Editorial

Improving follow up for thymic epithelial tumors

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We feel honored about the editorial in *Mediastinum* and highly welcome the title "Old wine in new bottles: C-reactive protein (CRP) is a promising tumor marker in thymic epithelial tumors" (1) written by Philipp Ströbel on our recent findings (2).

In addition of what Ströbel stated on radiological follow up, slow growth of many thymic epithelial tumors (TETs) (low rate of mitosis) may raise the suspicion for recurrence in radiological follow up with a delay. The window of opportunity for early detection before further dissemination and distant metastases occur may be missed. In such cases the treating physician/thoracic surgeon at the forefront of patient treatment needs additional evidence based medicine tools in order to be able to make the correct suggestion to the patient. Sensitive diagnostic tools even if they are not specific for TETs are needed. Biomarkers that react early (and can be detected early) in the course of recurrence development are needed—not to overreact and suggest invasive measures as tissue biopsies or surgery for radiological changes mimicking recurrence or on the contrary delaying treatment of recurrences with follow up radiological examinations. Further studies are warranted to test if CRP can fulfill this task. A rise in CRP on follow up would indicate further radiological examination and by no means invasive procedures without further evaluation.

In an ESTS Thymic Working Group study on thymic tumors including 2,151 cases from 35 institutions that were treated 1990–2010 the following was stated on follow-up: "the majority of institutions performed a follow-up schedule based on a 3- to 6-month computed tomography (CT) scan for the first 3 years, followed by annual CT scans lifelong." and "in most centres, more aggressive thymic tumours (TC and NETT) received a more strict imaging (CT) surveillance (3)." This comes close to the recommendations of ITMIG (4): "after R0 surgical resection—annual CT (with contrast) for 5 years, then annual CXR alternating with CT for 5 years is suggested as a minimum. After curative intent treatment for stage III, IVa—CT every 6 months for 3 years, then schedule noted above."

The observation of the high number of second primary cancers in patients with TETs (REF) was published by many investigators and is well accepted in the scientific community. The typical patient undergoing thymectomy for myasthenia gravis with an associated TET is in her mid-twenties. The cure rate of surgery for thymic cancer is high and the female in this example being 25 years old in 2017 has a life expectancy far beyond 80. Could the occurrence of other primary cancers in this patient population with excellent survival just be the result of the accumulated radiation exposure from tight follow up with chest computed tomography? Also, current follow up schedules seem to be taken over from clinicians' experience with follow up of lung cancer patients or patients with other primary cancers whose survival is much worse than those with TETs and thus may not be warranted for TETs. Replacing computed tomography by magnetic resonance imaging can successfully avoid radiation exposures but following such tight follow up protocols will put additional strain on today's health care systems and as stated above may not be warranted from the pathophysiological view. Current follow up recommendations by chest computed tomography may be too indiscriminate. For instance, they make no distinction of formerly as "benign" designated type A thymomas and (malignant) thymic carcinomas.

Chest CT scans, chest X-rays and alternatively magnetic resonance imaging are currently the only recommended tools for oncologic follow-up. No adequate markers exist that have changed this radiological secondary/tertiary prevention. We believe that prospective trials are warranted in patients with increased CRP serum concentrations at diagnosis of primary disease.

A first protocol would control serum CRP values at regular intervals (e.g., every 6 months) and may probably omit CT scans. It certainly would not completely replace surveillance by CT. Elevated CRP serum concentrations in the absence of other reasons (inflammatory disease, trauma, surgery…) for increased inflammatory parameters may indicate TET recurrence. We believe that CRP measurements will increase the chance of detecting recurrences earlier especially when radiological sensitivity is low, as is the case in surveillance with chest X-rays. Earlier detection of tumor recurrence may be associated with better treatment options and improved outcome for patients.

CRP is not a specific marker for TETs. It may serve as a prognostic tool and a tumor marker in various cancers, e.g., pleural mesothelioma (5). Specificity of a tumor marker—even we would like to have a serum biomarker specific for TETs—is not a prerequisite for improving current follow up. In our study we found a PPV of 71.4% and NPV of 88.9%, indicating that CRP could be helpful in oncologic follow-up to identify patients with increased risk of tumor recurrence. CRP is available in health care systems around the globe; it is inexpensive and clinicians have vast experience with CRP in daily practice in almost every patient undergoing a blood draw. CRP warrants future study as it is readily available and could possibly avoid costly and potentially cancerous radiological examinations.

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Footnote

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