

# Multi-institutional Survey of Malignant Pleural Mesothelioma Patients in the Hokushin Region

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## Research Article

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# Abstract

**Background:** Malignant pleural mesothelioma (MPM) is a major occupational and environmental neoplasm. The purpose of this study was to validate the clinical and epidemiological factors, diagnosis, and initial treatment among MPM patients.

**Methods:** We surveyed retrospective data from 152,921 cancer patients in 22 principal hospitals.

**Results:** A total of 166 MPM cases were newly diagnosed. These patients consisted of 136 men and 30 women, with a median age of 69 years old. We estimated the incidence rate for MPM to be 0.55 cases per 100,000 person-years in this study. The ratio per 100,000 population-years was 0.39 in Fukui, 0.60 in Ishikawa, 1.02 in Toyama and 0.35 in Nagano. Forty-five patients were discovered at follow-up of other diseases. Forty-six cases were diagnosed as localized disease, while 13 had accompanying regional lymph node metastasis. Furthermore, 44 cases showed infiltration into adjacent organs. A histological diagnosis was made in 164 cases (98.8%). A surgical approach, chemotherapy, and radiotherapy were performed for 33, 88, and 6 patients, respectively, while 44 patients (26.5%) received best supportive care. Multimodality therapy was conducted in just 3.0% of the MPM patients.

**Conclusion:** MPM has a tragically rapid progression if discovered during follow-up of other diseases. Workers in health-related fields should be on high alert for aggressive MPM. New therapeutic options for MPM are urgently required.

## Introduction

Malignant pleural mesothelioma (MPM) is a lethal cancer primarily caused by the inhalation of asbestos particles, with a latency period of up to several decades and a poor survival (Lanphear 1992). Over 70% of MPM cases in Japan are associated with asbestos exposure (Gemba 2012). In Europe, the MPM incidence rates have been expected to peak around the year 2020 in some countries, and a deceleration or decrease in the incidence may have already begun in the United States of America (Pelucchi 2004, Henley 2013). However, asbestos remains a subject of public interest in Japan. The spraying of asbestos was outlawed in 1975, and the manufacture of asbestos cement pipes ended in 1985. Asbestos disorder prevention regulations were established in 2005, and in principle, the manufacturing, import, and use of asbestos products are prohibited. However, millions of old buildings including asbestos in their makeup are likely still standing in Japan. As such buildings are ultimately destined for dismantling, a process by which asbestos can be easily spread, the number of cases in Japan is likely to peak around 20 years from now, according to predictions made by the Ministry of the Environment. In fact, the number of deaths due to MPM has increased 3-fold in the past 20 years. However, investigations concerning MPM are limited because of the rarity of the disease as well as its highly aggressive potential. Furthermore, while the role of chemotherapy has been partially established (Baas 2021), the roles of surgery (Hasegawa 2008, Rice 2011) and radiotherapy (Price 2011, Cho 2021) remain controversial. Several studies have focused on surgery (Treasure 2011, Rintoul 2014) or chemotherapy (Baas 2021) in

MPM patients, but data on patients who do not visit the hospital are scarce. Recently, the Japanese Joint Committee of Lung Cancer Registry (JJCLCR) established a project to develop a prospective registry database of patients with MPM with the goal of clarifying the epidemiology, pretreatment laboratory values, immunohistochemical evaluation, respiratory function, postoperative morbidity, and follow-up characteristics of MPM (Shintani 2018). This effort started in 2017 and will be conducted until 2026, so its findings have not yet been made public. Therefore, a fine-grained analysis of a wide area performed over a moderate duration is expected to provide useful data in the interim

The Hokushin region of Japan comprises the Hokuriku region (Ishikawa, Toyama and Fukui Prefectures) and Nagano Prefecture, which all have relatively old populations and snowy climates during the winter (Fig. 1). We created a database based on cancer registration in the Hokushin region, referred to as the Hokushin Ganpro Database, to clarify the circumstances concerning cancer patients in a super-aging society, which not only Japan but also countries all over the world will be faced with soon, as the risk of cancer increases with age. We surveyed retrospective data containing hospital-based cancer registries (HBCRs) and information on clinical epidemiological factors of MPM using the Hokushin Ganpro Database.

## **Materials And Methods**

### **Hokushin Ganpro Database**

Maintenance of an HBCR is mandated for all cancer care hospitals designated by the Ministry of Health, Labor and Welfare in Japan (Higashi 2014). These designated cancer care hospitals are expected to serve as hubs for providing standard care, including surgery, chemotherapy, and radiotherapy, to cancer patients in their respective regions and to register newly diagnosed and/or treated cancer cases at their hospitals every year (Koizumi 2020). These institutions maintain HBCRs and collect basic information on all newly encountered cancer cases, such as the tumor location, histology, route of referral to the hospital, and treatment (Sato 2021). The definition of malignancy corresponds to behavioral code 3 in the International Classification of Diseases for Oncology, third edition (ICD-O-3). All target neoplasms newly encountered at the hospitals are registered.

The Hokushin region has been considered a super-aging region according to the Statistics Data, Statistics Bureau, Ministry of Internal Affairs. Hokushin Ganpro is a program supported by the cooperation of six universities located in the Hokushin region: Kanazawa University, Kanazawa Medical University, Shinshu University, Toyama University, Fukui University, and Ishikawa Prefectural Nursing University (Fig. 1) (Sato 2021). Hokushin Ganpro established a large-scale database based on hospital cancer registration covering this region between January 1, 2010, and December 31, 2015 (data set 1). The database includes information on the number of patients in each prefecture, the patient age, sex, process of cancer detection, pre-treatment process, basis for the diagnosis, histological diagnosis, and treatment performed for the registered patients (Sato 2021). The present protocol was approved by the Kanazawa University

Institutional Review Board (IRB) (reference number: 2750-2), Kanazawa Medical University (I328), and the IRBs at the Hokushin Ganpro database project, all of which granted a waiver of consent for the study.

## Study cases and analyses

We surveyed retrospective data of 152,921 cancer patients in 22 principal hospitals in the Hokushin region registered with the Hokushin Ganpro Database. We collected MPM patients who were classified as code C384 (pleura) and analyzed the patients classified as code 2 (diagnosed and treated in the registering hospital) and code 3 (diagnosed in another hospital and treated at the currently registered hospital).

The extent of disease was classified as localized, regional lymph node metastasis, regional extension, or distant metastasis, defined as follows: 'localized', localized in the primary organ; 'regional lymph node metastasis', regional lymph node metastasis but no invasion to neighboring organs; 'regional extension', invasion to neighboring organs; 'distant metastasis', metastasis to other organs or distant lymph nodes (Koizumi 2020). We examined the histological subtype, patient age at the diagnosis, patient sex, and treatments. In addition, we calculated the incidence rate of MPM for each individual prefecture according to the total Japanese population using the numbers of cancer cases and national population statistics for each year. Population estimates in Japan and each prefecture were obtained from the official statistics of Japan portal site (<https://www.e-stat.go.jp/>).

## Results

### Patient characteristics

A total of 166 MPM cases were newly diagnosed. The number of patients with MPM in each prefecture were 18 in Fukui, 41 in Ishikawa, 64 in Toyama and 43 in Nagano (Fig. 1). The incidence rate was estimated to be 3.32/100,000 over the 6-year period. Therefore, we estimated the incidence rate for MPM to be 0.55 cases per 100,000 person-years in this study. The ratio per 100,000 population-years was 0.39 in Fukui, 0.60 in Ishikawa, 1.02 in Toyama and 0.35 in Nagano. These patients were 136 (82%) men and 30 (18%) women, with a median age of 69 years old (range, 45–92 years old). The age-specific number of patients during the observation period is shown in Fig. 2. The highest incidences were observed in those 60–69 years old.

### The diagnosis and stage of MPM

Actual numbers of MPM patients each year were 26 in 2010, 23 in 2011, 34 in 2012, 22 in 2013, 32 in 2014, and 26 in 2015. Next, we investigated the referral pathway. Nine patients were discovered at cancer screening, 9 at health checkups, 11 in a voluntary setting, 45 at follow-up of other diseases, and 92 cases by introduction from another hospital (Fig. 3). One hundred and forty-nine (89.8%), 15, 1, and 1 case were diagnosed as the first, second, third, and fourth cancer, respectively. Eighty-seven, 59, and 1 case were right-sided, left-sided, and bilateral MPM, respectively; 19 cases had 'unknown data'.

Figure 4 shows the data regarding the extent of disease. Forty-six cases were diagnosed as localized disease, while 13 had accompanying regional lymph node metastasis. Furthermore, 44 cases showed infiltration into adjacent organs, and 47 cases had distant metastasis; 16 cases reported to have 'unknown data'. The clinical stages were stage I in 39, II in 29, III in 34, and IV in 51 patients, with 13 cases having 'unknown data'. Only two cases were diagnosed by radiological imaging alone. On hundred sixty-four cases (98.8%) were diagnosed by a pathological diagnosis, with positive histology findings in 145 and positive cytology findings in 19. The histological subtypes were epithelioid (48 cases, 28.9%); sarcomatoid (24 cases), including desmoplastic in 13 cases; biphasic (19 cases); and not otherwise specified type (75 cases, 45.2%).

## Treatment

The therapies applied for MPM are summarized (Fig. 5). Overall, 73% of patients were recorded to have had at least one specific anti-cancer treatment (surgery, chemotherapy, or radiotherapy). A surgical approach was performed for 33 patients, with surgery alone performed in 29 and surgery plus radiotherapy in 4 cases. Chemotherapy was performed for 88 patients, including chemotherapy alone in 87 cases. Radiotherapy was performed for six patients, including radiotherapy alone and chemotherapy plus radiotherapy in one case each. Multimodality therapy (more than 2 approaches) was conducted in just 3.0% of MPM patients (5/166). Forty-four patients (26.5%) received best supportive care (BSC).

## Discussion

This study provided the latest data on the accurate epidemiology of MPM in a specific region of Japan. The ratios of staging recorded and actual rates of histopathological confirmation in this study were 92% and 98.8%, respectively, which is quite high compared with a recent UK report (Murphy 2020, Beckett 2015). These results suggest that the information obtained in this study is reliable. The incidence rates of MPM have been reported to be relatively high in some European countries (UK, the Netherlands) and Oceanian countries (Australia, New Zealand), whereas rates in Japan and countries from central Europe have shown relatively low incidence rates (Bianchi 2014). In fact, the incidence rate was estimated to be 0.55 cases per 100,000 person-years in this study, which is around half of the value in the United States from 2003–2008 (average of 1.05 cases per 100,000 person-years) (Henley 2013). Fortunately, the rates have decreased in the United States (Henley 2013). However, the actual annual numbers of MPM patients have not decreased according to our data, suggesting that closer attention should be paid to this disease, even in the face of governmental regulations.

Unfortunately, the number of the MPM cases in Japan is expected to rise (Maruyama 2006). Thus, regional differences might exist concerning the incidence of MPM due to differing concentrations of asbestos-related factories. Interestingly, the incidence rate in Toyama Prefecture was almost two to three times higher than that in nearby Nagano and Fukui Prefectures. Regarding why the incidence of MPM in Toyama is so high, Toyama Prefecture has the highest mortality rate due to mesothelioma in this area (<http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/tokusyu/chuuhisyu05/index.html>). We failed to obtain

adequate data related to differences in the usage of asbestos by prefecture. Furthermore, while Kanazawa did detect geographical differences in the standardized incidence ratios in Osaka Prefecture (Kanazawa 2006), they also failed to identify the locations of factories and did not obtain any information on what kind of asbestos was manufactured or when, how long and how much asbestos was handled. Detailed information concerning asbestos use, including the type of material, dose, time, duration, factory location, and type of factory will be essential for evaluating the geographical distribution properly. Zha et al. observed that, among long-term residents of Amagasaki, a city in Japan with many asbestos factories, 6.75 times more men and 14.99 times more women than their age mates in the national general population died of mesothelioma (Zha 2019). Furthermore, various investigations have shown a high level of asbestos exposure in Japanese shipyards on the coast side facing the Pacific Ocean or sea, such as Kure and Yokosuka city on the mainland of Japan. These cities were the site of Japanese naval shipyards before World War II (Kurumatani 1999, Morinaga 2001). There is a fisheries grounds linked to shipbuilding in the world at Himi Bay in Toyama. The high incidence rate reported by fish industry officials might therefore be related to the shipbuilding industry. Kishimoto et al. concluded that 79.2% of cases of mesothelioma in Japan were caused by asbestos exposure. According to their report concerning occupational histories of asbestos exposure, 'shipyard worker' is the occupation with the second highest frequency of cases (Kishimoto 2010, Gemba 2012).

In the present study, we found that 45 cases were newly diagnosed during follow-up of other diseases. In general, there are more hospitals and diagnostic modalities in Japan than in Western countries. Today Japan faces the problem of a rapidly aging population. Therefore, the high rate of discovery of MPM during follow-up of other diseases might be unique to Japan. One issue needs to be addressed: the ratio of localized disease reached 27.7% (46/166), but a surgical approach which specifically cytoreductive treatment as part of a multimodality approach (Waller), was performed in only 33 patients (19.9%). This result is unexpected because the diagnosis of one disease during follow-up for another is usually expected to indicate early detection. These discrepancies suggest that the Hokushin region is a reasonable example of an area with an ultra-declining birthrate and aging population. Ninety-two cases were also newly diagnosed by introduction from another hospital. These findings suggest that this disease has widely affected various area.

Unfortunately, there was a high incidence of BSC in the present study (26.5% 44/166), and 47 patients (28.3%) had distant metastasis. The age was significantly higher in the BSC group (mean 77.5 years old) than in the treatment group (mean 67.4 years old) ( $p < 0.0001$ ). However, there were no significant differences between the two groups in terms of the extent of disease. Multimodality therapy was conducted in only 3.0% of MPM patients. This ratio seems to be very low from the perspective of general clinical practice and may be due to the extremely biologically malignant behavior of MPM and its rapid progression. There is some concern that most physicians do not have experience diagnosing this rare disease. Clinicians should therefore ask about a patient's occupational history in order to check for asbestos-related diseases, especially among patients with a history of involvement in the asbestos product industry or shipbuilding.

Several limitations associated with the present study warrant mention. These include the retrospective nature of the study and the fact that it was carried out at domestic institution based on cancer registration data. Therefore, the survival information, treatment sequence, and therapeutic effect were unclear. The type of asbestos fibers in the pleura of the patients could not be analyzed because surgery or autopsies were not performed in these limited cases. Nevertheless, the current findings highlight an important issue, namely our study highlights the added value of a multi-institutional survey to analyze one type of rare cancer which was conducted in this area over a long period of time. Innovative modalities for curing MPM are needed. We recently conducted an observation study of a regional cancer database between 2016 and 2017 as dataset 2, including the Diagnosis Procedure Combination (DPC) survey data in the Hokushin region. A detailed examination conducting using data from a continuous study will provide new findings to help health-related staff monitor and control the disease through various new approaches (Baas 2021).

## Declarations

### Acknowledgements

The authors thank the investigators and institutions involved in Hokushin Ganpro database project: Kanazawa Medical University, Kanazawa University, Shinshu University School of Medicine, Toyama University Hospital, University of Fukui, Ishikawa prefectural central Hospital, Toyama prefectural central Hospital, Kurobe city Hospital, Toyama rousai Hospital, Kouseiren Takaoka Hospital, Takaoka city Hospital, Tonami general Hospital, Toyama city Hospital, National Hospital organization Kanazawa medical center, Fukui prefectural central Hospital, Tsuruga medical center, Saku central Hospital advanced center, Suwa *red cross* Hospital, Nagano *red cross* Hospital, Nagano city Hospital, Nagano children's Hospital, and Aizawa Hospital.

### Author Contributions

**Conception/design:** Hidetaka Uramoto

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**Final approval of manuscript:** Hidetaka Uramoto, Tomoya Takiguchi, Tomonobu Koizumi, Azusa Tanimoto, Ryuji Hayashi, Yozo Nakazawa, Kenichi Ito, Mitsutoshi Nakada, Yasuo Hirono, Yoshikazu Nishino, Seiji Yano

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### **Data availability**

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

**Code availability** Not applicable.

### **Compliance with ethical standards**

### **Conflict of Interest**

TK received honoraria for AstraZeneca Co. LTD, and Ono Pharmaceutical Co., LTD. MN received honoraria for DAIICHI SANKYO COMPANY and Eisai Japan Co and received a research grant from Eisai Japan Co. All other authors declared no conflict of interest.

### **Ethics approval and consent to participate**

The present protocol was approved by the Kanazawa University Institutional Review Board (IRB) (reference number: 2750-2), Kanazawa Medical University (I328), and the IRBs at Hokushin Ganpro database project, all of which granted a waiver of consent for the study.

**Consent for publication** Not applicable.

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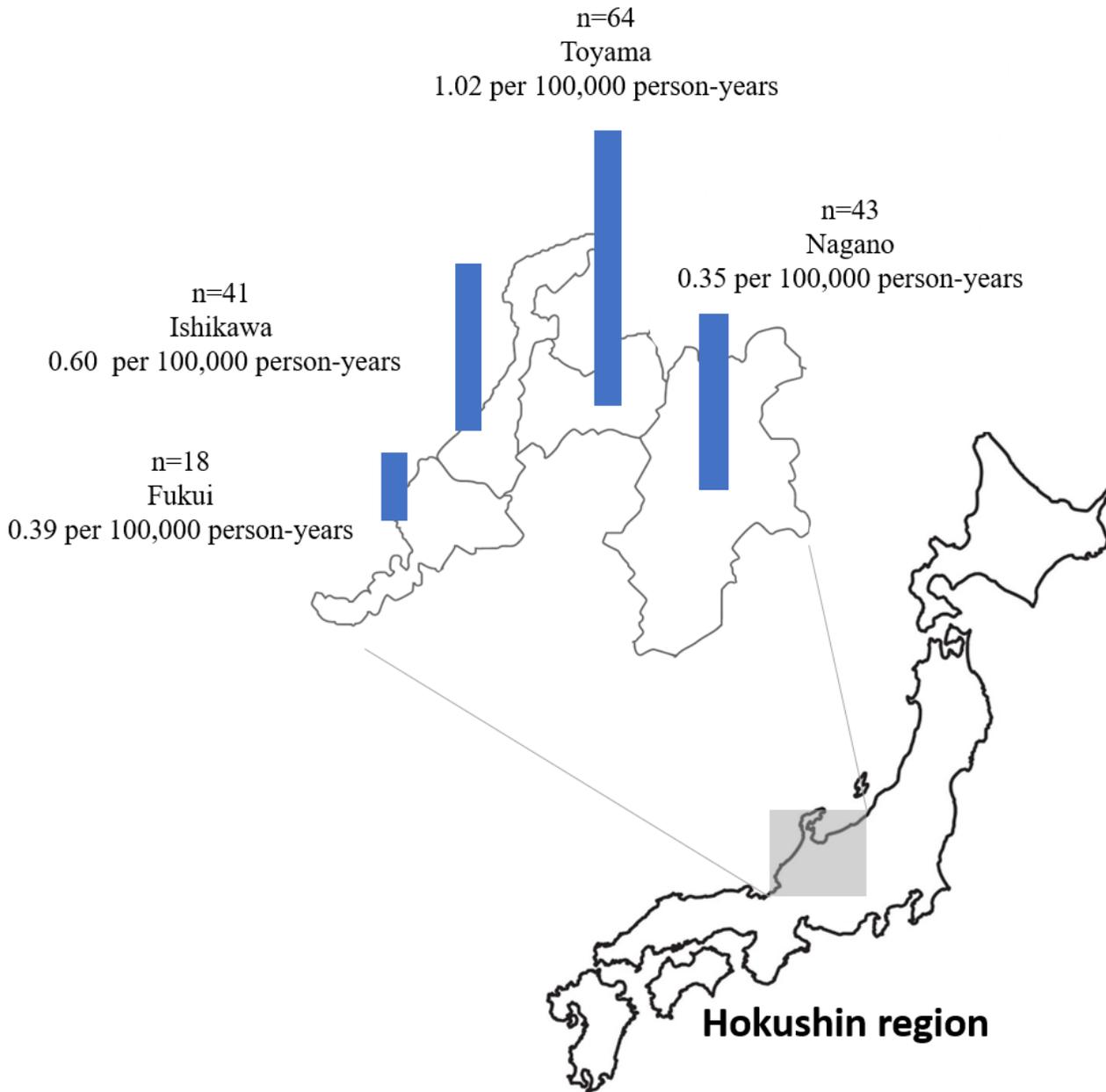
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## Figures

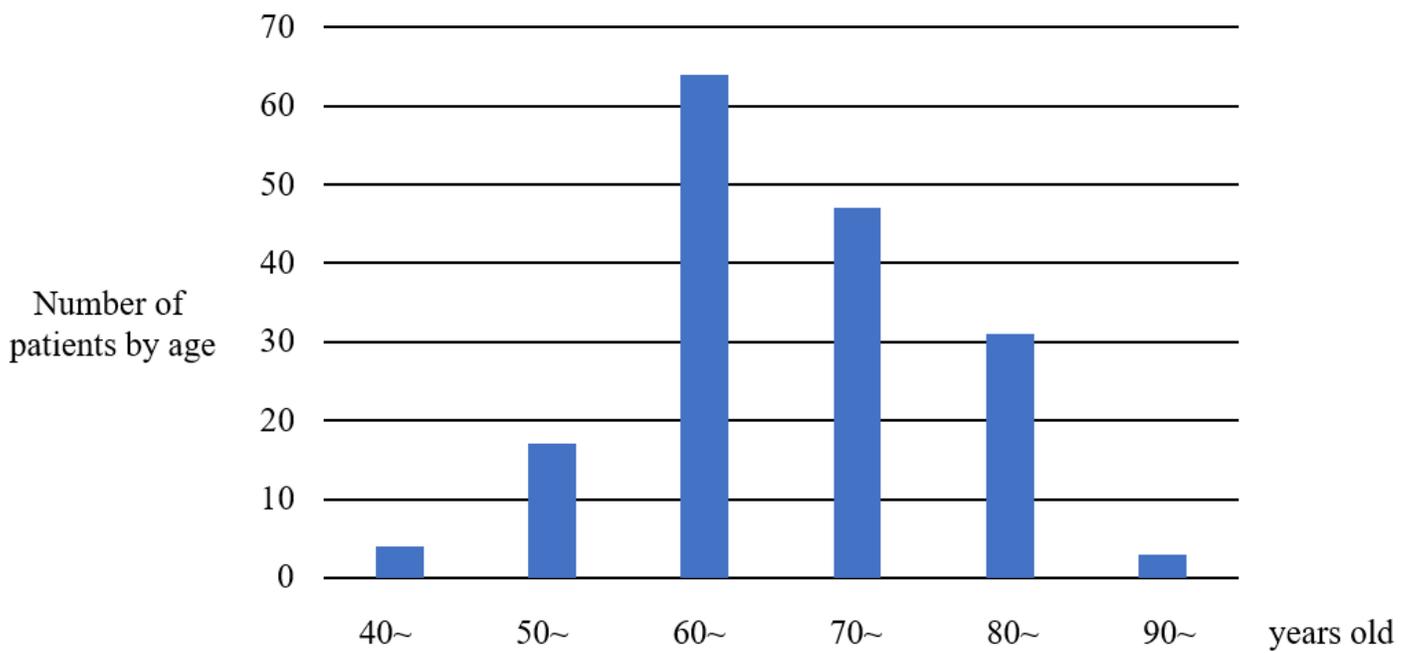
**Fig. 1**



**Figure 1**

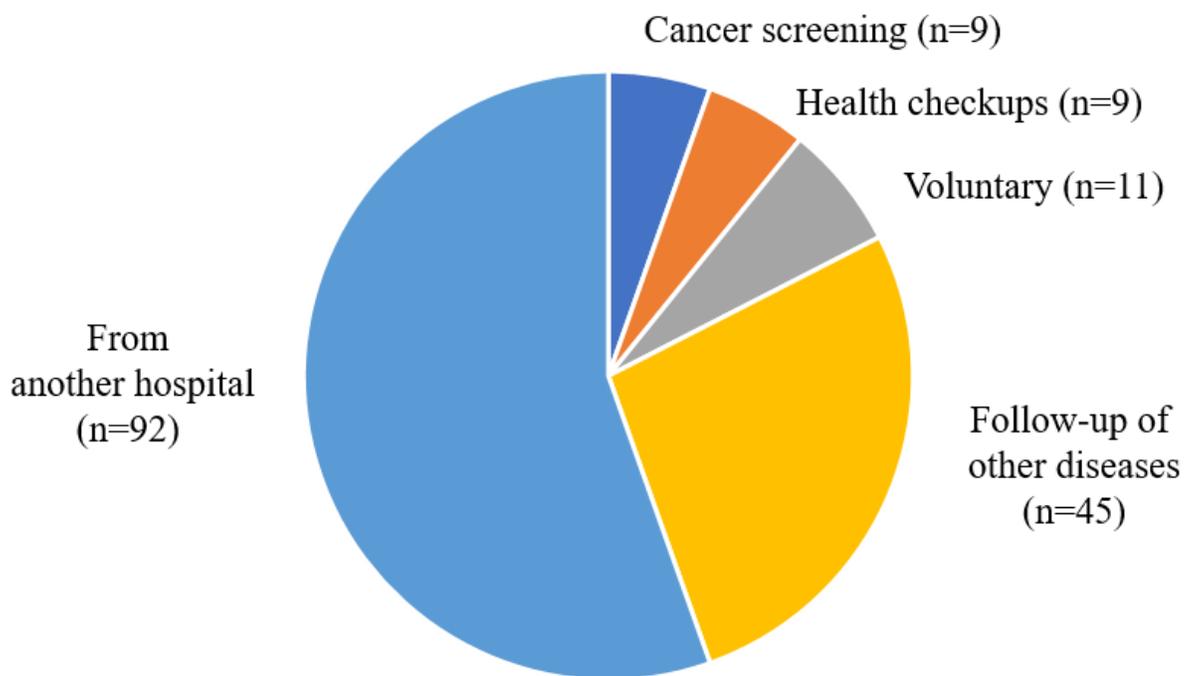
The numbers of MPM patients and the ratio per 100,000 population-years in each prefecture of the Hokushin region are shown. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

**Fig. 2**



**Figure 2**

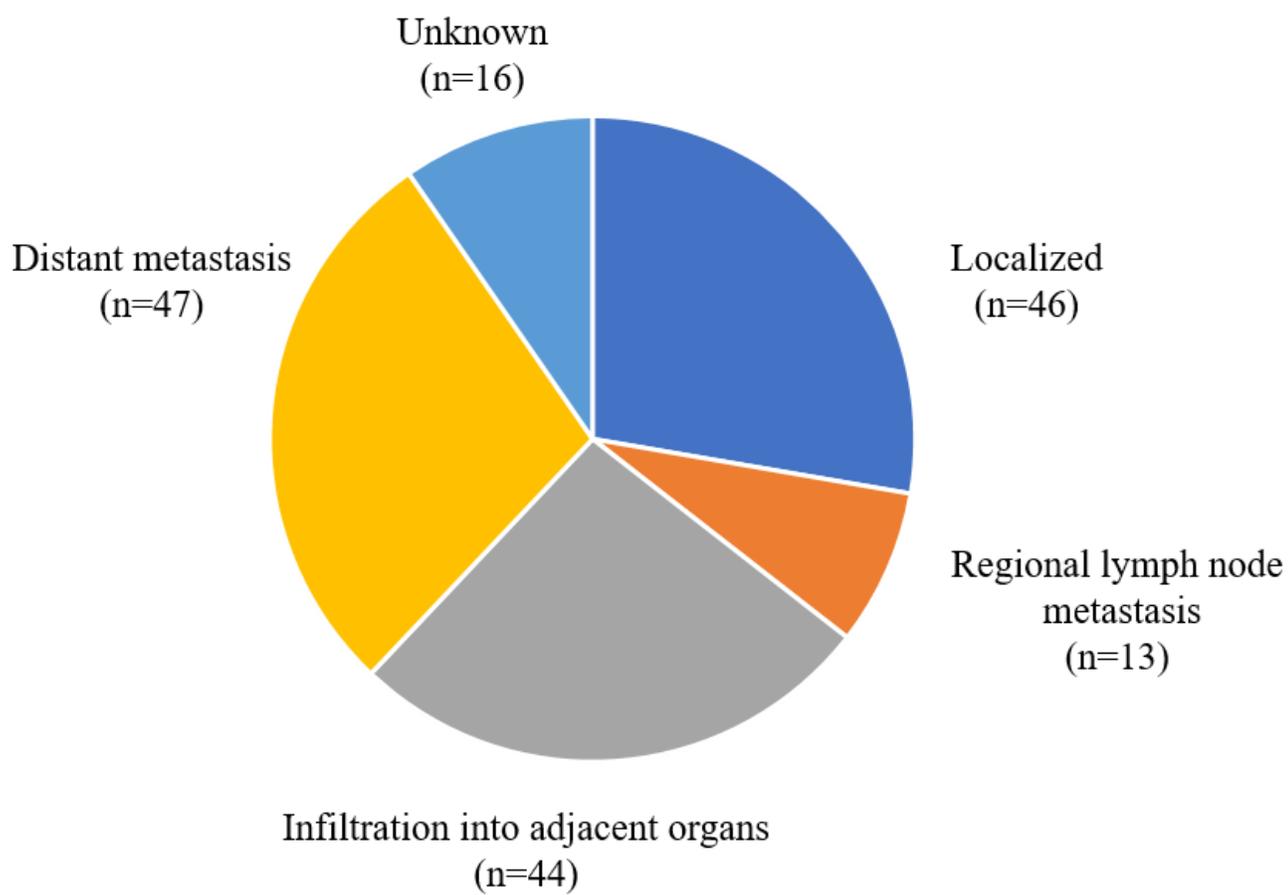
A comparison of the age distribution of MPM patients in the Hokushin region.



**Figure 3**

Actual numbers for the history of discovery.

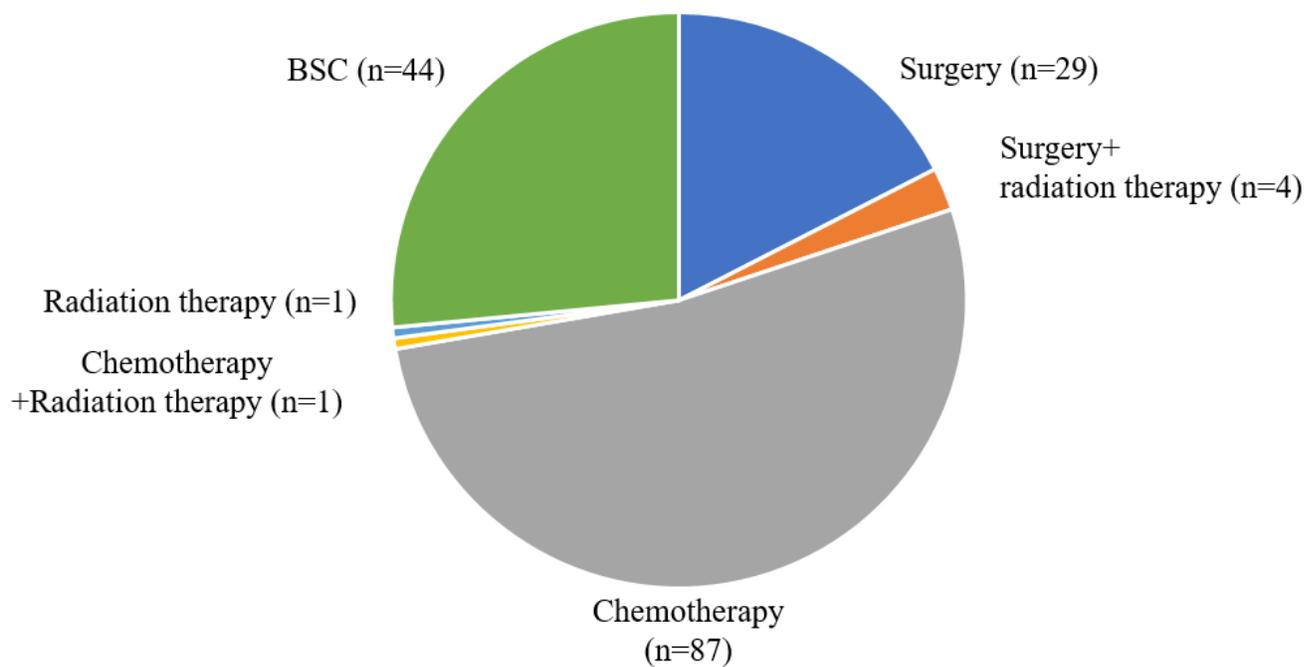
**Fig. 4**



**Figure 4**

Disease extent among patients with MPM in the present study.

**Fig. 5**



**Figure 5**

Therapies administered to patients with MPM in the present study.