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The Clinicopathologic Features and Management of Recurrent Thymoma

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Abstract

Thymoma is a relatively rare tumor. Thymoma can relapse after operation or radiochemotherapy. The definitions of recurrent thymoma have been made by ITMIG. It is necessary to find the risk factors for recurrence based on the clinicopathologic features. Masaoka stage, WHO histological type, tumor size and treatment modalities are all the risk factor of recurrent thymoma. The diagnosis of recurrence is very important for thymoma. Surgery is a main therapy for thymoma. Complete re-resection can achieve a better prognosis than non-surgical therapy or incomplete re-resection. Radiotherapy and chemotherapy are still the important non-surgical therapy. Other treatment, such as targeted therapy, immunotherapy and percutaneous cryoablation can be used in recurrent thymoma.

Keywords: Recurrent thymoma; Clinicopathologic features; Treatment

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Introduction

Thymoma is relatively rare, but is the main neoplasm in anterior mediastinum. Doctors were not in agreeing with the nature of thymoma previously. Some thymoma showed as benign behavior, and would not recurrent in a long period. However, thymoma could relapse after all. Thymoma has its staging system and pathology classification system from international organizations. However, even in stage I or type A thymoma, recurrence could occur in some cases [1,2]. Therefore, thymoma is a kind of elusive tumor. But, benign thymoma cannot be distinguished from malignant tumor in most cases. Recurrent thymoma can be found after a long time after a radical thymectomy has been done, and follow-up should be done for long enough to find its recurrence [1,3].

Because of its recurrence property, it is suitable to take thymoma as malignancy. The relapse rate of thymoma ranges from 5% to 50% in different stage after radical resection [4]. A study from Japanese Association for Research on Thymus (JART) showed 420 in 2,835 thymoma post-operation cases (14.8 %) relapsed [5]. The managements of thymoma include surgery, radiotherapy, chemotherapy and other treatment methods. However, recurrence is still inevitable. Therefore, it is necessary to find the risk factors for recurrence based on the clinicopathologic features. The diagnosis and treatment are still very important for the prognosis of thymoma. International Thymic Malignancy Interest Group (ITMIG) proposed the treatment efficacy is best evaluated by recurrence rate. Overall Survival (OS) is a standard prognosis parameter for almost all kinds of carcinomas. But, most thymoma patients would live a long life even after recurrence, and die of other causes [3]. In that way, OS is not a good parameter for thymoma. Freedom-from-recurrence, however, is the best measure for patients after a radical treatment. For freedom-from-recurrence, 5-year follow-up is necessary, and 10-year follow-up is a better index for stage I thymoma [3]. Therefore, recurrence is a very important definition for thymoma.

Definition of Recurrence

The definitions of recurrent thymoma have been made by ITMIG [3]. Only when all tumors have been potentially eradicated (an R0 resection or a complete radiographic response has been achieved), the term recurrence has its meaning. This definition gives us some guide to the recurrent thymoma. This definition gives us two criteria for two kinds of treatment (surgery and non-surgery).

For surgery treatment, R0 resection is prerequisite for the recurrence diagnosis. R1 and R2 resection represent the tumor residue, which means that it should be tumor progression when the tumor grows up. For non-surgery, complete radiographic response is prerequisite for the recurrence diagnosis. However, complete radiographic response does not equal to pathological Complete Response (pCR). That is, complete radiographic response does not mean any tumor residues. Even in R1 and partial R2 resection for surgery treatment, tumors cannot be found in radiology. Tumor may exist in some "complete radiographic response" cases. Then, putting the surgical and non-surgical definition together for recurrent thymoma seems not advisable. Non-surgical definition for recurrent thymoma should be considered carefully. As to the relapse time, ITMIG proposes it should be considered as recurrence once a strong clinical suspicion exists, even without test (radiology or pathology) to confirm. In some cases, thymoma is indolent tumor and grows slowly. Therefore, when the recurrence is so obvious to diagnosis, many years may be past. So, that is right to diagnose once a strong clinical suspicion exists. However, when there are some evidences to prove the recurrence is a mistake, the diagnosis of recurrence should be rescinded. Recurrence can be divided as local, regional, and distant. Local recurrence occurs in tumor bed. Regional recurrence occurs in thoracic cavity away from the tumor bed. Distant recurrence occurs intrapulmonary or extrathorax. Recurrence mainly occurs in local or region [6,7]. Distant metastases usually occur in less than 5% recurrent thymoma [8].

The Related Clinicopathologic Features of Recurrent Thymoma

Recurrence is a character of malignancy. Whether the thymoma will relapse depend on its biological behaviors. Invasiveness is the attribute of malignant tumors. Then, how to estimate thymoma's invasiveness? The stage of thymoma defines the invasiveness of thymoma. Although IASLC/ITMIG proposes another staging system, which is called TNM stage [9], the Masaoka stage was still the most popular staging system for thymoma [10,11]. TNM stage was not popularly accepted because the lymph node metastasis rate was very low [12]. Stage I was defined as grossly and microscopically encapsulated. It is also called a noninvasive thymoma. That is, it has not spread beyond the thymus. Stage II-IV means invasive thymoma. From this meaning, Stage II and above have the possibility to relapse. So, stage should be the most related factor for recurrence. Many studies have proved stage system, especially Masaoka stage was an independent risk factor of recurrence [13-15]. Stage I and II thymomas relapse mainly in local or region. A large proportion of recurrent thymoma is in Stage III and IV. The more advanced the Masaoka stage was at diagnosis, the higher the recurrence rates were. However, stage alone may not be enough. Other factors should also be considered for reference. Another important factor relating to recurrent thymoma is WHO histological type. According to the morphology of epithelial cells and the lymphocyte-to-epithelial cell ratio, the World Health Organization (WHO) classified thymoma into different types. For clinical use, thymoma can be classified into A (A, AB), early B (B1, B2), advanced B (B3), and C (Thymic carcinoma) [16]. Generally, Type A and AB are considered as benign, type B1 and B2 are low-grade malignancy, type B3 has a malignant behavior, and type C is cancer [17]. WHO histological type is correlated with tumor invasiveness, completeness of resection, recurrence, and Masaoka stage [18-20]. However, a few reports showed WHO histological classification lacked significance correlation with risk of relapses [21]. Tumor size reflects tumor's growth. The faster tumor grows, the larger it will be. Generally, benign tumor is small and grows slowly; malignancy can be larger and grow faster. Actually, tumor doubling time is applied in many kinds of carcinoma to assess tumor's growth speed in clinic. However, because of thymoma's indolent nature, tumor doubling time may be very long. And surgery was applied in most thymoma when it was found. Tumor doubling time was seldom applied in thymoma. So, tumor size is still very important in thymoma. Tumor size is associated with recurrence [1,15,16]. 8 cm is the cut-off values to predict recurrence in some studies [1, 16,22,23]. Treatment modalities are very important to recurrent thymoma. Surgery is the radical treatment. The effect of radiotherapy and chemotherapy can achieve tumor regression from imaging, but cannot be proved by histopathology. At present, according to the definition of ITMIG, the effect of radiotherapy and chemotherapy are evaluated by radiographic response, but surgery is confirmed according to pathology. Surgery has a better curative effect than non-surgery. Therefore, the recurrence rate by surgery may be lower than that by non-surgery. However, from the concept of recurrence, surgery should achieve R0 resection, which requires strict pathology confirmation. However, at present, many previous reports have not the relevant pathology confirmation. So, the recurrence rate in previous reports may be overestimated. As local or regional relapse is the common recurrent site, radiotherapy seems necessary for thymoma to reduce recurrence. However, adjuvant radiotherapy cannot reach an agreement [20]. Haniuda stratified the involvement of the parietal pleural (pleural factor, p) and pericardium (pericardial factor, c) into different types [24]. Adhesion but not invasion was classified as p1 or c1, microscopic invasion was classified as p2 or c2. All of them have the risk to relapse. Postoperative irradiation was effective in preventing recurrence in p1 or c1 patients but not in p2 or c2 patients. In addition, postoperative radiotherapy may lead to morbidities to the lungs, heart, and other mediastinal structures [25-27]. Chemotherapy seems not necessary because thymoma usually relapse in local or region. Recurrence cannot be altered by adjuvant chemotherapy [28].

Diagnosis of Recurrent Thymoma

The diagnosis of recurrence is very important for thymoma. In most cases, even if thymoma recurs, it grows slow and is indolent. And most thymoma relapses in local or region. So, recurrent thymoma usually occurs insidiously. Thymoma may recur long after operation. The recurrence may take a long time to be found in imaging. Sometimes tissue is so hard to get that pathological diagnosis is difficult to carry out. Therefore, ITMIG propose it should be considered as recurrence once a strong clinical suspicion exists. This is a prospective diagnosis, but not a retrospective diagnosis. Imaging plays an important role in the diagnosis of recurrence. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are conventional examine for thymoma and recurrent thymoma, and usually are applied to find recurrent focus during follow-up. It is recommended that CT should be check every year in 5 years after complete thymectomy, every two years after 5 years, and should be performed at least 20 years [29]. However, there will be some fibrosis and scarring post operation or post-irradiation. It is difficult to differentiate fibrosis and scarring with recurrent nodule just by morphological imaging. Positron Emission Tomography (PET-CT) can make up the shortness of CT by providing both morphological imaging and metabolic information, therefore, is more accurate than conventional imaging [30]. PET-CT can distinguish recurrent nodules from post-treatment changes in the mediastinum. Pathology

plays an important role in carcinoma diagnosis, and is still taken as gold standard. Generally, cytopathology can be got by puncture. Histopathology can be achieved by biopsy or resection in operation. Histopathology is more accurate than cytopathology. However, when surgery cannot be performed, cytopathology became an important pathology form in diagnosis. Pathological examination is sometimes difficult due to the size and location of the nodules. However, if possible, fine needle aspiration biopsy still can be performed to get the pathological diagnosis.

Treatment

The choice for the treatment is very important to recurrent thymoma. It is necessary to make sure the clinical stage once recurrence appears. Treatment should be decided after definite stage is determined. If surgery is needed, it is necessary to determine whether radical treatment is feasible.

Surgery

Surgery is a main therapy for thymoma. However, whether it is necessary for recurrent thymoma is a question. Many studies showed that complete re-resection can achieve a better prognosis than non-surgical therapy or incomplete re-resection [6,31-33]. Complete re-resection was comparable with those without recurrence in prognosis [22,29]. Incomplete re-resection was comparable with chemo/radiotherapy alone in 10-year Long-Term Survivals (LTSs) rates [2]. Debulking surgery leads to a worse prognosis than non-surgical treatment for recurrent thymoma [34]. Morbidity and mortality with re-resection are 0 -13.3% and 0-32.1%, respectively [35]. Therefore, surgery is still the main therapy for recurrent thymoma. Clinical stage should be made clear. Recurrent site should be ascertained to identify local, regional, or distant recurrence. It is important to make sure the resectability before operation. R0, R1 or R2 resection should be assessed by clinical experience according to the imaging information. If R0 resection or even R1 resection can be achieved, surgery is advisable. When the tumor cannot be removed completely, Debulking surgery seems not suitable. However, Debulking surgery can be taken as a kind of means for salvage therapy in some occasion.

Radiotherapy and chemotherapy

Radiotherapy and chemotherapy are important non-surgical therapy. Radiotherapy can control local and regional recurrence. Chemotherapy can control distant recurrence. So, when the recurrent thymoma is inoperable, radiotherapy and chemotherapy are reasonable choice [36-38]. To the patient's surgery has been done, radiotherapy and chemotherapy may be taken into consideration. No studies about radiotherapy and chemotherapy after re-resection for recurrent thymoma have been reported until now, because the recurrent thymoma is rare for a single institute and may take a long time to occur. So, the study for recurrent thymoma is difficult to carry out. Therefore, we just can refer to the study on postoperative radiotherapy and chemotherapy for thymoma. Postoperative radiation can decrease the burden of microscopic residual focus in tumor bed [39,40]. However, Postoperative radiotherapy for thymoma is still controversial. Some study showed postoperative radiotherapy decrease the recurrence rate [14,41], however, others cannot get the similar result [32-34]. If complete resection can be achieved, radiotherapy seems redundant. So, in most cases, for R0 resection, adjuvant radiotherapy and chemotherapy are not necessary. For R1 and R2 resection, radiotherapy and chemotherapy is crucial to control the residual focus in tumor bed.

Other treatment

Percutaneous cryoablation is a locally ablative technique, which is usually used in carcinoma treatment. In recurrent thymoma, percutaneous cryoablation also can be used [42], especially to multiple lesions. No or minimal complications occurred in most cases. So, it is a safe and effective therapy for local control of recurrent thymoma. Many drivers' genes mutation has been found in multiple carcinomas. Targeted therapy has become a promising treatment modality for cancer. Many signaling pathways for targeted therapy have been discovered in thymoma. Many targeted agents have been applied in clinical trials [43]. However, most of them are Phase II clinical trials. Further clinical trials should be carried out to verify the feasibility of targeted drugs. Recently, Immunotherapy with immune checkpoint inhibitors has become a promising therapeutic method for various malignancies. The most research on immune checkpoint inhibitors is PD-1/PD-L1 monoclonal antibody. When PD-1, mainly being present on the surface of activated T cells, binds to PD-L1 on tumour cells, the cytotoxic T-cell response is down regulated. PD-1/PD-L1 monoclonal antibody would solve this problem. When PD-L1 expresses high, the effect of PD-1 or PD-L1 antibodies will be good. The expression of PD-L1 in thymic carcinomas is high. A single-arm, single-centre, phase 2 study showed the effect of pembrolizumab in thymic carcinoma was comparable with that in another carcinoma [44]. So, pembrolizumab may be a promising therapy for thymic carcinoma. Best supportive treatment may still be feasible to low PS score patients.

Problems and future

With the development of evidence-based medicine, the diagnosis and treatment of various tumors should be proved by clinical trials. Thymoma is a kind of rare tumor. Most of thymomas are in early stage. Furthermore, thymoma has an indolent nature. It may take many years of follow-up to find the recurrence. So, a large number of thymoma cases may be needed to meet the needs of clinical research. However, the thymoma cases are limit in single institution. A large number of thymoma cases in multiple centers will be needed to get scientific research conclusions. In addition, a real prognosis data can be got through a long period of follow-up. ITMIG has been set up for many years, and subsequently, organizations for thymoma study have been set up in a lot of countries. In China, Chinese Alliance for Research in Thymoma (ChART) has done amount of works. The research on thymoma will be carried up in a few years. The guideline will be improved soon. In future, the research on thymoma will be promising. In addition, the age of Big Data is coming. Artificial Intelligence, basing upon Big Data, gradually comes to reality. Artificial intelligence plays an important role in many medical areas such as imaging diagnosis, pathology diagnosis and tumor radiotherapy target delineation. It is believed that with the development of science and technology, artificial intelligence will bring a better future for the diagnosis, treatment and follow-up of recurrent thymoma.

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