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Multiple primary cancers in patients treated for squamous cell carcinoma of the esophagus

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

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ABSTRACT: Treatment of squamous cell carcinoma is associated with an increased risk of other primary malignancies, mainly within the head and neck, as well as in the oesophageal gastric graft. More frequent recognition of multiple primary cancers associated with esophageal cancer, both synchronous and metachronous, is associated with longer follow-up after radical cancer treatment for esophageal cancer and high quality diagnostic procedures, both before and after surgery. The paper reviews the available literature and describes the molecular basis of the formation of multiple primary tumors associated with squamous cell carcinoma of the esophagus.

KEYWORDS: second primary tumors (SPTs), squamous cell carcinoma of the esophagus

Squamous cell carcinoma of the esophagus ranks 8th amongst the most common malignant tumors and is the 6th reason for deaths caused by malignant tumors in the world. Squamous cell carcinoma of the esophagus is 2 to 4 times more frequent in men [1]. In Europe, the incidence of esophageal cancer is 5.39 cases per 100,000 men, and 1.13 cases per 100,000 women [2]. The incidence rate of esophageal cancer in Poland in 2009 was 3.8/100,000 in men and 0.6/100,000 in women [3]. In the United States of America and western European countries, there is a significant increase in the incidence of esophageal adenocarcinoma caused by gastro-oesophageal reflux and Barrett's esophagus [2. 4]. At the same time, southern and western European countries show a decrease in the incidence of squamous cell carcinoma of the esophagus in men, which is caused by alcohol consumption and smoking [2]. In contrast to the above observations, in Japan, squamous cell carcinoma is still the most common type of histology found in patients with esophageal cancer [5].

Prognosis in esophageal cancer remains poor. In European countries, the 5-year survival rate regards 9,8% of patients [2]. More optimistic data concern the Japanese population, where the period of 5-year survival in patients after surgical treatment of esophageal cancer in the best medical centers is almost 50%. This phenomenon is connected to progress, which has been made in the system of screening, diagnosis, and therapy [6]. The largest number of scientific reports on plural primary cancer associated with esophageal cancer originates in Japan, which was influenced by the introduction of screening tests (upper GI endoscopy) towards the detection of stomach cancer – one of the most commonly diagnosed cancers in the Japanese population [7]. This fact is associated with the diagnosis of esophageal cancer in lower staging of cancer, resulting in better statistics on patients' long-term survival and longer follow-up after radical treatment for esophageal cancer [5, 6, 8].

Treatment for squamous cell carcinoma is associated with an increased risk of other primary malignancies. The percentage of these cancers is higher than it would appear from the general statistics of incidence of all malignant tumors in a given age range [5, 6]. The first definition of a second primary tumor (SPTs – second primary tumors), was given by Billroth in 1869. Billroth also presented the first criteria for diagnosis of two independent cancers, which were subject to the following conditions: both tumors had different histological structure, they had to appear in different locations and both had to give their own metastases [9]. In 1932, Warren and Gates were the first to present an epidemiology and an overview of cases of two independent cancers. They concluded that diagnosis of two cancers must be divided by a time interval of more than a year, and the possibility that the second cancer could be metastatic should be ruled out [10]. The current definition of multiple primary malignancies was defined in 1991 by the International Agency for Research on Cancer (IRAC). The following criteria must be met for the diagnosis of two primary malignancies:

1. Histological confirmation that both tumors are malignant.

2. Tumors must have a separate location, and if they are located in the immediate vicinity, they must be separated by at least a 2-cm area of healthy mucous membrane, and if they develop in the same organ, a period of over 5 years after diagnosis must pass.

3. The possibility is ruled out that the second tumor is a metastatic lesion arising from the primary site [11].

A national study by Nakayama and Abo found that in 1979 in Japan, combined risk of a second primary tumor after surgery for esophageal cancer was 0.4% [12]. Due to the diagnosis of subsequent primary tumor, after treatment for esophageal cancer, in advanced clinical staging, often not allowing for their radical treatment, a screening scheme was elaborated, allowing to diagnose those lesions in staging allowing to undertake radical therapy before the manifestation of clinical symptoms connected with their presence [5]. According to Matsubara et al. follow-up examinations after esophageal resection included: physical examination, blood test and CT scan every 6 months and endoscopic examination of the upper gastrointestinal tract every 1 year [6]. Since 1989, Motoyama et al. have been using a scheme that includes: a control test at the hospital every month for 5 years after surgery. Blood tests, including the examination of tumor markers [SCCA

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(squamous cell carcinoma antigen), CEA, cytokeratin 19] every months, chest X-ray every 2 months for the first 2 years, and every 6 months in subsequent years, consultation with head and neck surgeons CT of the neck, chest and abdomen every 6 months for the first 2 years and every year in the following years. Gastroscopy is performed once a year and fecal occult blood test twice a year [5]. Because the stomach is the most frequently used organ to replace the esophagus after its resection, while being one of the most common organs in which synchronic and metachronous tumors develop in patients after treatment for esophageal squamous cell carcinoma, prior to surgery, each patient requires detailed endoscopic and radiological diagnostics not only of the esophagus but also of the stomach. At the same time, an esophageal replacement made from the stomach requires routine endoscopic monitoring to detect early forms of cancer [8, 13]. The period from esophagus resection to diagnosis of the primary cancer in the stomach used as a substitute for the esophagus ranges from 1 year and 4 months to 21 years [14], including an average of 50 to 72 months [15, 16, 17]. Gastric tumors that display clinical symptoms are poor prognosis and are associated with a short survival time, in contrast to cancers detected during endoscopic follow-up [16, 17]. It should be emphasized that endoscopic treatment is possible in gastric cancer detected in the early stages of clinical development: endoscopic mucosal resection (EMR) [14, 15, 16] or endoscopic submucosal dissection (ESD) with a high percentage of five-year survival (84.7%) [14]. In contrast to the Japanese population in European countries, as well as in Poland, reports of second primary tumors following esophageal resection for squamous cell carcinoma are rare [18] and most descriptions refer to adenocarcinomas in the esophagus substitute after excision of the esophagus due to adenocarcinoma in its lower section [19, 20].

The frequency of detection of second primary tumors increases with the prolongation of survival after surgery for esophageal cancer [5, 6, 8, 13]. The development of second primary tumor in patients after esophageal cancer resection is most common in the head and neck as well as in such organs as the stomach, lungs, left part of the esophagus, and the colon and rectum [5, 6]. In the study of Motoyama et al., organs in which, in addition to the presented above, second primary tumor occurred were: liver (hepatocellular carcinoma), pancreas (adenocarcinoma), and blood (leukemia). In his publication, Matsubara et al. reports that the total risk of a second primary tumor during the 5-year observation period is 16.1%, and during the 10-year follow-up period it is 34.9%, with head and neck cancers as the most common in his study. The risk of head and neck cancer in patients after oesophageal resection due to cancer was 7.3%, while the risk of gastric and lung cancer was below 2% [6]. Location in the head and neck as the site of the second primary cancer after treatment for squamous cell carcinoma of the esophagus is also confirmed in the Kumagai study, drawing attention to the fact that the cancer process most often includes the pharynx and then the larynx [8]. This is also confirmed by reports from Welz et al [21]. Fukuzawa et al. describes cases of synchronous tumors of the mouth, gums and tongue as well as esophagus and stomach, stressing that the same carcinogens, by acting on their epithelium, cause cancer [22]. The increased risk of developing a second primary tumor following esophageal resection due to squamous cell carcinoma mainly affects male cigarette smokers and abusing alcohol [6, 8, 21, 22]. In turn, Motoyama et al. report that the risk of a second primary tumor within the 5-year follow-up period was 16.5%, and the organ in which second primary tumor was most frequently detected was the stomach used as replacement for the esophagus [5]. Koide et al. also state that the organ in which the second primary tumor was detected was the stomach used as replacement for the esophagus. Koide also reports the risk of developing a third primary tumor in patients after treatment for esophageal cancer, which in his study is 1.5% and the fourth primary tumor is 0.5% [13].

The period between the detection of esophageal cancer and the emergence of a second primary tumor was 48 months on average [5]. The coexistence of primary tumors arising from the epithelium in the respiratory tract and upper gastrointestinal tract results from the fact that these organs are considered as a single duct [23, 24]. Exposure of the epithelium in the head, neck, lungs and esophagus to common carcinogens leads to the formation of many cancers in this region [6, 8, 21, 22]. The concept described is called field cancerization. It was first introduced in 1953 by Slaughter et al [5, 24, 25]. Already in 1969, Wynder et al. observed that smoking and alcohol abuse have a significant impact on the emergence of subsequent primary tumors in the head and neck [26]. This thesis was also confirmed by other studies [6, 23, 27]. In recent years, significant progress has been made in studies on the molecular analysis of carcinogenesis in the head and neck. The accumulation of genetic changes in epithelial cells leads to the transformation of a healthy cell into a cancerous cell, which is called multistep carcinogenesis. Using research on genetic mutations in tumor cells, it was found that some of the tumors previously recognized as a second primary tumor should be considered as a tumor metastasis. Recognizing another tumor, it should be decided whether it has a common clonal origin with the primary tumor [28, 29]. Given the genetic tests, a modification of the Warren and Gates definitions was proposed. The division was made depending on the anatomical location of the secondary lesion: tumors in the same anatomical location and tumors developing in other anatomic locations.

1. The same anatomical location – when the second tumor develops in the mouth or pharynx:

   - Cancerous recurrence – identical genetic mutations;
   - The second tumor of the "second field tumor" (SFT) when tumors are initially genetically connected but differentiate in later stages. Some genetic markers are similar, but there are differences in other markers;
   - Real "SPT" when molecular profiles of tumors are completely different.

2. Another anatomical location – when the second cancer develops in the larynx, lungs or esophagus:

   - Metastasis – identical genetic mutations;
   - SFT – some of the genetic markers are similar, but there are differences in other markers;
   - SPT – when molecular profiles of tumors are completely different [29].

Upon differentiating between recurrent metastasis and separate primary tumor, genetic background should be considered in addition to histopathological examination, especially within the p53 protein mutation. Cancer develops as a result of the accumulation of genetic mutations in oncogenes and suppressor genes [30]. The accumulation of genetic changes forms the basis for the de-

velopment of a cancer cell from a healthy cell in a process called "multistep carcinogenesis" [31]. This process comprises three phases. In the initial phase, the stem cell acquires a genetic mutation and forms a "patch" – a clonal unit of altered cells. Such sites can be recognized by mutations in the TP53 gene [32]. Next, the "patches" - clonal units of altered cells are transformed into expanding areas for which subsequent genetic changes are necessary. Expanding areas of altered proliferating cells gradually replace the healthy mucosa. Both in the mucosa in the head and neck organs, as well as in the esophagus, such areas, with a diameter exceeding as much as 7 cm, were found using molecular analysis, while they were not detected in routine histopathological examination [28]. After applying molecular analysis, a model of cancer was confirmed in which developing areas of genetically altered cells replacing the normal mucosa play a key role. Their presence was confirmed in biopsies of the histopathologically unaltered mucosa surrounding the tumor and unaltered mucosa of surgical margins [31, 32]. These areas often remain after the surgical excision of primary tumor and may lead to the formation of another tumor. These findings partially explain the frequent occurrence of local recurrence and secondary primary tumors in the head and neck [31]. The above reports prove that diagnosis and treatment of epithelial cancers should not only concern the tumor but also the area from which it originated [33]. Better results of combined treatment of synchronous tumors originating from squamous epithelial cells of the head and neck and esophagus - radiotherapy and chemotherapy in comparison with surgical treatment itself are emphasized [34].

Despite the costs of observation, the possibility of detecting the second cancer in preclinical stage, when clinical symptoms are still present, gives the possibility of curing a significant group of patients [5.6]. In Japanese reports, almost half of patients undergo a 5-year observation period from the diagnosis of a second, primary cancer in patients previously treated for squamous cell carcinoma of the esophagus [5, 6]. According to various authors, from 45 to 48,6% [5, 6], where prognosis in head and neck cancer is worse than in other cancers [6]. In the Motoyam et al study, in the group of patients who had second primary tumor detected before the associated clinical symptoms occurred, the 5-year survival after treatment concerned 70.7% of patients, whereas in the group of patients diagnosed with second primary tumor on the basis of clinical symptoms, 5-year survival after treatment concerned only 17.1% of patients [5].

This article aimed to draw the attention of doctors participating in the treatment of patients with squamous cell carcinoma of the esophagus to the need of these patients' long-term observation as well as their detailed monitoring and control tests, not only due to the possibility of local recurrence and distant metastases, but also because of primary synchronous and metachronous tumors in other organs. To conclude, we would like to emphasize that it is also in the Department in which the authors of this article work that we have met cases of too late diagnosis of tumor in the esophageal replacement from the stomach described in the PPCh in February 2015, in which the lesion, due to its local staging, was not eligible for radical surgical treatment, which drew our attention to the medical problem described above and encouraged further analysis of the above topic.

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