

# New aspects in esophageal cancer surgery: our experiences

Assoc. Prof. Papp András, MD, PhD

*Sebészeti Klinika, Department of Surgery, PTE ÁOK KK, Clinical Centre, Medical School, University of Pécs, 7624, Pécs, Ifjúság u.13., Hungary*

E-mail: papp.andras@pte.hu

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25 years ago in Hungary, we mostly found esophageal squamous cell carcinoma, with a squamous cell carcinoma to adenocarcinoma ratio of 10:1. Patients with advanced cancer underwent open surgery, with a perioperative mortality rate of around 10–15%, and an expected 5-year survival rate of below 20%.

**Epidemiology:** We performed a cross-sectional study using data from esophageal cancer patients diagnosed between 1992 and 2018 at eight tertiary referral centers in four major cities of Hungary. We retrospectively identified cases in the electronic databases of each center and collected data on gender, age at diagnosis, year of diagnosis, specialty of the origin center, histological type and localization of the tumor. Patients were grouped based on the two main histological types: AC or SCC. We extracted data on 3283 patients with esophageal cancer. 2632 of these were diagnosed with either of the two main histological types; 737 had AC and 1895 SCC. There was no significant difference in the gender ratio of the patients between AC and SCC (80.1% vs 81.8% males, respectively;  $p = 0.261$ ). The relative incidence of AC increased over the years ( $p < 0.001$ ,  $b = 1.19$  54 CI: 0.84–1.54). AC patients were older at diagnosis than SCC patients ( $64.37 \pm 11.59$  vs  $55.60 \pm 10.07$  years,  $p < 0.001$ ). The age of patients at the diagnosis of primary esophageal cancer increased over time ( $p < 0.001$ ,  $R = 0.119$ ). The rapid increase in the relative incidence of AC and simultaneous decrease of the relative incidence of SCC suggest that this well-established Western phenomenon is also present in Hungary. (1)

**Neoadjuvant therapy:** In 1997, we were the first in Hungary to use neoadjuvant treatment for esophageal cancer. As is well known, this is now evidence-based. However, based on our initial experience, it was an interesting observation that upper third tumors responded better to treatment, and we observed more complete remissions. (2) As a result, we introduced organ-preserving resections for tumors at the entrance of the esophagus. (3)

**Predictive factors:** These above-mentioned observations then prompted us to search for clinical factors which can predict the effectiveness of treatment. At that time, we confirmed that certain heat-shock proteins show correlation with the response to treatment. We showed that high levels of Hsp 16.2, Hsp 90, p-Akt and SOUL were negative prognostic factors in response to therapy and that a high level of these proteins was correlated with decreased 3-year overall survival. These findings underline the significance of these markers as potential predictors of response which possibly can be applied in clinical practice. (4, 5) In a similar study, we also confirmed the presence of HPV infection in esophageal cancer for the first time in Hungary and found a correlation between the response to treatment, the presence of HPV infection, and the expression of HSP proteins. (6)

**Surgical technic:** In the past decade, there have been significant changes in the surgery of esophageal cancer in our country as well. It has become clear that minimal invasiveness is a clear advantage in the case of esophageal resections. In Hungary, we were among

the first to introduce minimal invasive esophageal resections, and today about 40–50% of our surgeries are performed this way. We conducted and published a meta-analysis to demonstrate the advantages of minimal invasive esophageal resections (MIE). (7) In addition, we introduced robot-assisted surgery last year and after the learning period, we started performing robot-assisted esophageal resections (RAMIE). However, the introduction of the minimal invasive technique has also resulted in the abandonment of the previously mandatory pylorus plasty during the operation. To demonstrate the validity of this decision, we also conducted a meta-analysis using data from the literature.

**Preoperative patient care:** The advantages provided by MIE result in earlier discharge of patients. However, according to previous principles, patients should not consume anything orally for 5–7 days after esophageal resection, thus reducing the likelihood of anastomotic insufficiency. The application of this rule significantly increases the length of hospital stay. The use of ERAS principles is increasingly spreading in surgery around the world, including in UGI surgery. With the help of prehabilitation, early per oral nutrition during UGI surgical interventions can be started without increasing the number of complications. We conducted a meta-analysis to prove the correctness of this proposition (8), and in line with this, we demonstrated the application of new principles by conducting a propensity score matching study on our own patient material.

**Special reconstructions:** We consider it extremely important to centralize esophageal surgery to ensure the appropriate level of care, which has only just begun in Hungary. One of the most important reasons for this is that one or two skilled esophageal surgeons are not enough to ensure good results; this can only be achieved through highly trained teamwork in the treatment of esophageal diseases. This also includes cases where classical surgical methods are no longer effective. In such situations, plastic surgeons can be of great help, aiding with free jejunum or supercharged colon replacements, as well as employing other

seemingly hopeless situations using plastic and microsurgical methods to find successful solutions. As this is available at our clinic, we have published several articles on the possibilities of special esophageal replacements. (9, 10) We believe that such a possibility should be available in a serious esophageal surgical center to ensure quality care.

## SUMMARY

Our retrospective cross-sectional study aimed to confirm or disprove the presence of the so-called “esophageal adenocarcinoma epidemic” in Hungary.

Neoadjuvant treatment is now clearly evidence-based, and the new immunotherapy further enhances its effectiveness. Our description of better treatment response for tumors located in the upper part of the esophagus has created the possibility of performing organ-preserving surgeries.

During the examination of predictors of treatment response, the expression of tumor-associated proteins, including Hsp, showed a clear correlation with treatment response. Similarly, interesting correlations were seen in the case of HPV infection, Hsp expression, and treatment response.

In terms of surgical technique, MIE and now perhaps RAMIE clearly provide an advantage over open surgeries. The introduction of minimally invasive techniques resulted in the abandonment of pylorusplastica, which was previously considered obligatory, and our own study supports this.

Another major change in perioperative patient management is the introduction of ERAS principles, including prehabilitation and early oral feeding, which not only shorten hospital stays and improve quality of life but also do not increase complications or perioperative mortality.

Finally, it is important to centralize care in centers with appropriate quality indicators where high-level teamwork takes place. This includes involving plastic

surgeons, who can help achieve good results even in previously hopeless situations.

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