Multi-institutional Survey of Thymic Carcinoma Patients in Hokushin Region

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Abstract

Background: The purpose of this study was to validate the clinical and epidemiological factors, diagnosis and initial treatment among thymic carcinoma patients.

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

Results: A total of 88 thymic carcinoma cases were newly diagnosed. These patients consisted of 49 men and 38 women, with a median age of 66 years old. Eight patients were discovered in cancer screening, 9 in a voluntary setting, 14 at health checkups, 25 at follow-up of other diseases, and 32 cases by introduction from another hospital. Only 14 cases had been diagnosed with localized disease, but 5 cases were accompanied by regional lymph node metastasis. Furthermore, 12 cases showed infiltration into adjacent organs, and 24 cases had distant metastasis. Eighty-three cases were diagnosed by a pathological diagnosis. A surgical approach, chemotherapy, and radiotherapy were performed for 29, 35 patients, and 31 patients, respectively, while 17 patients received best supportive care.

Conclusion: The diagnosis of thymic carcinoma is still difficult, and this disease has a tragically rapid progression if when discovered during follow-up of other diseases. An innovative modality for the early detection of thymic carcinoma is needed in modern medical society.

Introduction

The basic act on cancer control started in 2007, and this plan enabled each prefecture to formulate their own original plan depending on the actual circumstances of prevention, screening, and treatment for cancer patients. To fully evaluate such circumstances, cancer registration including information on registered patients has been promoted in core cancer treatment hospitals (Higashi 2014). 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 Japan will be faced with the near future because the risk of cancer increases with age. Indeed, cancer is already a major cause of death among the Japanese.

While lung cancer, which is the representative thoracic malignant tumor, remains a leading cause of death (Uramoto 2015), the age-adjusted mortality for lung cancer has been improving recently thanks to developments in diagnostic imaging and therapies (Ortega-Franco 2020). However, the prognosis of thymic carcinoma, which is similarly to lung cancer and has malignant potential in thoracic spaces while being much more aggressive than thymoma, is very poor (Yano 2008). Several studies have focused on surgery including our previous report (Yasuda 2011, Hishida 2016, Zhao 2013) or chemotherapy (Ko 2018) in thymic carcinoma patients, but data on patients who do not visit the hospital are scarce.

Because clinical differences and outcome comparisons of thymic neoplasms have been rarely investigated, due to the rarity of the entity itself, a multicenter study will be necessary for the accumulation of cases (Shitara 2014, Filosso 2016). Recently, the national incidence of thymic carcinoma in the Japanese population was reported (Koizumi 2020). The authors summarized the clinical profile of 2587 cases of thymic carcinoma treated surgically between 2009 and 2015 using a hospital-based cancer registry (HBCR). However, detailed information, such as the pre-treatment process and basis for the diagnosis of thymic carcinoma, were limited, and the precise incidence rates in specific areas remain unclear. Therefore, a fine-grained analysis in a wide area performed over a moderate duration should be performed.

We surveyed retrospective data containing HBCR and information on clinical epidemiological factors of thymic carcinoma 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. The definition of malignancy corresponds to behavioral code 2 or 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). 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. 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.

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 thymic epithelial tumor patients in class with code C37.9 (thymus), C38.1(anterior mediastinum), and C38.3 (mediastinum: Unknown location) and analyzed the patients in class of cases of code 2 and 3. These are coded as 2 (diagnosed and treated in the registering hospital) and 3 (diagnosed in another hospital and treated in the registering hospital), respectively.

Among the cases, we excluded those diagnosed as thymoma, neuroendocrine tumor and combined thymic epithelial tumors. Thus, we limited our study sample to patients diagnosed with thymic carcinoma. 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. We examined the histological subtype, patient age at the diagnosis, patient sex, and treatments. In addition, we calculated the incidence rate of thymic carcinoma 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 88 thymic carcinoma cases were newly diagnosed. The number of patients with thymic carcinoma in each prefecture were 9 in Fukui, 14 in Ishikawa, 24 in Toyama and 41 in Nagano (Fig. 1). The incidence rate was estimated to be 1.76/100,000 over the 6-year period. Therefore, we estimated the incidence rate for thymic carcinoma to be 0.29 cases per 100,000 person-years in this study. The ratio per 100,000population-years was 0.19 in Fukui, 0.21 in Ishikawa, 0.38 in Toyama and 0.33 in Nagano. These patients were 49 (56%) men and 38 (43%) women, with a median age of 66 years old (range, 38–92 years old). The age-specific number of patients during the observation period were shown in Figure 2. The highest incidences were observed in those 60–69 years old.

Cancer diagnosis

Next, we investigated the reason for visiting the hospital. Eight patients were discovered at cancer screening, 9 in a voluntary setting, 14 at health checkups, 25 at follow-up of other diseases, and 32 cases by introduction from another hospital (Fig. 3). Eighty (90.9%), 6 and 5 cases were diagnosed as the first, second and third cancer, respectively.

Figure 4 shows the data regarding the extent of disease. Fourteen cases were diagnosed as localized disease, while 5 had accompanying regional lymph node metastasis. Furthermore, 12 cases showed infiltration into adjacent organs, and 24 cases had distant metastasis; 33 cases reported to have

‘unknown data’. Five cases were diagnosed by radiological imaging alone. Eighty-three cases (94.3%) were diagnosed by a pathological diagnosis with positive histology findings in 79 and positive cytology findings in 4 cases. Squamous cell carcinoma was the most common histological type (44 cases; 53%). The histological subtypes were squamous cell carcinoma (44 cases, 53.0%), adenocarcinoma (4 cases), basaloid cell carcinoma (3 cases), not otherwise specified type (NOS, 29 cases, 34.9%), and adenosquamous cell carcinoma, lymphoepithelioma like carcinoma, and sarcomatoid carcinoma in 1 case each.

Treatment

The therapies applied for thymic carcinoma are summarized (Fig. 5). A surgical approach was performed for 29 patients, with surgery only in 16, surgery plus chemotherapy in 3, surgery plus radiotherapy in 9, and surgery plus chemotherapy plus radiotherapy in 1 case. Chemotherapy was performed for 35 patients, including chemotherapy only in 21 cases. Radiotherapy was performed for 31 patients, including radiotherapy only in 11 cases. Multimodality therapy (more than 2 approaches) was conducted in 26.1% of thymic carcinoma patients (23/88). Seventeen patients (19.3%) received best supportive care (BSC).

Discussion

This study included two expected and two novel finding. First, the incidence rate was estimated to be 0.29 cases per 100,000 person-years in this study, which is completely consistent with the Japanese hospital-based cancer registry. These results suggest the accuracy of the data used in this study. Interestingly, the incidence rate in Toyama Prefecture was almost twice that of nearby Ishikawa and Fukui Prefectures. Koizumi et al. compared the frequency of thymic carcinoma in eight areas of Japan. They found that the incidence rates in the Chubu and Shikoku Regions was 0.43 and 0.44, respectively, while those in the Hokkaido District and Kanto Regions were both 0.29 (Koizumi 2020). Regional differences might exist on the incidence of thymic carcinoma. Engels et al. reported that the thymoma incidence was over twice as high in Hawaii as in other registries, and this incidence was highest among Asians/Pacific Islanders (0.49 per 100,000 person-years) (Engels 2003).

Second, the median age (66 years old) of the thymic carcinoma patients in this study was relatively high compared with the ESTS data (56 years old) (Ruffini 2014), NEJ023 study (58 years old) (Ko 2018), ESTS+ITIMG (61 years old) (Filosso 2016), JART (61 years old) (Hishida 2016) and HBCR data (65.5 years old) (Koizumi 2020). The frequency of women in the above reports was around 30%-40%. The relatively high rate of women (43%) in this study might also be due to the aging population, as the highest incidence rate was observed in women 70–74 years old (Koizumi 2020). Multimodality therapy, which included ≥2 approaches, was conducted in 26.1% of thymic carcinoma patients. This ratio was very low compared with the national incidence in Japan (51.5%) (Koizumi 2020). These comparisons suggest that the Hokushin region is a reasonable example of an area with an ultra-declining birthrate and aging population. However, clinical physicians must keep in mind the fact that thymic carcinoma tends to

have a younger age distribution than other cancers (Koizumi 2020) because thymic epithelial tumors most commonly affect people between the ages of 40 and 60 (Knetki-Wróblewska 2021).

Third, 25 cases were newly diagnosed during follow-up of other diseases. It is difficult to detect thymic carcinoma in the early stage, since the symptoms of the disease are not remarkable until it invades or compromises other organs, including the heart, nerves, bronchus and blood vessels (Weksler 2013). In general, there are more hospitals and hospital beds and diagnostic modalities, such as computed tomography, in Japan than in Western countries. In addition, Japancurrentlyhas anaging population. Therefore, the high rate of discovery of thymic carcinoma during follow-up of other diseases might be unique to Japan. However, one issue needs to be addressed: only 14 cases were diagnosed as localized disease, and most patients had advanced disease before treatment. Among the 55 evaluable cases, 41 (75%) had disease progression beyond regional lymph node metastasis (stage III to IV disease). This result is unexpected because the diagnosis of one disease during follow-up for another is usually expected to indicate early detection. However, localized cases were found in just 7 (28.0%) of the 25 patients diagnosed during follow-up of other diseases in our data set. As a result, it is important to increase the overall awareness of 'thymic carcinoma', especially among non-professionalhealthcarepractitioners.

Fourth, a surgical approach was performed for only 29 patients, and only chemotherapy was performed for 21 cases. Even more miserable, 17 patients (19.3%) simply received BSC. Of note, 80 cases (90.9%) were diagnosed as a primary, not secondary, cancer. This phenomenon might be due to the extremely biologically malignant behavior of thymic carcinoma and its rapid progression.

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, complete staging system, treatment sequence, and therapeutic effect were unclear. Nevertheless, the current findings highlight an important issue, as this was a multi-institutional survey for a rare cancer conducted in a wide area with a set duration, with a focus on preparing for the near future of an ultra-declining birthrate and aging population. Innovative modalities for the early detection of thymic carcinoma and improved treatment for cases in the advanced stage are needed. We recently launched an observation study of a regional cancer database between 2016 and 2017 as dataset 2 including **Diagnosis Procedure** Combination (DPC) survey data in the Hokushin region. A detailed examination conducting using data from a continuous study will provide new findings regarding patient selection and the relationships between the survival and timing of various treatments, as well as the therapeutic effects.

Declarations

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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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Figures

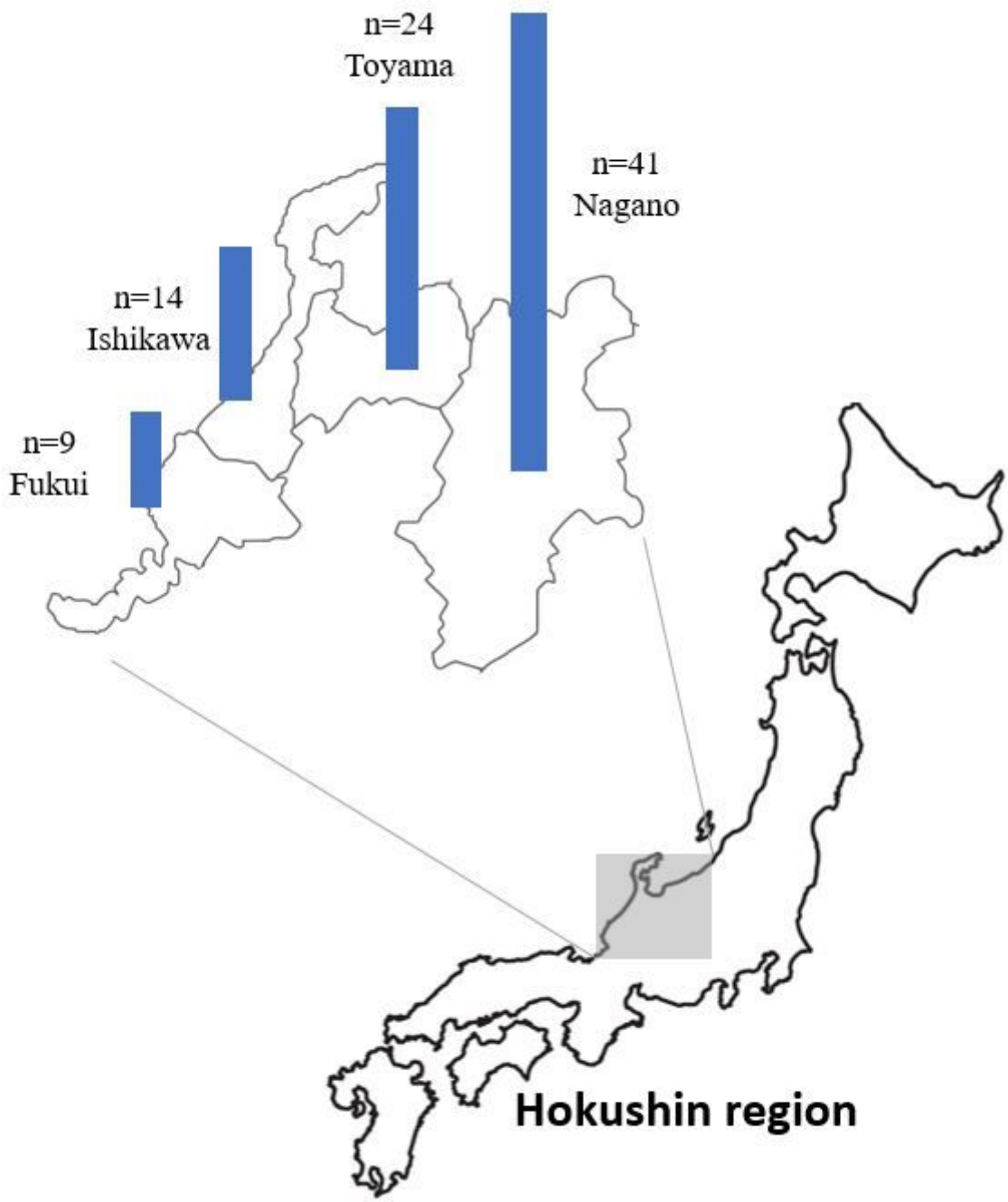

Figure 1

The number of thymic carcinoma patients in each prefecture of the area of 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.

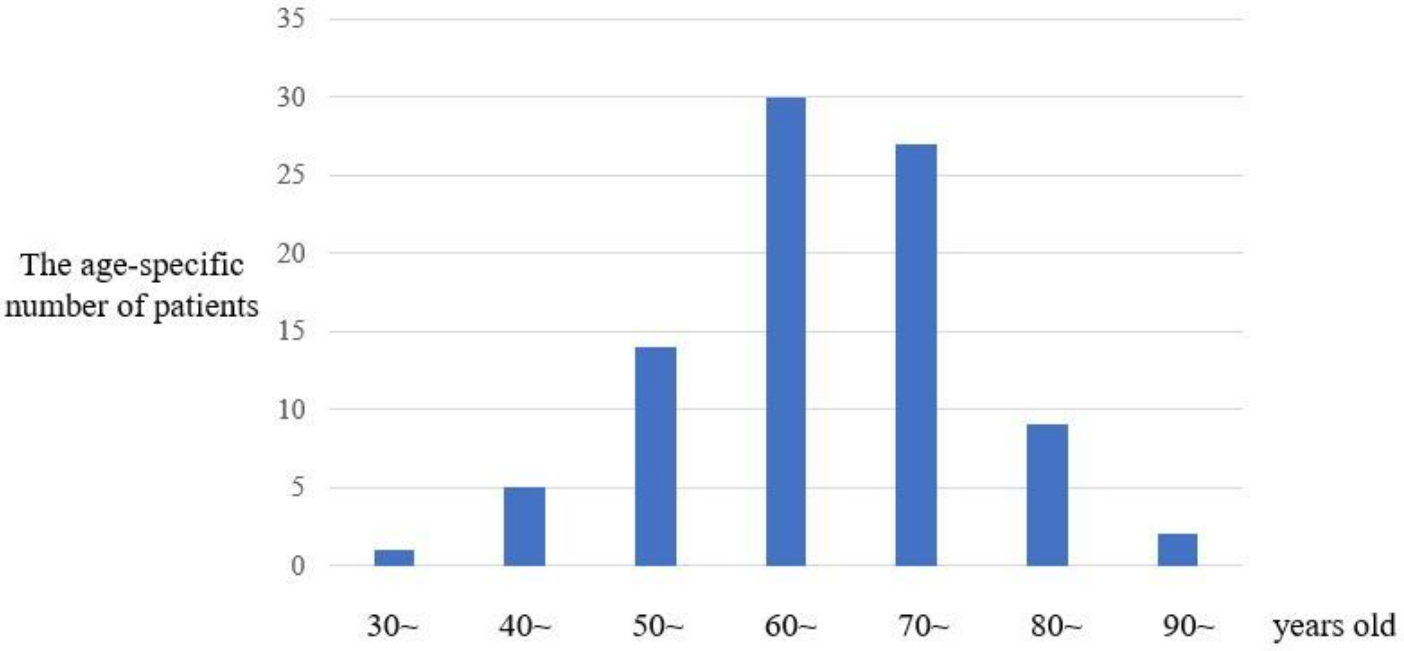

Figure 2

The comparison of the age distribution of thymic carcinoma patients in the Hokushin region.

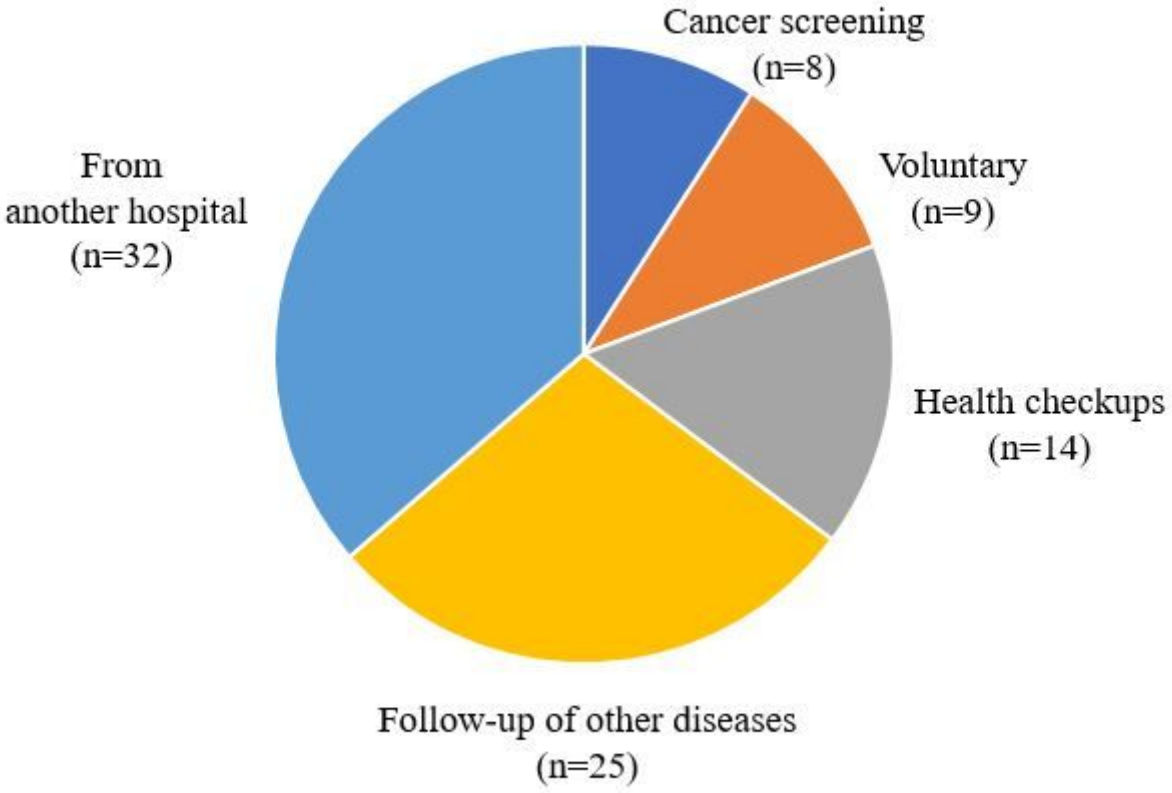

Figure 3

Actual numbers for the history of discovery.

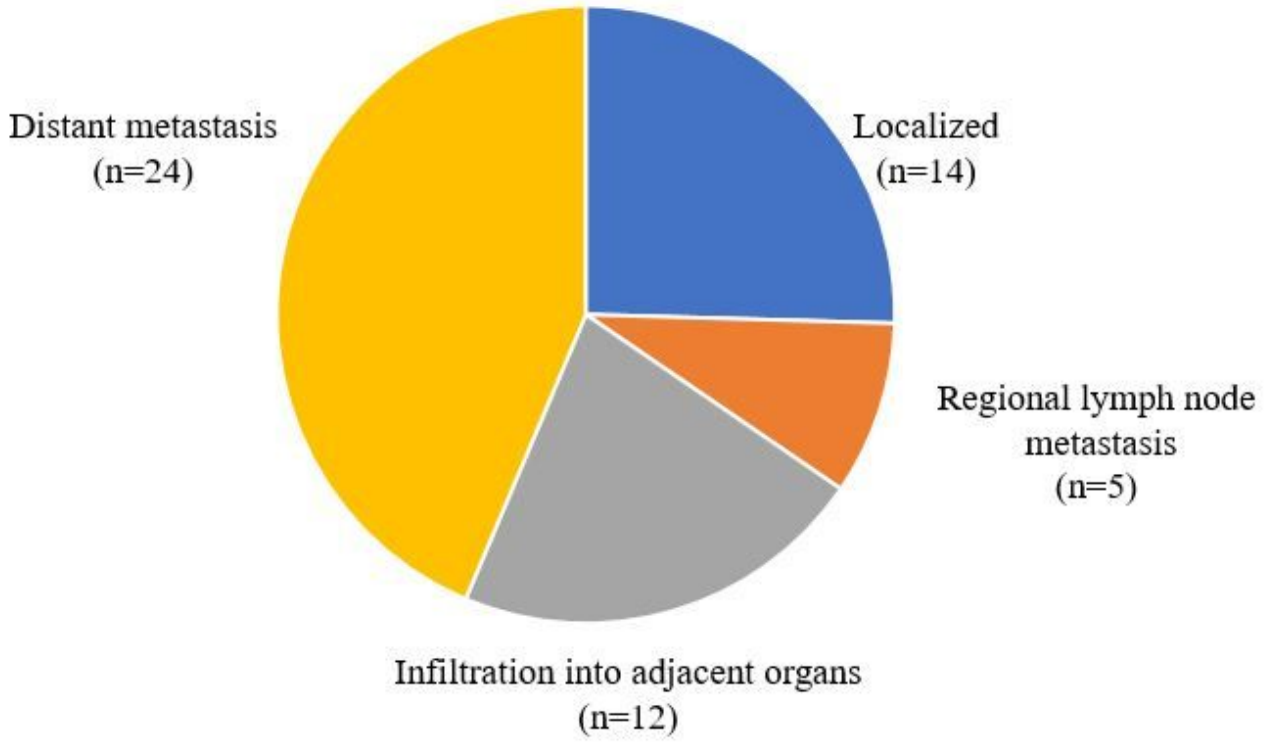

Figure 4

Disease extent among patients with thymic carcinoma in the present study.

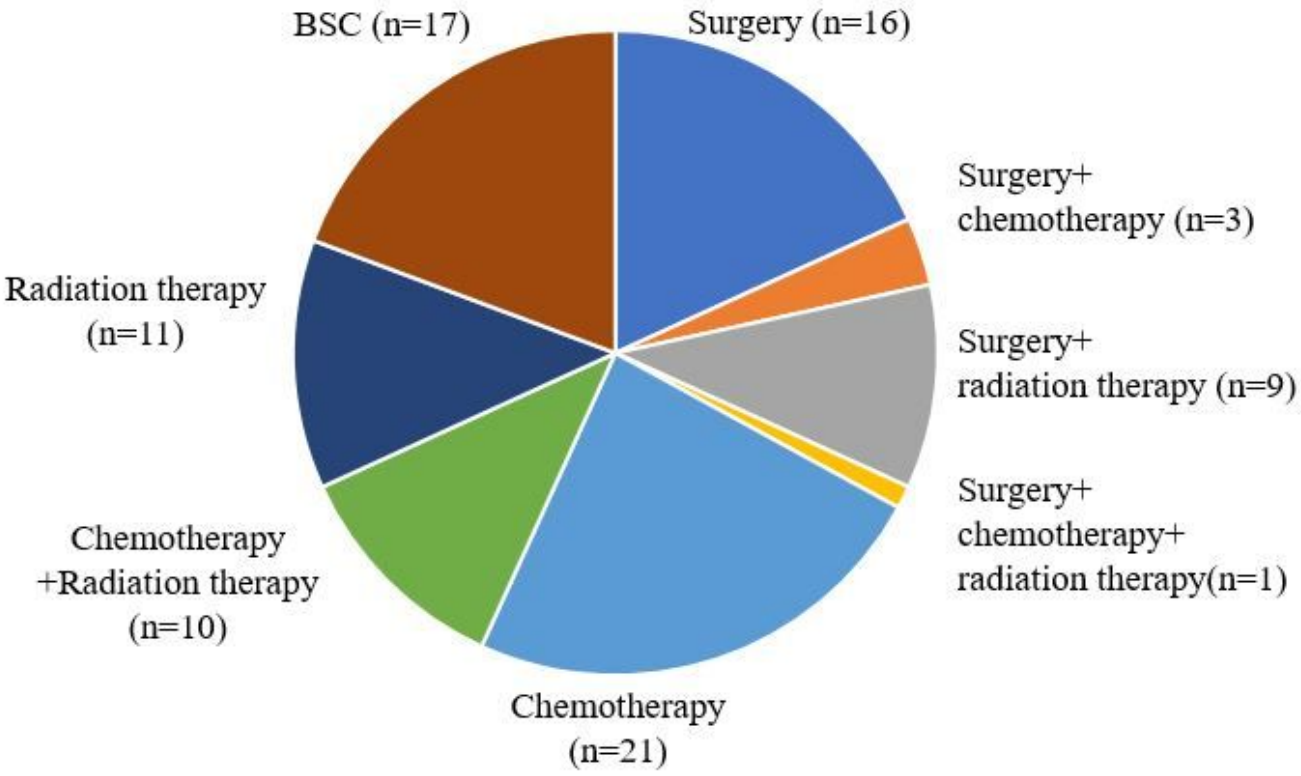

Figure 5

Therapies administered to patients with thymic carcinoma in the present study.