JLCS medical practice guidelines for thymic tumors: summary of recommendations

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Running head: Medical practice guideline for thymic tumors

Abstract

The Guideline Committee of the Japan Lung Cancer Society (JLCS) for Thymic Tumors published the Medical Practice Guideline for Thymic Tumors in Japanese as Chapter 3 of the Medical Practice Guidelines for Lung Cancers according to evidence-based medicine in December 2016. This medical practice guideline is the first for thymic epithelial tumors in Japan, and comprises a set of recommendations covering clinical diagnosis, treatment, and pathological diagnosis. Thymic epithelial tumors include thymoma, thymic carcinoma, and thymic neuroendocrine tumor. The recommendations for clinical diagnosis concern detection of the symptoms, blood and serum tests according to clinical presentation, essential imaging for differential diagnosis and staging, and the necessity and methods of definitive diagnosis. The recommendations for treatment are dependent on tumor stage and recurrence status, and the treatment modalities included surgery, radiation therapy, chemotherapy and multimodality therapy. Those for pathological diagnosis deal with the handing methods of resected specimen and essential reporting contents for pathological diagnosis. Since data from large-scale analyses or clinical studies of thymic epithelial tumor are limited due to its low prevalence, the relevant recommendations and grading were based on available reported evidence and expert opinions as well as diagnostic methods and treatments commonly

used in Japan. This report summarizes the recommendations concerning each topic addressed by this JLCS guideline for thymic tumors.

Mini-abstract

The Guideline Committee of the Japan Lung Cancer Society published the Medical Practice Guideline for Thymic Tumors. This guideline is the first for thymic epithelial tumors in Japan.

Key words: thymic epithelial tumor, thymoma, thymic carcinoma, diagnosis, treatment

Introduction

The Guideline Committee of the Japan Lung Cancer Society (JLCS) for Thymic Tumors published the Medical Practice Guideline for Thymic Tumors in Japanese as Chapter 3 of the Medical Practice Guidelines for Lung Cancers according to evidence-based medicine in December 2016 (1). This medical practice guideline is the first for thymic epithelial tumors in Japan and comprises a set of recommendations covering clinical diagnosis, treatment, and pathological diagnosis.

Thymic epithelial tumors are a group of rare thoracic neoplasms including thymomas thymic carcinomas, and thymic neuroendocrine tumors, with a reported annual incidence of 1.3 to 3.2 per million. Therefore, a few guidelines have been proposed by the European Society Medical Oncology (2) and the National Comprehensive Cancer Network (3).

In our guideline, since the data from large-scale analyses or clinical studies of thymic epithelial tumor are limited due to its low prevalence, the relevant recommendations and grading are based on available reported evidences and expert opinions as well as diagnostic methods and treatments commonly used in Japan. In this article, only topic-specific recommendations are addressed by the JLCS Medical Practice Guideline

for Thymic Tumors based on tumor staging by the Masaoka's classification (4), in principle, as well as on histological classification according to the World Health Organization (WHO) criteria (5). Literature search was conducted over the period from January 1, 1980 to October 31, 2015 using PubMed.

Recommendation grades are defined as follows:

A: There is firm scientific evidence to strongly recommend the practice.

B: There is scientific evidence to recommend the practice.

C1: The practice may be considered, although there is insufficient scientific evidence.

C2: There is no clear scientific evidence to recommend the practice.

D: Since there is scientific evidence showing ineffectiveness or harm, the practice is not recommended.

Recommendations for each topic

1. Clinical symptoms and blood tests

a. For possible thymic epithelial tumor with symptoms of myasthenia gravis, measurement of serum acetylcholine receptor antibody levels is recommended. (Grade B)

b. For possible thymic epithelial tumor with symptoms of anemia, measurement of blood cell count is recommended. (Grade B)

c. For possible thymic epithelial tumor with increased susceptibility to infection, measurement of serum γ-globulin levels is recommended. (Grade B)

d. For possible thymic epithelial tumor without symptoms of myasthenia gravis, measurement of serum acetylcholine receptor antibody levels may be considered. (Grade C1)

2. Detection and imaging differential diagnosis

a. Chest CT is recommended to detect thymic epithelial tumor. (Grade A)

b. Contrast-enhanced CT is recommended to differentiate mediastinal lesions. (Grade B)

- MRI may be considered if iodinated contrast media are contraindicated or to differentiate thymic epithelial tumor from thymic hyperplasia, cystic lesions, or other tumors.

3. Definitive diagnosis

a. If deemed resectable, surgical resection without needle biopsy for definitive

diagnosis is recommended. (Grade B)

b. If deemed unresectable, a preoperative treatment is planned, or there is a need to differentiate from other diseases, percutaneous needle biopsy is recommended. (Grade B)

c. Percutaneous needle biopsy should be performed using a needle that allows sufficient tissue sampling while avoiding a transpleural approach. (Grade B)

4. Staging

a. For possible thymic epithelial tumor, contrast-enhanced chest CT including the upper abdomen is recommended for staging. (Grade B)

- Chest MRI may be considered if iodinated contrast media are contraindicated.
- FDG-PET or PET/CT may reveal unexpected metastasis, but there is no clear scientific evidence to recommend these investigations for preoperative detection of lymph node and/or distant metastases.

5. Surgical therapy

5-1. Surgical therapy for stage I-II diseases

a. For clinical stage I-II thymic epithelial tumor, surgical resection is recommended. (Grade A)

b. For clinical stage I-II thymic epithelial tumor, total thymectomy with complete excision of tumor is recommended. (Grade B)

c. For clinical stage I-II thymic epithelial tumor, thoracoscopic resection may be considered, although there is insufficient scientific evidence. (Grade C1)

5-2. Surgical therapy for stage III diseases

5-2-1. Surgical indication/treatment strategy

a. For clinical stage III thymic epithelial tumor, total thymectomy with complete excision of tumor is recommended. (Grade A)

b. For clinical stage III thymic epithelial tumor that is not completely resectable, development of a treatment strategy based on evaluation by a multidisciplinary team is recommended. (Grade A)

c. For clinical stage III thymic epithelial tumor that is not completely resectable, multidisciplinary treatment is recommended. (Grade B)

5-2-2. Combined resection

a. For clinical stage III thymic epithelial tumor, combined resection of involved

adjacent organs is recommended, if feasible, to achieve complete resection. (Grade B)

b. If the phrenic nerve is involved, phrenic nerve-sparing surgery may be considered depending on the patient's condition. (Grade C1)

5-3. Surgical therapy for stage IV diseases

a. For clinical stage IV thymic epithelial tumor, development of a treatment strategy based on evaluation by a multidisciplinary team is recommended. (Grade A)

b. For clinical stage IV thymic epithelial tumor deemed macroscopically completely resectable, surgical resection is recommended. (Grade B)

c. For clinical stage IV thymoma, tumor reduction surgery may be considered if not completely resectable. (Grade C1)

6. Radiation therapy

6-1. Postoperative radiation therapy for resectable thymic epithelial tumor

a. For completely resected stage I-II thymoma and stage I thymic carcinoma, postoperative radiation therapy is not recommended. (Grade D)

b. For completely resected stage III thymoma, there is no clear scientific evidence to recommend postoperative radiation therapy. (Grade C2)

c. For completely resected stage II-III thymic carcinoma, postoperative radiation therapy may be considered. (Grade C1)

d. If incompletely resected, either microscopically or macroscopically, postoperative radiation therapy for thymoma and postoperative radiation therapy (chemoradiation therapy) for thymic carcinoma are recommended. (Grade B)

6-2. Radiation therapy for locally advanced and/or unresectable thymic epithelial tumor

a. Preoperative treatment with chemotherapy for locally advanced thymoma and chemotherapy (chemoradiation therapy) for locally advanced thymic carcinoma may be considered. (Grade C1)

b. For locally advanced, unresectable thymic epithelial tumor, radiation therapy or chemoradiation therapy is recommended. (Grade B)

c. For medically inoperable stage I-II thymic epithelial tumor, radiation therapy may be considered if feasible. (Grade C1)

6-3. Radiation therapy procedures

a. For radiation therapy, a minimum application of a 3-dimensional conformal radiotherapy (3D-CRT) technique with a target volume of the tumor bed and residual lesion is recommended. (Grade B)

b. There is no clear scientific evidence to recommend elective irradiation of the mediastinal or supraclavicular nodal regions. (Grade C2)

c. For postoperative radiation therapy, conventional fractionation at a dose of 1.8-2 Gy with a total dose of 40-50 Gy for patients with complete resection, approximately 50-54 Gy for patients with microscopically incomplete resection, or 60 Gy or more for patients with macroscopically incomplete resection is recommended. (Grade B)

d. For radiation therapy for locally advanced, unresectable thymoma, conventional fractionation at a total dose of 50 Gy or more is recommended. (Grade B)

- While the dose to normal tissues should be constrained in the same manner as for lung cancer, it is recommended to pay special attention to the cardiac

dose, given that there are many young and/or long-term survivors.

7. Chemotherapy (Table 1)

7-1. Chemotherapy for thymoma

Initial treatment

a. For clinical stage IV (AnyTAnyNM1a,b) or recurrent thymoma, chemotherapy may be considered, although there is no clear scientific evidence. (Grade C1)

Regimen

b. Combination therapy with cisplatin and anthracycline anticancer drugs may be considered, although there is no clear scientific evidence. (Grade C1)

c. If anthracycline drugs cannot be used, combination therapy with cisplatin and non-anthracycline anticancer drugs may be considered, although there is no clear scientific evidence. (Grade C1)

d. Chemotherapy with cisplatin alone is not recommended. (Grade D)

Second-line treatment

e. For thymoma resistant to first-line treatment, there is no clear scientific evidence to recommend second-line chemotherapy. (Grade C2)

7-2. Chemotherapy for thymic carcinoma

a. For recurrent or metastatic thymic carcinoma, chemotherapy may be considered, although there is no clear scientific evidence. (Grade C1)

Regimen

b. Combination therapy with carboplatin and paclitaxel may be considered, although there is no clear scientific evidence. (Grade C1)

c. There is no clear scientific evidence to recommend the ADOC regimen. (Grade C2)

d. Imatinib is not recommended. (Grade D)

Second-line treatment

e. For thymic carcinoma resistant to first-line treatment, there is no clear scientific evidence to recommend second-line chemotherapy. (Grade C2)

8. Post-treatment follow-up

If thymic epithelial tumor is curatively treated,

a. At least 10 years of follow-up for thymoma and at least 5 years of follow-up for thymic carcinoma are recommended. (Grade B)

b. Imaging follow-up, including thoracoabdominal CT at intervals of 6 or 12

months depending on the histological type, may be considered. (Grade C1)

- For thymoma, measurement of serum acetylcholine receptor antibody levels is recommended.
- For thymoma, follow-up with special attention to the development of multiple primary cancers is recommended.

9. Treatment of recurrent tumor

a. For a resectable recurrent lesion, surgical resection may be considered. (Grade C1)

b. Multidisciplinary treatment, including surgical treatment, may be considered if feasible. (Grade C1)

c. For an unresectable recurrent lesion, chemoradiation therapy, chemotherapy, or radiation therapy may be considered. (Grade C1)

10. Pathological diagnosis

Pathological diagnosis comprises cytology, biopsy, and the resected surgical specimen. Given few reports, the usefulness of cytological diagnosis is unclear.

a. Processing of resected specimens: A resected tumor is recommended to be

marked by the surgeon to indicate the anatomical relationship with surrounding tissues and organs, and to be extended on a board and then immediately fixed with sufficient fixative. It is recommended to make the largest cross-cut section of the tumor along horizontal CT plane, followed by additional parallel slices at intervals of 3-5 mm. Histology sections should be sampled from each site with distinct gross findings, as well as from sites showing invasion into surrounding tissues and organs. At least 5 sections should be sampled, and 1 section per centimeter is recommended for tumors with a maximum size of 5 cm or more.

b. Histopathological classification: Tumor should be histologically classified according to the WHO Classification (3), which is used worldwide. Immunostaining is useful for differential diagnosis.

c. Pathology report: A final pathology report should include the surgical procedure, gross findings, tumor size, histological type, extent of invasion, resection margin, pathological stage, and degree of effectiveness of preoperative treatment (if applicable).

d. Biopsy diagnosis: A pathological diagnosis may be made by biopsy when preoperative diagnosis is needed or complete resection is impossible. However, since tissue sampling and histopathological interpretation require some practice,

caution is advised.

e. Intraoperative consultation: An intraoperative frozen section diagnosis for mediastinal tumors is very difficult to make and is of limited usefulness.

Conclusion

Since there are few studies of thymic tumor with high level evidence due to relatively low prevalence, this guideline was prepared based on the opinions of a small number of experts, as well as diagnostic methods and treatments commonly used in Japan. Due to the scarcity, it may not be uncommon to have difficulty in diagnosing or treating thymic tumor in clinical practice. We sincerely hope that the guideline will be helpful in daily practice.

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