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Optimism with caution for patients with advanced thymoma and thymic carcinoma

Marcello Migliore ^{a,b,*}, Marco Lucchi ^c and Norberto Santana Rodriguez^d

^a Thoracic Surgery & Lung Transplant, Lung Health Centre, Organ Transplant Center of Excellence (OTCoE), King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, KSA

^b Department of General Surgery and Medical Specialties, Minimally Invasive Thoracic Surgery and New Technology, Policlinic University Hospital, University of Catania, Catania, Italy

^c Thoracic Surgery, Department Cardio-Thoraco-Vascular Azienda Ospedaliero-Universitaria Pisana, University of Pisa, Pisa, Italy

^d Thoracic Surgery, Department of Surgery, Sheikh Shakhbout Medical City-Mayo Clinic, Abu Dhabi, United Arab Emirates

* Corresponding author. Thoracic Surgery & Lung Transplant, Lung Health Centre, Organ Transplant Center of Excellence (OTCoE), King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia; Tel: +393787007229; e-mail: mmiglior@hotmail.com (M. Migliore).

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Thymoma (T) and thymic carcinoma (TC) are rare tumours. The former is a low-grade tumour, and the latter is a highly aggressive tumour. Most thymic tumours are T, and only 20% correspond to TC. It is estimated that only 3.2 per million people will be discovered with T [1].

Surgery has limited indications in advanced T and TC invading the mediastinal pleura, parietal pleura, lung and pericardium. Cytoreductive surgery followed by hyperthermic intrathoracic chemotherapy (HITHOC) as a type of adjuvant treatment is barely used in few specialized centres worldwide. This is supported by the evidence of few articles reported about the use of HITHOC to treat patients with T in stage IVa or TC. Furthermore, it is important to note that HITHOC is not yet a standard practice in the care of advanced thoracic cancers.

In a few words, if T and TC are rare tumours rarely operated on in advanced stages, and HITHOC is barely used to deal with these tumours, why the editors of the *Interactive Cardio-Vascular and Thoracic Journal* invited to comment on this article?

The answer to this question could be found in the good results reported from the multicentre German HITOC study entitled 'Surgical cytoreduction and hyperthermic intrathoracic chemotherapy for thymic tumours with pleural spread is effective on survival: results from the multicentre German HITOC-study' [2]. The study includes 42 patients with T and 15 patients with TC with pleural metastases or recurrences. Complete tumour resection was achieved in 85% of patients. Cisplatin alone (66%) or in combination with doxorubicin was used to perform HITHOC. Five-year survival rates were impressive, 94% in patients with stage IVa thymoma and 41% in TC.

Looking at survival, the second question arises. Are these results based on the use of HITHOC or the availability of a better multidisciplinary approach, adjuvant or neoadjuvant treatment?

HITHOC is not a new procedure since it has been introduced >20 years ago [3]. The effect of hyperthermia on human neoplastic

cells was understood in the 1970s when *in vitro* studies demonstrated that hyperthermia had a deleterious effect on cancer cells. A synergism between hyperthermia and chemotherapy was successively shown too [4]. However, many of us remained sceptical about the role of HITHOC because *in vitro* experiments demonstrated that the pleural perfusion at 42°C for 1 h with single-agent cisplatin was likely ineffective [5]; on the contrary, *ex vivo* experiments demonstrated that hyperthermia with a chemotherapy agent works [4].

This quarrel between *in vitro* and *in vivo* studies has generated some controversy between patients, thoracic surgeons and oncologists. It seems evident that clinical data reported worldwide, although are mostly retrospective, confirm that HITHOC is useful. Furthermore, we are witnessing another clinical success of the use of HITHOC combined with cytoreductive surgery for advanced thoracic cancers [2]. It appears clear that HITHOC is contributing to adding years of survival after surgery for advanced thoracic cancers such as mesotheliomas, stage IV–M1a pleural effusion lung cancer, and pseudomyxoma [6–9].

Despite the possibility of being an occasional cure, does HITHOC prolong the survival of patients with TC?

Although it is not a surprise that patients with T had significantly better survival compared to patients with TC (P -value ≤ 0.001), it is certainly a very good revelation that 41% of patients with TC survive 5 years. Evidently, the data presented by the multicentre German group are significant, but confirmation by others authors is demanded. To reinforce the data obtained by Ried *et al.* [2], Chappuy *et al.* [10] reported an important experience with 40 patients with T IVa pleural involvement treated with partial pleurectomy and HITHOC showing a median length of survival of 118 months and a median DFI of 70 months [10]. The group of Pisa in Italy had also similar results [11].

Nevertheless, we must admit that the only accepted answer for this question requires to resolve the weak point of the study since there is no randomized data from where a high degree of

confidence can be delivered to state that cytoreductive surgery and HITHOC prolong survival in patients with advanced T or TC. A clinical pilot study with a control group, against which any effect can be measured, is the greatest method to response the query, but at this moment there are no reported trials including a control group.

Furthermore, we recommend the readers who want to go into detail on HITHOC to use the following keywords HITOC, HITHOC and HIOC since the nomenclature has not been well established yet, and therefore some, interesting papers can be missed if the key search words are not used adequately.

Finally, oncologists and thoracic surgeons who treat patients with advanced thoracic cancer usually follow the published guidelines. The standard practice in the event of advanced T or TC spread into the thorax is in fact to avoid surgery or to perform debulking surgery (even without HITHOC) for thymomas [12, 13]. However, the hesitancy to operate should be overcome by the good data has been published, and HITHOC should be feasible and developed further.

It is evident that the success obtained with the use of HITHOC will certainly contribute to creating an increase of interest for surgical treatment in advanced locally thoracic cancers.

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