop smoking. The risk associated with alcohol was mostly evident for wine (cancer of the tongue) and "cachaça" (all sites), a hard liquor distilled from sugar cane. (Other important risk factors were drinking "chimarrão"(a tea-like infusion), use of wood-stove for cooking and frequent consumption of charcoal-grilled meat. A significant protective effect was observed for consumption of carotene-rich vegetables and citric fruits, but not for green vegetable.

Larynx cancer case-control study: this study have shown the importance of regional lifestyle factors ("chimarrão", high consumption of coffee, and the use of wood-stove for cooking), occupational exposures (wood working), behavioral characteristics (smoking and drinking), and family history of cancer with the risk of laryngeal cancer.

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GENETIC ALTERATIONS IN HUMAN CANCER

Ricardo R. Brentani

We have examined sporadic colon cancer specimens for APC gene alterations such as loss of heterozigosy for two polymorphic sites at chromosomes 11 and 15 respectively. We have also examined the same specimens for mutations by SSCP analysis. In conjunct such alterations comprise as much as 40% of our samples. Furthermore, we have looked at a family with the Gardner syndrome. All affected siblings displayed a mutation which consisted in the introduction of a T residue which creates a frameshift mutation leading to the creation of a stop codon some amino acids downstream, corresponding to the translation of a truncated protein. APC alterations were also found in breast cancer and in the benign tumor nasopharyngeal carcinoma. In stomach cancer we have looked instead for mutations affecting the p53 supressor gene and CA repeats. A significant fraction of specimens presented such alterations. In head and neck tumors we found alterations of p53 which correlated significantly with tumor staging and with smoking habits.

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MULTI-INSTITUTIONAL TRIALS ON NECK DISSECTIONS IN ORAL AND LARYNGEAL CARCINOMA

Luiz P. Kowalski

Brazilian Head And Neck Cancer Study Group

The elective treatment of the neck in oral and laryngeal carcinomas has been changed over the last 20 years. The main object of this report is to present the preliminary results of two multi-institutional prospective studies designed to compare standard treatment (modified radical classical neck dissection) (MRND) to supraomohyoid neck dissection (SOH) on the management of clinically negative neck in oral cancer patients (HN004/89 protocol), and MRND (Suarez technique) to lateral neck dissection (LND) on the treatment of supraglottic and transglottic carcinoma (HN003/89 protocol).

Protocol HN004/89: The first 142 patients who had completed planned treatment will be analyzed. All patients had not previously treated T2-T4 N0 squamous cell carcinoma of the oral tongue (60 cases), floor of the mouth (46 cases), inferior gingiva (12 cases), or retromolar trigone (24 cases). There was no significant imbalances between groups. The false-negative rate was 25,4%, and most positive nodes were sited at level II and III. Complications were seen in 43% MRND patients and in 25,7% of SOH patients (P=0,03). Median total duration of hospitalization were 9 days in MRND patients and 7 days in SOH. To date 9 and 14 patients presented, respectively, local and neck recurrences. The 24

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month actuarial survival rates were 53.3% in MRND group and 78.2% in SOH group (P=0,612).

Protocol HN003/89: This study began on 1990 and patient accrual was concluded on December 1993. We will analyze the first 91 who had completed the planned treatment and all clinical and pathological information were available. All patients had not previously treated T2-T4, N0 supraglottic and transglottic squamous cell carcinoma. There were no significant imbalances between groups with respect to demographic, clinical, pathological, and other therapeutic variables. Forty-seven patients underwent MRND and 44 a LND. Complication rates were similar in both groups. The 3-year actuarial survival rates were 74% in MRND group and 61.9% in LND group (P=0,99).

Conclusions: Although the preliminary survival results were similar in both groups of both studies, a longer follow-up and larger series are mandatory to validate definitive conclusions.

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CHANGING CONCEPTS ON THE TREATMENT OF ADVANCED TONGUE CANCER

Luiz P. Kowalski

Advanced cancers of the tongue continue to be a therapeutic challenge. In spite of the significant improvements of radiotherapeutic techniques and addition of adjuvant chemotherapy, patients usually die after a short period. The five-year overal survival in patients submitted to radiotherapy is 5% to 10%. The most recent progress in reconstructive techniques made major glossectomy (subtotal, near total, total or extended total) a reasonable palliative and potentially curative approach. It is the purpose of this review to report a series of 106 consecutive patients treated from 1985 to 1993 regarding to surgical complications and prognosis.

All but one patient undergoing major glossectomy had squamous cell carcinoma. Primary tumor sites were: tongue (50 cases), floor of the mouth (28 cases) and other parts of the mouth (28 cases). The type of glossectomy were as follows: 24 subtotal, 31 near-total and 51 total). A total laryngectomy was performed in 6 cases. A neck dissection was performed in all but 3 patients. A pectoralis major myocutaneous flap was used to repair the operative defect in 96 cases. Complications were seen in 52 cases (49%). The most common complications were wound infection, flap necrosis and fistula. At the study closing date, 30 patients were alive without disease, 5 patients had recurrent disease, 47 died of cancer, 14 died of causes not related to cancer or treatment and 10 were lost to follow-up. The 5 years actuarial survival rates were respectively 45%, 18% and 18% for T3, T4 and Tx.

In conclusion: a major glossectomy without laryngectomy whenever possible is a safe procedure for a selected group of patients with advanced tongue and floor of the mouth cancer. The actuarial survival rates presented suggests that in a very selected group of patients major glossectomy is a surgical procedure to be considered.

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SURGICAL TREATMENT FOR CANCER OF HYPOPHARYNX AND CERVICAL ESOPHAGUS

Takashi Yoshizumi • Satoshi Ebihara • Masahisa Saikawa

Between 1982 and 1991, 200 patients with carcinoma of the hypopharynx and cervical esophagus were treated at National Cancer Center Hospital. Of these, 153 patients who underwent surgical excision of the primary tumor form the basis of this report.

1 - Fifty - two patients had lesions in the cervical esophagus and 101 patients in the hypopharynx. Of the 153 patients, 14 were seen at National Cancer Center Hospital with recurrence after primary treatment had been given elsewhere and 16 had recurrence after treatment with radical irradiation at our hospital.

2 - The surgical procedures involved total laryngopharyngectomy with partial esophagectomy in 105 cases, with total esophagectomy in 26 cases, and partial pharyngectomy with total laryngectomy in 8 cases.

3 - Fourteen patients underwent tumor resection preserving the larynx. Immediate reconstruction with free tissue transfer was adopted in 11 cases gastric pull-up in 3 cases.

4 - Of the 123 previously untreated patients, 24 patients were treated in combination with radiotherapy and 21 with chemotherapy pre or postoperatively.

5 - The five-year cumulative survival rates of the patient with carcinoma of the hypopharynx and the cervical esophagus were 43% and 20.7%, respectively.

The high incidence of locoregional recurrent disease (at least 48% in this series) emphasizes the need for aggressive surgical treatment, but on the other hand, it is also important to establish surgical procedures that preserve not only swallowing but also laryngeal function for patients with localized disease.