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# Nowotwory

## Journal of Oncology

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*Aleksandra Kapała, Katarzyna Różycka, Marta Dąbrowska-Bender*

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*Monika Leżanko, Błażej A. Pilch, Anna Czechowska, Dawid Sigorski, Paweł Sobczuk, Sergiusz Nawrocki*

**Coordinated medical care program for neurofibromatosis type 1 children and youth in Poland influences the future of their affected parents as well — a single academic reference center experience and national program description**
*Marek W. Karwacki*

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ul. Roentgena 5
02–781 Warszawa, Poland

**Address for correspondence:**
Krakowska Akademia im. Andrzeja Frycza-Modrzewskiego
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room 309
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# Contents


## Original articles

### Nutrition

**A clinical retrospective study — the investigation of folic acid concentration in caucasian cancer patients . . . . . 1**
*Aleksandra Kapała, Katarzyna Różycka, Marta Dąbrowska-Bender*

### Tumor biology

**Knowledge about the European Code Against Cancer, and adherence to the principles of a healthy lifestyle among students in Poland . . . . . 10**
*Monika Leżanko, Błażej A. Pilch, Anna Czechowska, Dawid Sigorski, Paweł Sobczuk, Sergiusz Nawrocki*

### Rare tumors

**Coordinated medical care program for neurofibromatosis type 1 children and youth in Poland influences the future of their affected parents as well — a single academic reference center experience and national program description . . . . . 19**
*Marek W. Karwacki*

## Review articles

### Tumor pathology

**Endoscopic ultrasound-guided fine needle aspiration biopsy — diagnostic principles and workup . . . . . 29**
*Małgorzata Lenarcik, Magdalena Misiak-Gałązka, Andrzej Mróz*

### Radiotherapy

**Combined CONVentional with HYPOfractionated regimen (CONV-HYPO) alternative instead of conventionally fractionated radiotherapy to improve treatment outcomes . . . . . 35**
*Bogusław Maciejewski, Małgorzata Kraszkiewicz, Piotr Wojcierszek, Jean-Pierre Gerard*

### Liver tumors

**New targeted therapies used in the treatment of patients with advanced cholangiocarcinoma . . . . . 42**
*Aleksandra Śnios, Natalia Ziaja, Maksymilian Kruczała*

## Pictures in Oncology

**The positive significance of skin complications after immunotherapy . . . . . 45**
*Aneta Podczerwińska, Clara Kuzminski, Marek Ziobro, Aleksandra Grela-Wojewoda*

**Breast cancer 3 years after a contralateral risk reduction mastectomy . . . . . 46**
*Wojciech Figurny, Maciej Łukaszek, Mateusz Wichtowski*

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Original article

Nutrition

# A clinical retrospective study — the investigation of folic acid concentration in caucasian cancer patients

Aleksandra Kapała[1, 2], Katarzyna Różycka[2], Marta Dąbrowska-Bender[2]

[1]*Department of Oncology Diagnostics, Cardio-Oncology and Palliative Medicine, Maria Skłodowska-Curie National Research Institute of Oncology, Poland*
[2]*Department of Clinical Nutrition, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

**Introduction.** Folates are one of the essential coenzymes for the proper synthesis, stability, and repair of DNA, playing a crucial role in renewing the population of rapidly dividing cells. Folates may act as a "double-edged sword". Folate in the diet may reduce the risk of cancer. However, folates may contribute to the progression of precancerous conditions or cancer. The study's primary objective was to evaluate the frequency of folic acid deficiency (FAD) in cancer patients and determine clinical factors associated with FAD.

**Material and methods.** Retrospective data were analyzed from 150 consecutive Caucasian cancer patients admitted to a major oncology hospital for cancer treatment. Folic acid (FA) plasma concentration, cancer and treatment type, histology, staging, comorbidities, nutritional status, body composition, and medical history of ailments were recorded.

**Results.** FAD was diagnosed in 18% of cancer patients. FAD was significantly more frequent in women than in men (81.5 *vs.* 18.5%; $p = 0.028$), in squamous cell carcinoma $p < 0.001$, in patients undergoing radiotherapy $p < 0.001$ and in dysphagic patients $p = 0.011$. The anthropometric and biochemical data analysis had no significant relationship with the occurrence of FAD.

**Conclusions.** FAD is more common in women with cancer than in men, regardless of the nutritional status determined by anthropometric or biochemical methods. Gender may play a role when assessing micronutrient status. Nutritional guidelines for cancer patients should include screening for micronutrient deficiencies. Further studies are needed to determine the role, dosage, and duration of FA supplementation recommended for specific cancer diagnoses and gender.

**Keywords:** cancer, folate, folic acid, folic acid deficiency, vitamins

## Introduction

### *Folates in the general population*

Folic acid (FA) and its derivatives belong to the group of folates, and differ in the degree of oxidation of the pyridine ring and the number of glutamic acid residues [1]. Folate is a naturally occurring form of vitamin B9 in food, while FA is a synthetic compound manifesting as a food additive or dietary supplement. Food folates have lower bioavailability than synthetic FA, 50% and 85%, respectively. Due to differences in the bioavailability of folates from food, their total amount is defined as the Dietary Folate Equivalent (DFE), where 1 µg of DFE is 1 µg of dietary folate, which in turn is equal to 0.6 µg of FA from fortified foods and dietary supplements or 0.5 µg of FA from a dietary supplement taken on an empty stomach [2].

The primary sources of folate are green vegetables such as spinach, parsley, asparagus, brussels sprouts, and broccoli. Legume seeds contain significant folates — edamame, beans, peas, and broad beans. Animal products are also sources

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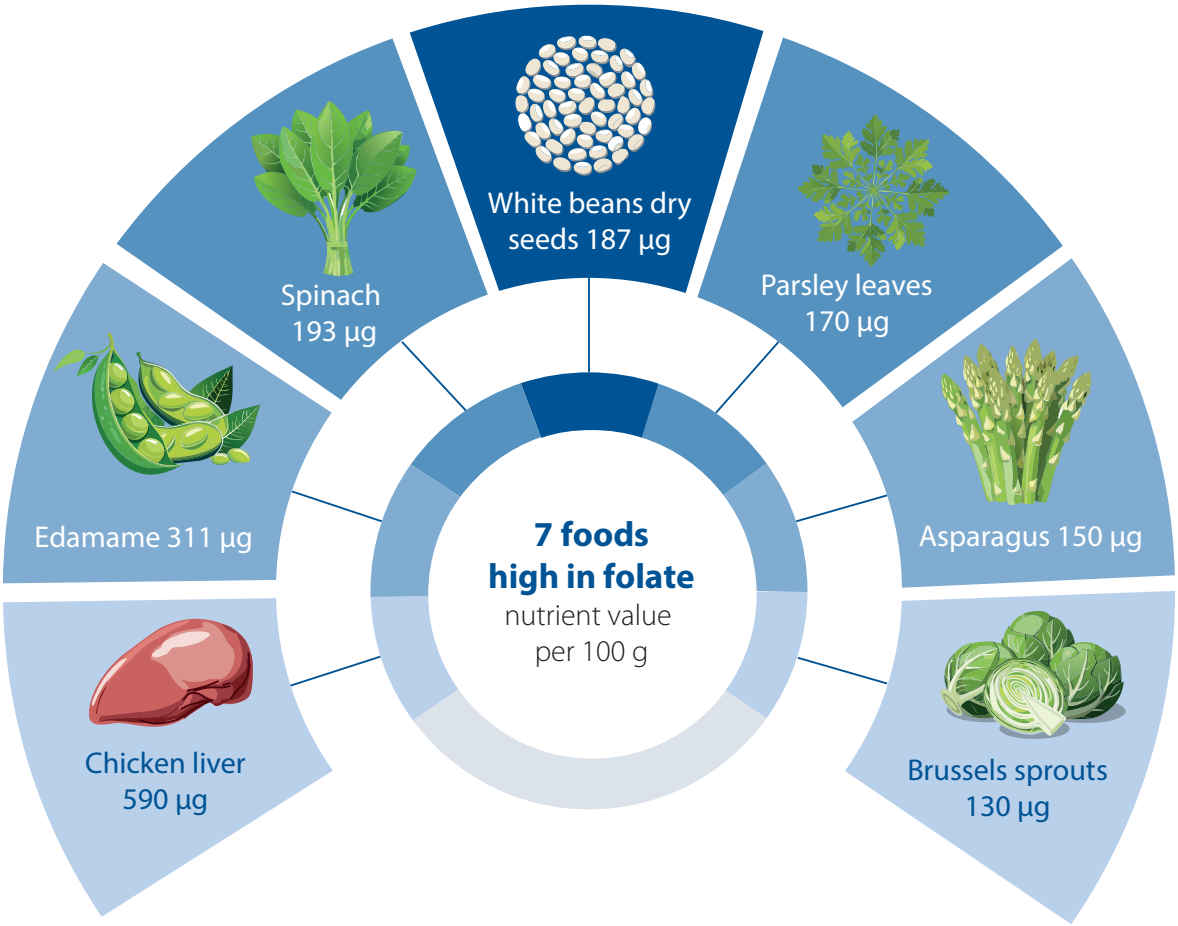


**Figure 1.** Folate content in food

of folates – mainly liver and egg yolks [3]. The richest sources of folate are shown in Figure 1.

Folates found in food products are unstable and sensitive to high temperatures, sunlight, oxygen, copper and iron ions, and the acidic pH of the environment. Significant folate losses occur during thermal processing — up to 30% during bread baking and up to 80% during cooking. The presence of ascorbic acid in food products has significantly reduced folates loss [4, 5].

There can be many causes of folate deficiency, including insufficient supply from the diet, alcohol consumption, malabsorption syndrome (inflammatory bowel disease, celiac disease, chronic intestinal failure), increased demand (pregnancy and lactation, inflammatory and cancer diseases, dialysis, dermatological diseases), taking certain medications (sulfasalazine, methotrexate, anticonvulsants, metformin) [6]. The National Institutes of Health (NIH) recommends 400 µg DFE for the American population for both women and men. Pregnant and breastfeeding women require 600 and 500 µg of DFE daily [1]. The guidelines of the European Food Safety Authority (EFSA) suggest a supply of 330 µg for the general population and a double dose for pregnant and breastfeeding women [7]. The European Society of Clinical Nutrition and Metabolism recommends a daily supply of 400–600 µg of FA. The upper level (UL) for adults for FA from fortified food or supplements (not including folate from food) is set at 1,000 µg a day. The harmful effects of FA overdosing have not been described [8].

Data from the 2013–2014 National Health and Nutrition Examination Survey (NHANES) show that most people in the United States consume adequate amounts of folates. The average daily intake of folate from food among adults is 602 µg DFE for men and 455 µg DFE for women. Still, certain groups, including women of childbearing age and African American women, are at risk of inadequate folate intake. In order to prevent complications resulting from folate deficiency, the US Food and Drug Administration (FDA) in January 1998 introduced the obligation to fortify certain food products with FA [9, 10]. The analysis of studies on folate intake in the Polish population in 2000–2010 showed that the average folate intake among adults ranged from 110 to 352 µg/person/ /day, depending on the subpopulation studied. In Poland, like in many European countries, there is no obligation to enrich

food products with FA, but there is still a growing range of fortified products, mainly breakfast cereals, juices, drinks, sweets, flour, cocoa, and margarine [11].

Folates and its derivatives are transformed in the human body into the biologically active form of tetrahydrofolate. It functions as a coenzyme in transferring one-carbon formalyl and hydroxymethyl groups and synthesizing purine and pyrimidine bases — the fundamental components of nucleic acids. Therefore, folates are necessary for all body cells to survive and proliferate, especially those that divide frequently (blood cells, epithelia). Folates also plays a significant role in the metabolism of amino acids, thanks to which it is possible to remethylate homocysteine to methionine, which is necessary for methylation reactions.

Folate deficiency leads to impaired cell division and methylation reactions necessary to regulate gene expression, as well as to the accumulation of toxic metabolites. Folic acid supplementation may reduce the risk of death from cardiovascular disease, which may be attributable to a reduction in serum homocysteine concentrations [12]. Due to improving nitric oxide bioavailability, folates can prevent and reverse endothelial dysfunction, a significant risk factor for cardiovascular disease [13]. Folic acid supplementation was associated with a lower risk of certain pregnancy complications — neural tube defect, megaloblastic anemia, low fetal weight, cleft lip and palate, preeclampsia, and congenital heart defects [14, 15].

### *Folates in the cancer patient population*

Epidemiologic studies have suggested the protective role of folates on the risk of cancer of the colon, lungs, pancreas, esophagus, stomach, cervix, ovary, and breast [16]. Perinatal supplementation of FA reduces the incidence of neuroblastoma among children aged ≤ 17 years [17, 18]. Beneficial observations from epidemiological studies and the undeniable value of FA supplementation in reducing the risk of severe congenital neural tube defects and cardiovascular disease contributed to the introduction of mandatory food fortification with FA in North America, South Africa, Canada, and Australia in 1998. However, in subsequent years, studies have suggested the negative impact on transforming precancerous colorectal adenomas into malignant tumors [19–21]. The Aspirin and Folic Acid Polyp Prevention Study [19] reported in 2007 an unexpected increase in the incidence of advanced colorectal adenomas and prostate cancer during seven years of treatment with FA. Aspirin (300 mg/day) but not folate (0.5 mg/day) use was found to reduce the risk of colorectal adenoma recurrence in 945 patients in a double-blind, randomized trial by Logan and colleagues [20].

Moreover, the hypothesis that a temporal association exists between FA fortification and an increase in colorectal cancer raised more doubts about the safety of FA supplementation [22]. Based on animal studies, it has been observed that FA can act as a double-edged sword. On the one hand, its supplementation reduces the risk of cancer in healthy tissues. However, in the case of precancerous or already malignant lesions, it may be the cause of their accelerated progression [23]. In neoplastic cells, where DNA replication and cell division occur at an accelerated rate, interruption of folate metabolism causes ineffective DNA synthesis, inhibiting tumor growth. The first valuable lesson was learned in 1940 when Sidney Faber tried to use FA conjugates as a treatment in oncology. In a group of children with leukemia, the disease progressed rapidly after using FA [24]. This observation became the starting point for work on drugs from the antimetabolites group that block the action of folates, DNA replication, and restoration of the cancer cell population. Indeed, this has been the basis for cancer chemotherapy with several antifolate agents like methotrexate and 5-fluorouracil. All these contradictory and unclear reports on the role of folates and FA in carcinogenesis led to a meta-analysis involving 13 randomized trials and 50,000 individuals by Vollset E.S. and colleagues in 2013 [25]. During a weighted average scheduled treatment duration of 5 years, allocation to FA quadrupled plasma concentrations of FA (57,3 nmol/L for the FA groups *vs.* 13,5 nmol/L for the placebo groups) but had no significant effect on overall cancer incidence (1904 cancers in the FA groups *vs.* 1809 cancers in the placebo groups [risk ratio (RR) = 1.06; 95% confidence interval (CI) 0.99–1.13; p = 0, 10]. Supplemented dosage of FA was 0,5-5mg daily; only in one study was the dosage 40 mg daily.

Moreover, there was no significant effect of FA supplementation on the incidence of cancer of the large intestine, prostate, lung, breast, or any other specific site. Folic acid supplementation does not substantially increase or decrease cancer incidence during the first five years of treatment. Food fortification with FA is safe, and the amount of FA delivered with fortified food is definitely below the doses used in clinical trials.

## Material and methods

The study population comprised 150 consecutive outpatients of the Maria Skłodowska-Curie National Research Institute of Oncology in Warsaw, recruited for the study between June 2022 and June 2023. The study received the positive opinion of Bioethics Committee (KB-078-10/24). The study population were divided into six cancer groups: head and neck, upper gastrointestinal tract, pancreas, colon, breast, and gynecological. The groups were equal in size, 25 patients each.

The primary goal of the analysis was the prevalence of FA deficiency in cancer patients. Then, we tried to find clinical factors associated with FA deficiency (FAD). The concentration of FA was determined during the patient's first visit to the Institute's nutritional outpatient clinic.

Data about the type and stage of cancer, histopathological diagnosis, treatment type, nutritional status, and ailments were collected. Nutritional status was determined based on anthropometric analysis [body weight, body mass index (BMI), weight loss over the last six months], body composition [lean body

mass and adipose tissue from bioelectrical impedance testing (BIA), Body Composition Analyzer MC-780MA] and laboratory parameters (albumin, blood cells count). The local laboratory has established a folate concentration in blood samples with a cut-off value of 4.80 to 37.30 ng/mL. Folic acid deficiency was defined as < 4.80 ng/mL. Folic acid concentration was determined in serum using the electrochemiluminescence method Elecsys® Folate III on a Roche Cobas analyzer. Measuring range is 0.6–20.0 ng/mL or 1.36–45.4 nmol/L, with limit of detection = 1.2 ng/mL (2.72 nmol/L). Blood for testing was collected on an empty stomach.

Statistical analysis was performed using IBM SPSS Statistics v. 29.0. To determine the relationship between qualitative variables, Fisher's exact test was performed. The phi coefficient for $2 \times 2$ tables or the Cramers'V coefficient for larger tables were used as the effect size. To compare the two groups in terms of quantitative variables, an analysis was performed using the Mann-Whitney U test. The significance level was taken as $\alpha \leq 0.05$.

## Results

The general group characteristic n = 150, divided into six equal groups according to a cancer diagnosis is presented in Table I. The investigated group was assessed using clinical variables like sex, age, cancer type, histopathology, ailments, BMI, BIA, albumin concentration, and blood count.

### *Folic acid deficiency and gender*

Folic acid deficiency was recognized in 18% of patients in the study group (Tab. II) and statistically more often in women than in men (81,5 *vs.* 18,5% p = 0,028) (Tab. III).

### *Folic acid deficiency and cancer type*

Folic acid deficiency was more common with head and neck cancer than pancreas (32% *vs.* 4%; p = 0.023; φ = 0.36), with gynecological cancer more common than colorectal (40% *vs.* 8%; p = 0.018; φ = 0.38), pancreas (40% *vs.* 4%; p = 0.005; φ = 0.44). No differences were noted between the other types (p > 0.05). Data presented in Table IV.

### *Folic acid deficiency and histopathology*

The squamous cell carcinoma group had a higher incidence of FAD than the adenocarcinoma group (40% *vs.* 10.5%; p < 0.001; φ = 0.33). No differences were noted between the other groups (p > 0.05). Data presented in Table V.

### *Folic acid deficiency and oncological treatment*

It was shown that among patients undergoing radiotherapy, the percentage of FAD was significantly more frequent than among patients undergoing chemotherapy (64.3% *vs.* 6.1%; p < 0.001, φ = 0.62), hormonotherapy (64.3% *vs.* 16.7%; p = 0.010; φ = 0.49) and cancer survivors (64.3% *vs.* 16.1%; p < 0.001; φ = 0.44). Folic acid deficiency was more common among patients undergoing surgery than chemotherapy (37.5% *vs.* 6.1%; p = 0.031; φ = 0.36). Data presented in Table VI.

### *Folic acid deficiency and ailments*

During oncological treatment, various symptoms were recorded: nausea and vomiting, diarrhea, constipation, dysphagia, pain, smell and taste disturbances, anorexia, and dry mouth. Other symptoms reported by patients were tiredness and flatulence.

Among patients experiencing dysphagia, FAD was significantly more frequently than when experiencing pain (40% *vs.* 0%; p = 0.005; φ = 0.48) and in the group with no ailments (40% *vs.* 14.8%; p = 0.028; φ = 0.27; Tab. VII).

The analysis did not show a significant relationship between the concentration of FA and age or nutritional status — body mass index, lean and fat body mass, albumin concentration or blood count.

No significant association was found between disease advancement (local *vs.* metastatic) and FAD.

## Discussion

A deficiency of vitamins and trace elements in oncological patients is common. Recommendations regarding micronutrient supplementation are dedicated to the general population, not cancer patients. The current ESPEN recommendation on the use of micronutrient supplementation does not recommend exceeding the recommended dietary allowance (RDA), adequate intake (AI) in the group of cancer patients [5]. Nevertheless, it is known that the demand for micronutrients in oncological patients may be significantly increased in various clinical situations and concerns primarily water-soluble vitamins and zinc [26, 27].

Vitamin D deficiency in cancer patients examined in the same oncology center reached 66.8% [28], and zinc deficiency 68% [29]. Deficiencies of micronutrients such as vitamin D, zinc or folate have been considered an important factor in increasing cancer risk [30, 31].

There is little data in the literature on the prevalence of FAD in the general population, in older adults it is 12.6–16.4% [32]. However, there is no data on the frequency of FAD in oncological patients. Therefore, FAD found in our study, reaching 18%, can be defined as a significant clinical problem.

Scarce data are available for FAD in cancer patients in association with gender. In the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), dietary folate intake was investigated, and the risk of pancreatic cancer among women with the highest folate intake significantly decreased [hazard ratio (HR) = 0.47; 95% CI: 0.23–0.94; p for trend = 0.09)] but not among men [33]. In a study based on a self-administered dietary questionnaire analysis filled out by 56,837 women enrolled in the Canadian National Breast Screening Study, folate intake was inversely associated with colorectal cancer risk in women [incidence rate ratio (IRR) = 0.6;

**Table I.** General group characteristics

| Variable | Statistics |
|---|---|
| Sex, n (%) | |
| Women | 93 (62.0%) |
| Men | 57 (38.0%) |
| Age, mean (SD) | 62.67 (11.13) |
| Cancer type, n (%) | |
| Head and neck | 25 (16.7%) |
| Esophagus and stomach | 25 (16.7%) |
| Colorectal | 25 (16.7%) |
| Breast | 25 (16.7%) |
| Pancreas | 25 (16.7%) |
| Gynecological | 25 (16.7%) |
| Histopathology, n (%) | |
| Squamous cell carcinoma | 35 (23.3%) |
| Adenocarcinoma | 105 (70.0%) |
| Low-differentiated or undifferentiated cancer | 8 (5.3%) |
| Sarcoma | 2 (1.3%) |
| Ailments, n (%) | |
| Smell or taste disorders | 8 (5.3%) |
| Nausea and vomiting | 5 (3.3%) |
| Lack of appetite | 49 (32.7%) |
| Early satiety | 54 (36.0%) |
| Dysphagia | 20 (13.3%) |
| Dry mouth | 7 (4.7%) |
| Diarrhea | 19 (12.7%) |
| Constipation | 25 (16.7%) |
| Pain | 16 (10.7%) |
| Aphthae | 1 (0.7%) |
| Other | 9 (6.0%) |
| No ailments | 21 (14.0%) |
| BMI [kg/m$^2$], n (%) | |
| < 18.9 | 21 (14.0%) |
| 19–24.9 | 68 (45.3%) |
| 25–29.9 | 44 (29.3%) |
| 30–34.9 | 12 (8.0%) |
| > 35 | 5 (3.3%) |
| BIA — lean body mass — FFM, n (%) | |
| Deficiency | 8 |
| Standard | 54 |
| Excess | 29 |
| BIA — adipose tissue, n (%) | |
| Deficiency | 23 |
| Standard | 46 |
| Excess | 22 |
| Treatment, n (%) | |
| Chemotherapy | 48 (32.0%) |
| Radiotherapy | 14 (9.3%) |
| Chemoradiotherapy | 3 (2.0%) |
| Immunotherapy | 1 (0.7%) |
| Surgery | 10 (6.7%) |
| Hormone therapy | 18 (12.0%) |
| Cancer survivors | 56 (37.3%) |
| Albumin concentration, [g/L] M (SD) | 39.21 (3.15) |
| WBC [g/L], M (SD) | 6.91 (5.12) |
| Hbg [g/dL], M(SD) | 12.22 (1.60) |
| MCV [fl], M (SD) | 90.10 (8.16) |
| Neutrocytes [g/L], M (SD) | 4.51 (4.55) |
| Lymphocytes [g/L], M (SD) | 1.57 (0.75) |

BIA study norms:
Body fat women: deficiency < 24%, standard ≥ 24%, < 36%, excess ≥ 36%
Body fat men: deficiency < 12%, standard ≥ 12%, < 25%, excess ≥ 25%
Lean body mass women: deficiency: < 50%, standard ≥ 50%
Lean body mass men: deficiency: < 53%, standard ≥ 53%
BIA — bioelectrical impedance analysis; BMI — body mass index; FFM — fat-free mass; SD — standard deviation

95% CI: 0.4–1.1; p for trend = 0.25] [34]. Dietary folate intake, especially in case of alcohol consumption > 4 g/daily, was associated with a 25% decrease in the risk of ovarian cancer for the highest *versus* the lowest quartile level of intake [35]. Female gender and high folate intake probably play a role in the risk of developing some types of cancer. In our study, the reproductive organ patient group has a significantly higher incidence of FAD. However, how to treat the deficiency of FA in this group of patients needs to be investigated. Folates are crucial for the DNA metabolism of any cell, including cancer cells. Folate receptor alpha (FRα) is a folate-binding protein overexpressed on ovarian cancer cells (72% of primary and 82% of recurrent ovarian cancers) [36]. Folate receptor alpha, encoded by the FOLR1 gene, responsible for adequate neural and cardiovascular system development, has attracted considerable interest due to its high expression

**Table II.** Analysis of the prevalence of folic acid deficiency in the study sample

| Concentration | Folic acid | |
|---|---|---|
| | n | [%] |
| Deficiency | 27 | 18.0 |
| Norm | 123 | 82.0 |

in several lung, renal, and breast cancer types. Despite their anti-tumor effects in preclinical models, folate-cytotoxic drug conjugates and no conjugated humanized antibody have yet to demonstrate clinical efficacies [37]. Phase III trials with farletuzumab (anti-FRα antibody) showed a favorable toxicity profile but controversial antitumor activity [38]. Therefore,

**Table III.** Fisher's exact test for the prevalence of folic acid deficiency depending on gender

| Gender | Folic acid concentration | | | | | |
|---|---|---|---|---|---|---|
| | Deficiency | | Norm | | | |
| | n | [%] | n | [%] | p | φ |
| Women | 22 | 81.5 | 71 | 57.7 | **0.028** | 0.19 |
| Men | 5 | 18.5 | 52 | 42.3 | | |

**Table IV.** The prevalence of folic acid deficiency depending on cancer type

| Cancer type | Folic acid concentration (deficiency) | |
|---|---|---|
| | n | [%] |
| Head and neck | 8 | 32.0 |
| Esophagus and stomach | 3 | 12.0 |
| Colorectal | 2 | 8.0 |
| Pancreas | 1 | 4.0 |
| Breast | 4 | 16.0 |
| Gynecological | 10 | 40.0 |

**Table V.** The prevalence of folic acid deficiency depending on histopathology

| Histopathology | Deficiency | |
|---|---|---|
| | n | % |
| Squamous cell carcinoma | 14 | 40.0 |
| Adenocarcinoma | 11 | 10.5 |
| Low-differentiated or undifferentiated cancer | 2 | 25.0 |
| Sarcoma | 0 | 0.0 |

**Table VI.** The prevalence of folic acid deficiency depending on the oncological treatment type

| Oncological treatment type | Deficiency | |
|---|---|---|
| | n | [%] |
| Chemotherapy | 3 | 6.1 |
| Radiotherapy | 9 | 64.3 |
| Surgery | 3 | 37.5 |
| Hormonotherapy | 3 | 16.7 |
| Cancer survivors | 9 | 16.1 |

**Table VII.** The prevalence of folic acid deficiency depending on ailments

| Ailments | Deficiency | |
|---|---|---|
| | n | [%] |
| Smell or taste disturbances | 1 | 12.5 |
| Nausea and vomiting | 0 | 0.0 |
| Lack of appetite | 9 | 18.4 |
| Dysphagia | 8 | 40.0 |
| Dry mouth | 0 | 0.0 |
| Diarrhea | 2 | 10.5 |
| Constipation | 8 | 32.0 |
| Pain | 0 | 0.0 |
| Aphthae | 0 | 0.0 |
| Other (tiredness) | 4 | 19.0 |
| No ailments | 8 | 14.8 |

the results of our study, where FAD is significantly more common in women, prompt us not only to look for FAD but also to interpret the results in the context of gender. The finding may be significant for women of reproductive age who plan to have children after cancer therapy. Based on previous literature data, no relationship has ever been found between high, natural dietary folate intake and the risk of cancer progression. When comparing the highest to lowest intake of folate, higher intake was associated with a nearly 50% decreased risk for squamous cell carcinoma of the head and neck, analyses have shown that every 100 mcg/day increase in folate intake was associated with a 4.3% decrease in risk of head and neck cancer [39]. Another study found a 35% reduced risk for oral cavity and pharyngeal, 41% reduced risk of esophageal, 34% reduction in pancreatic, and 16% reduction in bladder cancers [40]. Furthermore, FA daily intake up to 5 mg does not appear to influence the risk of cancer progression [12]. Therefore, perhaps adopting a strategy of offering a folate-rich diet and moderate oral FA supplementation is a safe strategy for cancer patients with FAD. On the other hand, other factors may influence folate metabolism. One of them is gene polymorphism; the other is ethnicity [41]. Gene encoding methylenetetrahydrofolate reductase (MTHFR) directly affects DNA synthesis and methylation due to affecting nutrient bioavailability, and has been associated with an increased risk of certain cancers. A different mutation in the MTHFR genes has been associated with increased risk of lung, hepatocellular, breast, brain, and ovarian cancer in Asian populations and breast cancer in Turkish population [28].

Finally, our study draws attention to a dangerous triangle of variables with significantly frequent co-occurrence, namely squamous cell carcinoma — radiotherapy — dysphagia and micronutrient deficiency. We described similar observations among patients of our center when examining vitamin D and zinc deficiency [16, 17]. Squamous cell carcinomas are the dominant histopathological type among head and neck cancers. One of the primary methods of treating this group of cancers, apart from surgery, is chemoradiotherapy. Chemoradiation is an aggressive treatment method associated with numerous side effects, primarily post-radiation mucositis, which is stage III in 60% of patients [42]. Severe radiation exposure leads to dysphagia, weight loss, and the development of deficiencies in numerous micronutrients, including FAD. Various supportive treatment strategies were undertaken, including supplementation of micronutrients such as glutamine, arginine, omega-3 fatty acids, zinc and FA to reduce the severity of mucositis [43]. The more significant the FAD, the greater the risk of occurrence and severity of radiation-mucositis, especially in head and neck cancer patients [44]. In a preclinical study, FAD led to the misincorporation of uracyl into DNA, non-effective DNA repair, and chromosome breakage. This same ability has ionising radiation responsible for DNA and chromosome damage. Antioxidants during radiotherapy diminish free radicals' activity, managing inflammatory responses, and attenuating apoptosis signaling pathways in radiosensitive organs. Folic acid deficiency and radiotherapy work synergistically. Aneuploidy of chromosome 21, apoptosis, and necrosis were increased by FAD [45]. In a randomized trial, 540 patients diagnosed with head and neck cancer undergoing radiotherapy were enrolled in the study investigating the influence of antioxidants on adverse events like mucositis and QoL. The reduction of adverse events was statistically significant in antioxidants group (OR = 0.38; 95% CI: 0.21–0.71). However, the rate of local recurrence of the head and neck tumor tended to be higher in the supplement arm of the trial (HR = 1.37; 95% CI: 0.93 to 2.02) [46]. Several studies have shown that antioxidants can effectively reduce the toxicity of radiotherapy, but unfortunately, they also reduce the therapeutic effect of this treatment method [47, 48]. However, whether antioxidants alter antitumor effects during radiotherapy remains unclear. The systematic review with 49 RCTs concludes that the harm caused by antioxidant supplementation remains unclear for cancer therapy patients except for smokers undergoing radiotherapy, where it is significantly harmful [49].

### *Study limitations*

The heterogeneity of the study group and, consequently, different methods of oncological treatment may have different effects on FA resources in the body. In addition, variables related to lifestyle (addictions, physical activity, diet), the presence of other chronic diseases, and medications used may also affect the obtained results.

## Conclusions

Folic acid deficiency in cancer patients is common, especially in women, regardless of nutritional status measured by anthropometric or biochemical tools. Although folates may be involved in many ways in cancer proliferation, it seems to be underestimated. The question of how to treat FAD during active oncological treatment, especially radiotherapy, seems particularly interesting. In light of the results of our study, patients with reproductive organ cancer should be particularly screened for FAD. Nutrition guidelines for cancer patients should include screening for micronutrient deficiencies. Further studies are needed to determine the role, dosage, duration, and form of the supplementation recommended for specific cancer diagnoses and gender.

## Article information and declarations

### *Data availability statement*

Data are not available.

### *Ethics statement*

The study received a positive opinion of Bioethics Committee (KB-078-10/24).

### *Authors contributions*

Aleksandra Kapała — conceptualization, formal analysis, methodology, supervision, validation, writing — original draft preparation, writing — review & editing.
Katarzyna Różycka — data curation, investigation, visualization, writing — original draft preparation.
Marta Dąbrowska-Bender — data curation, investigation.


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### *Conflict of interest*

The authors declare no conflict of interest.

### *Supplementary material*

None.


**Aleksandra Kapała**
*Department of Oncology Diagnostics, Cardio-Oncology and Palliative Medicine*
*Maria Skłodowska-Curie National Research Institute of Oncology*
*W.K. Roentgena 5*
*02–871 Warsaw, Poland*
*e-mail: aleksandra.kapala@nio.gov.pl*



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## References


1. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. 1998, doi: 10.17226/6015.
2. Suitor CW, Bailey LB. Dietary folate equivalents: interpretation and application. J Am Diet Assoc. 2000; 100(1): 88–94, doi: 10.1016/S0002-8223(00)00027-4, indexed in Pubmed: 10646010.
3. McKillop DJ, Pentieva K, Daly D, et al. The effect of different cooking methods on folate retention in various foods that are amongst the major contributors to folate intake in the UK diet. Br J Nutr. 2002; 88(6): 681–688, doi: 10.1079/BJN2002733, indexed in Pubmed: 12493090.
4. McNulty H, Pentieva K. Folate bioavailability. Proc Nutr Soc. 2004; 63(4): 529–536, doi: 10.1079/pns2004383, indexed in Pubmed: 15831124.
5. Berger M, Shenkin A, Schweinlin A, et al. ESPEN micronutrient guideline. Clinical Nutrition. 2022; 41(6): 1357–1424, doi: 10.1016/j.clnu.2022.02.015.
6. Bailey RL, Dodd KW, Gahche JJ, et al. Total folate and folic acid intake from foods and dietary supplements in the United States: 2003-2006. Am J Clin Nutr. 2010; 91(1): 231–237, doi: 10.3945/ajcn.2009.28427, indexed in Pubmed: 19923379.
7. Crider KS, Bailey LB, Berry RJ. Folic acid food fortification-its history, effect, concerns, and future directions. Nutrients. 2011; 3(3): 370–384, doi: 10.3390/nu3030370, indexed in Pubmed: 22254102.
8. Reynolds EH. What is the safe upper intake level of folic acid for the nervous system? Implications for folic acid fortification policies. Eur J Clin Nutr. 2016; 70(5): 537–540, doi: 10.1038/ejcn.2015.231, indexed in Pubmed: 26862004.
9. Lewis CJ, Crane NT, Wilson DB, et al. Estimated folate intakes: data updated to reflect food fortification, increased bioavailability, and dietary supplement use. Am J Clin Nutr. 1999; 70(2): 198–207, doi: 10.1093/ajcn.70.2.198, indexed in Pubmed: 10426695.
10. Yetley EA, Pfeiffer CM, Phinney KW, et al. Biomarkers of folate status in NHANES: a roundtable summary. Am J Clin Nutr. 2011; 94(1): 303S–312S, doi: 10.3945/ajcn.111.013011, indexed in Pubmed: 21593502.
11. Sicińska E, Wyka J. Folate intake in Poland on the basis of literature from the last ten years (2000-2010). Rocz Panstw Zakl Hig. 2011; 62: 247–256.
12. Bo Y, Zhu Y, Tao Y, et al. Association Between Folate and Health Outcomes: An Umbrella Review of Meta-Analyses. Front Public Health. 2020; 8: 550753, doi: 10.3389/fpubh.2020.550753, indexed in Pubmed: 33384976.
13. Moat SJ, Lang D, McDowell IFW, et al. Folate, homocysteine, endothelial function and cardiovascular disease. J Nutr Biochem. 2004; 15(2): 64–79, doi: 10.1016/j.jnutbio.2003.08.010, indexed in Pubmed: 14972346.
14. Czeizel AE, Vereczkey A, Bánhidy F. Higher risk of orofacial clefts in children born to mothers with angina pectoris: a population-based case-control study. Congenit Anom (Kyoto). 2015; 55(1): 49–54, doi: 10.1111/cga.12074, indexed in Pubmed: 25059101.
15. Czeizel AE, Vereczkey A, Szabó I. Folic acid in pregnant women associated with reduced prevalence of severe congenital heart defects in their children: a national population-based case-control study. Eur J Obstet Gynecol Reprod Biol. 2015; 193: 34–39, doi: 10.1016/j.ejogrb.2015.06.024, indexed in Pubmed: 26225846.
16. Kim YI. Will mandatory folic acid fortification prevent or promote cancer? Am J Clin Nutr. 2004; 80(5): 1123–1128, doi: 10.1093/ajcn/80.5.1123, indexed in Pubmed: 15531657.
17. French AE, Grant R, Weitzman S, et al. Folic acid food fortification is associated with a decline in neuroblastoma. Clin Pharmacol Ther. 2003; 74(3): 288–294, doi: 10.1016/S0009-9236(03)00200-5, indexed in Pubmed: 12966372.
18. Preston-Martin, S, Pogoda J, Mueller B, et al. Prenatal vitamin supplementation and risk of childhood brain tumors. International Journal of Cancer. 1998; 78(S11): 17–22, doi: 10.1002/(sici)1097-0215(1998)78:11+<17::aid-ijc6>3.3.co;2-h.
19. Cole BF, Baron JA, Sandler RS, et al. Polyp Prevention Study Group. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. JAMA. 2007; 297(21): 2351–2359, doi: 10.1001/jama.297.21.2351, indexed in Pubmed: 17551129.
20. Logan RFA, Grainge MJ, Shepherd VC, et al. ukCAP Trial Group. Aspirin and folic acid for the prevention of recurrent colorectal adenomas. Gastroenterology. 2008; 134(1): 29–38, doi: 10.1053/j.gastro.2007.10.014, indexed in Pubmed: 18022173.
21. Wu K, Platz EA, Willett WC, et al. A randomized trial on folic acid supplementation and risk of recurrent colorectal adenoma. Am J Clin Nutr. 2009; 90(6): 1623–1631, doi: 10.3945/ajcn.2009.28319, indexed in Pubmed: 19864409.
22. Mason JB, Dickstein A, Jacques PF, et al. A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: a hypothesis. Cancer Epidemiol Biomarkers Prev. 2007; 16(7): 1325–1329, doi: 10.1158/1055-9965.EPI-07-0329, indexed in Pubmed: 17626997.
23. Kim YI. Folic acid supplementation and cancer risk: point. Cancer Epidemiol Biomarkers Prev. 2008; 17(9): 2220–2225, doi: 10.1158/1055-9965.EPI-07-2557, indexed in Pubmed: 18768486.
24. Farber S, Cutler EC, Hawkins JW, et al. The Action of Pteroylglutamic Conjugates on Man. Science. 1947; 106(2764): 619–621, doi: 10.1126/science.106.2764.619, indexed in Pubmed: 17831847.
25. Vollset SE, Clarke R, Lewington S, et al. B-Vitamin Treatment Trialists' Collaboration. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50,000 individuals. Lancet. 2013; 381(9871): 1029–1036, doi: 10.1016/S0140-6736(12)62001-7, indexed in Pubmed: 23352552.
26. Büntzel J, Glatzel M, Micke O, et al. [Status of essential trace elements in untreated carcinomas of the head and neck]. Laryngorhinootologie. 2003; 82(8): 573–577, doi: 10.1055/s-2003-41233, indexed in Pubmed: 12915990.
27. White R, Nonis M, Pearson JF, et al. Low Vitamin C Status in Patients with Cancer Is Associated with Patient and Tumor Characteristics. Nutrients. 2020; 12(8), doi: 10.3390/nu12082338, indexed in Pubmed: 32764253.
28. Kapała A, Szlendak M, Grochowska E. Cross-sectional observational study - Investigation of vitamin D concentration in Caucasian cancer patients. what is the adequate dose of vitamin D for these patients? Clin Nutr. 2021; 40(6): 3852–3858, doi: 10.1016/j.clnu.2021.04.026, indexed in Pubmed: 34130032.
29. Kapała A, Folwarski M, Gazi A. Cross-sectional observational study: Investigation of zinc concentration in white patients with cancer. Nutrition. 2024; 117: 112235, doi: 10.1016/j.nut.2023.112235, indexed in Pubmed: 37924623.
30. Skrajnowska D, Bobrowska-Korczak B. Role of Zinc in Immune System and Anti-Cancer Defense Mechanisms. Nutrients. 2019; 11(10), doi: 10.3390/nu11102273, indexed in Pubmed: 31546724.
31. Hobaus J, Thiem U, Hummel DM, et al. Role of Calcium, Vitamin D, and the Extrarenal Vitamin D Hydroxylases in Carcinogenesis. Anticancer Agents Med Chem. 2012; 13(1): 20–35, doi: 10.2174/18715206130105.
32. Figlin E, Chetrit A, Shahar A, et al. High prevalences of vitamin B12 and folic acid deficiency in elderly subjects in Israel. Br J Haematol. 2003; 123(4): 696–701, doi: 10.1046/j.1365-2141.2003.04658.x, indexed in Pubmed: 14616975.
33. Oaks BM, Dodd KW, Meinhold CL, et al. Folate intake, post-folic acid grain fortification, and pancreatic cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Am J Clin Nutr. 2010; 91(2): 449–455, doi: 10.3945/ajcn.2009.28433, indexed in Pubmed: 20007302.
34. Terry P, Jain M, Miller AB, et al. Dietary intake of folic acid and colorectal cancer risk in a cohort of women. Int J Cancer. 2002; 97(6): 864–867, doi: 10.1002/ijc.10138, indexed in Pubmed: 11857369.
35. Navarro Silvera SA, Jain M, Howe GR, et al. Dietary folate consumption and risk of ovarian cancer: a prospective cohort study. Eur J Cancer Prev. 2006; 15(6): 511–515, doi: 10.1097/01.cej.0000220627.54986.bf, indexed in Pubmed: 17106331.
36. Kalli KR, Oberg AL, Keeney GL, et al. Folate receptor alpha as a tumor target in epithelial ovarian cancer. Gynecol Oncol. 2008; 108(3): 619–626, doi: 10.1016/j.ygyno.2007.11.020, indexed in Pubmed: 18222534.
37. Mai J, Wu L, Yang L, et al. Therapeutic strategies targeting folate receptor α for ovarian cancer. Front Immunol. 2023; 14: 1254532, doi: 10.3389/fimmu.2023.1254532, indexed in Pubmed: 37711615.
38. Bergamini A, Ferrero S, Leone Roberti Maggiore U, et al. Folate receptor alpha antagonists in preclinical and early stage clinical development for the treatment of epithelial ovarian cancer. Expert Opin Investig Drugs. 2016; 25(12): 1405–1412, doi: 10.1080/13543784.2016.1254616, indexed in Pubmed: 27797594.
39. Fan C, Yu S, Zhang Si, et al. Association between folate intake and risk of head and neck squamous cell carcinoma: An overall and dose-response PRISMA meta-analysis. Medicine (Baltimore). 2017; 96(42): e8182, doi: 10.1097/MD.0000000000008182, indexed in Pubmed: 29049201.
40. Pieroth R, Paver S, Day S, et al. Folate and Its Impact on Cancer Risk. Curr Nutr Rep. 2018; 7(3): 70–84, doi: 10.1007/s13668-018-0237-y, indexed in Pubmed: 30099693.
41. Tang M, Wang SQ, Liu BJ, et al. The methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism and tumor risk: evidence from 134 case-control studies. Mol Biol Rep. 2014; 41(7): 4659–4673, doi: 10.1007/s11033-014-3337-9, indexed in Pubmed: 24744129.

42. Elting LS, Cooksley CD, Chambers MS, et al. Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and--neck malignancies. Int J Radiat Oncol Biol Phys. 2007; 68(4): 1110–1120, doi: 10.1016/j.ijrobp.2007.01.053, indexed in Pubmed: 17398022.
43. Elad S, Cheng KK, Lalla RV, et al. Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2020; 126(19): 4423–4431, doi: 10.1002/cncr.33100, indexed in Pubmed: 32786044.
44. Oronsky B, Goyal S, Kim MM, et al. A Review of Clinical Radioprotection and Chemoprotection for Oral Mucositis. Transl Oncol. 2018; 11(3): 771––778, doi: 10.1016/j.tranon.2018.03.014, indexed in Pubmed: 29698934.
45. Beetstra S, Thomas P, Salisbury C, et al. Folic acid deficiency increases chromosomal instability, chromosome 21 aneuploidy and sensitivity to radiation-induced micronuclei. Mutat Res. 2005; 578(1-2): 317–326, doi: 10.1016/j.mrfmmm.2005.05.012, indexed in Pubmed: 16005909.
46. Bairati I, Meyer F, Gélinas M, et al. Randomized trial of antioxidant vitamins to prevent acute adverse effects of radiation therapy in head and neck cancer patients. J Clin Oncol. 2005; 23(24): 5805–5813, doi: 10.1200/JCO.2005.05.514, indexed in Pubmed: 16027437.
47. Yahyapour R, Shabeeb D, Cheki M, et al. Radiation Protection and Mitigation by Natural Antioxidants and Flavonoids: Implications to Radiotherapy and Radiation Disasters. Curr Mol Pharmacol. 2018; 11(4): 285–304, doi: 10.2174/1874467211666180619125653, indexed in Pubmed: 29921213.
48. D'Andrea GM. Use of antioxidants during chemotherapy and radiotherapy should be avoided. CA Cancer J Clin. 2005; 55(5): 319–321, doi: 10.3322/canjclin.55.5.319, indexed in Pubmed: 16166076.
49. Yasueda A, Urushima H, Ito T. Efficacy and Interaction of Antioxidant Supplements as Adjuvant Therapy in Cancer Treatment: A Systematic Review. Integr Cancer Ther. 2016; 15(1): 17–39, doi: 10.1177/1534735415610427, indexed in Pubmed: 26503419.

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Original article

Tumor biology

# Knowledge about the European Code Against Cancer, and adherence to the principles of a healthy lifestyle among students in Poland

Monika Leżanko[1], Błażej A. Pilch[1], Anna Czechowska[1], Dawid Sigorski[2], Paweł Sobczuk[3], Sergiusz Nawrocki[2]

[1]*Immunooncology Students Club, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Poland*
[2]*Department of Oncology, University of Warmia and Mazury in Olsztyn, Poland*
[3]*Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Skłodowska-Curie National Research Institute of Oncology in Warsaw, Poland*

**Introduction.** The European Code Against Cancer (ECAC) was created to reduce the incidence and mortality of cancer. We conducted a study assessing students' knowledge of ECAC, and adherence to healthy lifestyle principles.

**Material and methods.** The study involved an anonymous validated online survey among the student community of 47 Polish universities. The questions pertained to knowledge about ECAC, awareness of cancer risk factors and health-related behaviours.

**Results.** A total of 1041 surveys were obtained (65% female). Knowledge of the term ECAC was seen in 9% of non-medical students (NMS) and 19% of medical students (MS). MS demonstrated higher awareness of cancer risk factors, such as smoking, obesity and sedentary lifestyle, and were more knowledgeable about screening tests compared to NMS ($p < 0.001$).

**Conclusions.** Knowledge about ECAC among Polish students, especially NMS, is insufficient. It is necessary to continue health-promoting initiatives to increase awareness of cancer risk factors, the importance of vaccinations and self-examinations.

**Keywords:** European Code Against Cancer, cancer, cancer awareness

## Introduction

In 2021, the Polish National Cancer Registry recorded approximately 171,558 new cancer cases and 93,652 deaths due to cancer [1]. In 2022, there were approximately 20 million new cancer cases and 9.7 million deaths from cancer globally. Europe faces a disproportionately high burden of cancer, accounting for 22.4% of global cancer cases and 20.4% of cancer deaths, despite having only 9.6% of the world's population [2]. Poland belongs to countries with the highest cancer mortality rates [1]. The European Code Against Cancer (ECAC) was established to decrease cancer risk and cancer-related deaths by promoting prevention and healthy behaviour [3].

Epidemiological observations prove that 80–90% of cancer cases in Western countries are associated with environmental factors [4]. Through the recommendations included in ECAC, about 40% of cancer cases can be prevented by actions that individual citizens can take to help prevent cancer [5].

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Unfortunately, awareness of the ECAC is still uncommon across the general population. [6].

Our study assessed knowledge about the ECAC among Polish students, and examined their approach to healthy lifestyle principles. The aim was to evaluate the awareness and attitudes to cancer prevention and early detection recommendations covered in the ECAC.

## Material and methods

The study was gathered on the initiative of the Immunooncology Student Club of The University of Warmia and Mazury in Olsztyn. The research data was based on a voluntary, anonymous online questionnaire sent out to 47 universities across Poland to respond to students studying various disciplines. The study was first sent out on March 14, 2022, and data gathering was concluded on May 21, 2022. The study was promoted through social media and by contacting university dean offices requesting that the survey be promoted. Upon inquiry, The Bioethics Committee confirmed that a formal opinion is unnecessary due to the voluntary nature of the questionnaire.

The questionnaire contained 59 questions. The questionnaire was divided into sections covering participant demographics, main sources of information and daily internet/social media usage. One section assessed awareness of the ECAC and sources of knowledge. Another tested respondents' knowledge of cancer screening tests available in Poland. A section for smokers inquired about tobacco use, while the lifestyle section included questions on diet, weight control, transportation, vaccinations and intentions to use screening programs. The ECAC section evaluated the understanding of cancer prevention and debunked common health misconceptions.

To measure the approach of the responders, the Likert scale was utilized in the construction of the answers as follows "Definitely yes", "Probably yes", "I have no opinion", "Probably not", "Definitely not". Questions were validated by distributing the questionnaire among 19 individuals collecting their responses. The results of validating individual questions are presented as a supplement.

The statistical significance of the relationship between the data gathered from the individual question was ascertained using the chi-square and the Fisher exact test.

## Results

### *Study group characteristics*

A total sample of 1041 students (average age: 22.4 years, median: 22.0 years) from 47 Polish universities responded to the survey. The characteristics of the study group is presented in Table I.

**Table I.** The characteristics of the study group

| General information, n (%) | | |
|---|---|---|
| Gender | Female | 680 (65.3%) |
| | Male | 342 (32.9%) |
| | Do not want to provide information | 19 (1.8%) |
| Year of study | I | 267 (25.6%) |
| | II | 275 (26.4%) |
| | III | 218 (20.9%) |
| | IV | 116 (11.1%) |
| | V | 134 (12.9%) |
| | VI | 31 (3.0%) |
| Field of study | Humanities | 267 (25.6%) |
| | Science | 244 (23.4%) |
| | Medical | 157 (15.1%) |
| | Technical | 139 (13.4%) |
| | Natural Sciences | 115 (11.0%) |
| | Arts | 70 (6.7%) |
| | Finance | 43 (4.1%) |
| | Physical culture | 6 (0.6%) |
| Number of inhabitants | > 100 000 | 364 (35.0%) |
| | 50 000–100 000 | 110 (10.6%) |
| | < 50 000 | 225 (21.6%) |
| | Countryside | 342 (32.9%) |
| BMI | < 18.5 (underweight) | 95 (9.1%) |
| | 18.5–24.9 (normal) | 705 (67.7%) |
| | 25.0–29.9 (overweight) | 176 (16.9%) |
| | > 30.0 (obese) | 61 (5.9%) |
| Chronic disease | No | 831 (79.8%) |
| | Yes | 210 (20.2%) |
| Main source of information | Internet | 508 (48.8%) |
| | Social media | 353 (33.9%) |
| | Radio and TV | 68 (6.5%) |
| | Family | 60 (5.8%) |
| | Specialist literature | 37 (3.6%) |
| | The press | 15 (1.4%) |

BMI — body mass index

### *Awareness of European Code Against Cancer*

Only 10.7% (n = 111) of responders were familiar with the term of ECAC. Women were more familiar with the ECAC term (13.7%; n = 93) than men (5.0%; n = 17) ($p < 0.001$). The highest familiarity with the ECAC term was found among medical students (MS; medical students, nursing students, midwifery students, emergency medical services students; 19.1%; n = 30). Among non-medical students (NMS), 9.2%

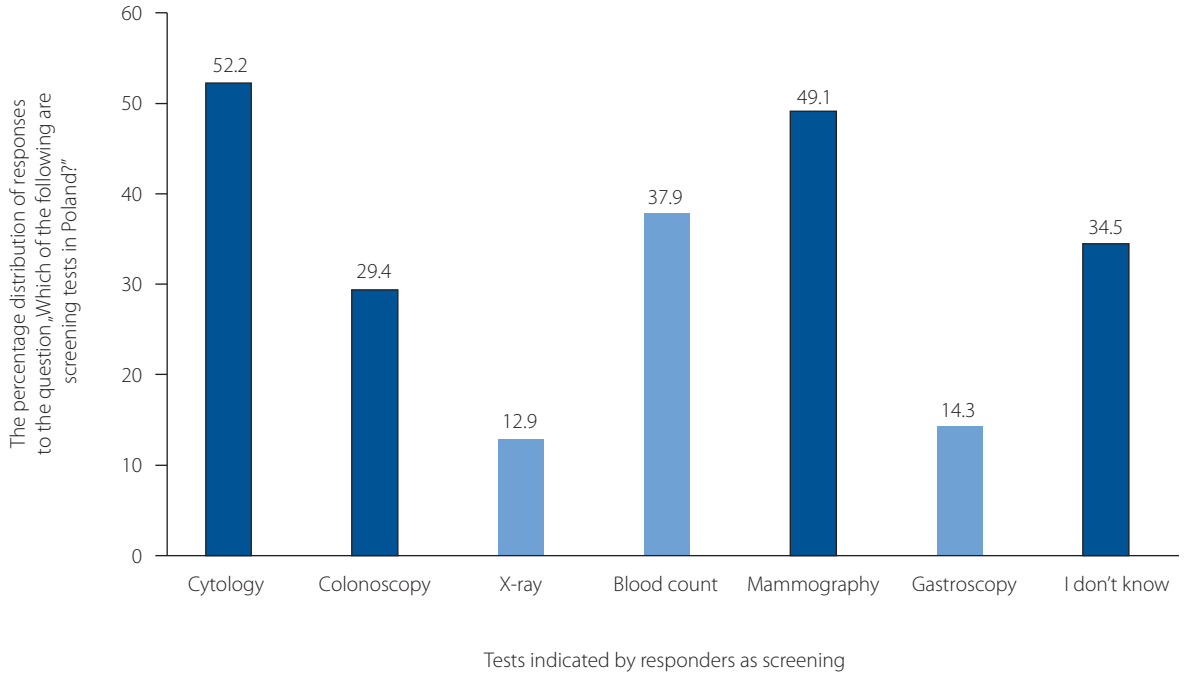


**Figure 1.** The ability to identify screening studies in Poland

**Table II.** The ability to correctly identify all screening tests in Poland and associate them with the cancers they detect depending on gender and field of study

| | Screening programmes | Cancers | Both cancers and screening programmes |
|---|---|---|---|
| Men | 24 (7.0%) | 32 (9.4%) | 20 (5.9%) |
| Women | 64 (9.4%) | 77 (11.3%) | 51 (7.5%) |
| Chose not to disclose | 2 (10.5%) | 3 (15.8%) | 1 (5.3%) |
| p | 0.405 | 0.473 | 0.58 |
| Medical | 40 (25.5%) | 47 (29.9%) | 38 (24.2%) |
| Non-medical | 50 (5.7%) | 65 (7.4%) | 34 (3.9%) |
| p | < 0.001 | < 0.001 | < 0.001 |

(n=81) were aware of the term ECAC ($p < 0.001$). Awareness varied significantly among the different student groups: 0% among physical culture students, 4.1% among science students and 5% among technology students ($p < 0.001$).

### *Screening test programmes*

The majority of students (52.2%; n = 543) correctly chose cytology, mammography 49.1% (n = 511) and colonoscopy as a screening test 29.4% (n = 306). 37.9% of respondents incorrectly considered complete blood count a screening test. Medical students exhibited considerably better knowledge of screening tests than the NMS (Fig. 1). Most students identified breast and cervical cancers as cancers which may be diagnosed through screening tests (Fig. S1). Among MS, 82.8% (n = 130) chose breast and cervical cancers. Colon cancer was identified by 33.4% (n = 348) of the general population and 70.7% (n = 111) of MS. Over one-fourth of MS (25.5%; n = 40) can correctly identify all screening tests in Poland. Nearly the same percentage (24.2%; n = 38) can correctly associate them with the cancers they detect. NMS correctly identified the set of screening tests in only 5.7% (n = 50) and cancers in 7.4% (n = 65) ($p < 0.001$). However, only 3.9% (n = 34) can correctly name both screening tests and the cancers they allow to detect ($p < 0.001$) (Tab. II). Only 2 of first-year students were able to correctly select all screening programs and just 1 was able to select tested for cancers. For students of sixth year, it was 88.9% (n = 8) for both questions ($p < 0.001$) (Tab. SI).

### *The awareness of cancer risk factors among students*

#### A. Recognition of cancer risk factors: smoking, lifestyle and misconceptions

Smoking was the most commonly recognized cancer risk factor, with 98.2% (n = 1023) indicating either "probably yes" or

**Table III.** Knowledge of cancer risk factors as listed by European Code Against Cancer (ECAC) among the general population of students

| Factor | Strongly agree | Agree | Neither agree nor disagree | Disagree | Strongly disagree |
|---|---|---|---|---|---|
| Smoking | 852 (81.8%) | 171 (16.4%) | 11 (1.1%) | 1 (0.1%) | 6 (0.6%) |
| Obesity | 511 (49.1%) | 383 (36.8%) | 104 (10.0%) | 39 (3.7%) | 4 (0.4%) |
| Sedentary lifestyle | 308 (29.6%) | 393 (37.8%) | 224 (21.5%) | 109 (10.5%) | 7 (0.7%) |
| Unhealthy eating habits | 505 (48.5%) | 406 (39.0%) | 88 (8.5%) | 36 (3.5%) | 6 (0.6%) |
| Drinking alcohol | 450 (43.2%) | 388 (37.3%) | 123 (11.8%) | 74 (7.1%) | 6 (0.6%) |
| Harmful substances in the workplace | 716 (68.8%) | 274 (26.3%) | 44 (4.2%) | 2 (0.2%) | 5 (0.5%) |
| Radon radiation | 333 (32.0%) | 314 (30.2%) | 302 (29.0%) | 78 (7.5%) | 14 (1.3%) |
| Not breastfeeding | 55 (5.3%) | 94 (9.0%) | 417 (40.1%) | 332 (31.9%) | 143 (13.7%) |
| Hormone replacement therapy | 74 (7.1%) | 123 (11.8%) | 682 (65.5%) | 152 (14.6%) | 10 (1.0%) |
| HPV infection | 266 (25.6%) | 259 (24.9%) | 468 (45.0%) | 44 (4.2%) | 4 (0.4%) |
| HBV infection | 197 (18.9%) | 307 (29.5%) | 478 (45.9%) | 56 (5.4%) | 3 (0.3%) |

HBV — hepatitis B virus; HPV — human papilloma virus

"definitely yes" (Tab. III). Over half of the respondents recognized obesity (85.9%, n = 894), a sedentary lifestyle (67.4%, n = 701), unhealthy eating habits (87.5%, n = 911), alcohol consumption (80.5%, n = 838), harmful substances in the workplace (95.1%, n = 990), radon radiation (62.2%, n = 647) and HPV infection (50.5%, n = 525) as carcinogenic. Only 48.4% (n = 504) agreed that HBV infection is a cancer risk factor. Less than one-fifth of the responders agreed that lack of breastfeeding is a cancer risk factor (14.3%, n = 149). Nearly two-thirds (65.5%, n = 682) had no opinion on whether hormone replacement therapy (HRT) is a cancer risk. Furthermore, 34.2% (n = 356) incorrectly believed that consuming genetically modified organisms (GMOs) poses a cancer risk. Regarding remaining popular misconceptions about cancer risks, respondents most commonly agreed with energy drink consumption (56.6%, n = 589). Only 6.4% (n = 67) view 5G technology as a cancer risk, and a minority of students (14.1%, n = 147) agree that dietary supplements decrease the risk of cancer (Tab. SII).

### B. Gender differences in perceptions of cancer risk factors

The majority of both men and women agree that smoking (99.1%, n = 339 and 98.0%, n = 666 respectively, p = 0.05), obesity (88.9%, n = 304 and 85.0%, n = 578 respectively, p = 0.009) and radon radiation (56.5%, n = 193 and 64.8%, n = 441, p = 0.021) are cancer risk factors (Tab. SIII). Only 12.2% of men and 15.6% of women agree that lack of breastfeeding increases cancer risk with over half of the men (57.9%, n = 198) marking the "I have no opinion" (p < 0.001). Over half of the women agree that HPV and HBV infections are a cancer risk (54.7%, n = 372 and 53.5%, n = 364) with less than half of men agreeing (42.1%, n = 144 for HPV and 38.3%, n = 131 for HBV) (p = 0.005 and p = 0.003). The minority of both men and women considered HRT as a cancer risk factor (16.6% men and 19.8% women, p < 0.001). Regarding common misconceptions, 27.7% of men and 37.7% of women consider GMO consumption a cancer risk factor (p < 0.001), more women than men think of 5G technology (7.6% and 3.5%, p < 0.001) or energy drink consumption (60.4% and 49.2%, p = 0.019) as cancer risk factors (Tab. SIV).

### C. Medical students recognize cancer risk factors better than non-medical students

Medical students recognize cancer risk factors more accurately than NMS. Both groups largely agreed that smoking (MS 99.4%, n = 156; NMS 98.1%, n = 867, p < 0.001), obesity (MS 96.8%, n = 152; NMS 83.9%, n = 742, p < 0.001), unhealthy eating habits (MS 97.4%, n = 153; NMS 85.8%, n = 758, p < 0.001), alcohol consumption (MS 94.9%, n = 149; NMS 77.9%, n = 689, p < 0.001) and sedentary lifestyle (MS 87.3%, n = 137; NMS 63.8%, n = 564, p < 0.001) are cancer risk factors (Tab. SV). However, disparities emerged with other cancer risk factors. About 50% of NMS had no opinion on whether HPV infection (50.5%, n = 446) or HBV infection (50.1%, n = 443) are cancer risk factors. At the same time, 45.3% of NMS and 79.7% of MS recognized HPV infection as a risk factor. Similarly, 44.5% of NMS and 70.7% of MS considered HBV infection a risk factor. The difference in knowledge between both groups was proven to be statistically significant for both HBV and HPV (p < 0.001 for both). Hormone replacement therapy and not breastfeeding were less commonly recognized as risk factors, even among

MS. Only 9.8% of NMS and 39.5% of MS agreed that not breastfeeding is a risk factor ($p < 0.001$). Similarly, 13.9% (n = 123) of NMS and 47.2% (n = 74) of MS considered hormone replacement therapy a risk factor ($p < 0.001$).

### *Lifestyle habits*

#### A. Lifestyle habits among responders

Smokers made up 18.6% (n = 194) of the respondents. Regarding diet and weight control, 50.4% (n = 525) monitored their body mass index (BMI), and 59.1% (n = 615) reported following healthy eating guidelines. Additionally, 69.3% (n = 721) either did not consume red meat or did so less than once per week, and 94.2% (n = 981) consumed fruits and vegetables daily or at least more than once per week. Over one-third (37.5%, n = 390) were physically active two to three times per week, while 57.5% (n = 599) exercised sporadically.

More than half of the respondents (64.2%, n = 668) abstain from alcohol consumption entirely. Additionally, over half of the respondents (55.2%, n = 575) use ultraviolet radiation (UV) filters and limit their time outdoors between 10 am and 4 pm during summer months. The majority of respondents (66.5%, n = 692) regularly check their skin lesions, but 64.6% (n = 672) do not undergo regular checks at the doctor's office, and 30% (n = 312) do so irregularly. Less than half (49.2%, n = 512) consider potential exposure to carcinogenic hazards when choosing their future careers. Over half of the respondents (51.5%, n = 536) claim they have not been vaccinated against HBV, and 61.6% (n = 641) against HPV, but 84.9% (n = 884) express willingness to vaccinate their children against both.

Among the responding women, 68.6% (n = 432) intend to breastfeed in the future; however, 33.3% (n = 230) do not perform breast self-examinations, and 35.3% (n = 244) do so less than once per month. Additionally, 46.4% (n = 163) of male respondents do not perform testicular self-examinations.

#### B. Gender differences in lifestyle habits

Over half of the women (54.1%, n = 368) control their BMI and attempt to maintain it within the healthy range, meanwhile, less than half of men do so (43.9%, n = 150; $p = 0.004$). Additionally, almost two-thirds of women and over half of male responders follow healthy eating guidelines (62.8%, n = 427, and 52.0%, n = 178 respectively; $p = 0.003$). Over 75 percent of women do not consume red meat or do so less than once per week (77.5%, n = 527) while more than half of men do so (51.8%, n = 177; $p < 0.001$). A similar difference was in reported daily consumption of fruit and vegetables (75.7%, n = 515 of women and 58.2%, n = 199 of men; $p < 0.001$). Over half of both men and women abstain from alcohol, but for women, it is a more common choice (68.4%, n = 465 for women and 55.8%, n = 191 for men; $p < 0.001$). Just under 66% (65.6%, n = 446) of women use UV light protection filters, with less than 35% (34,8%, n = 119) of men doing so ($p < 0.001$). Additionally, when it comes to checking their skin lesions, 72.1% (n = 490) of women and 55.6% (n = 190) of men do that ($p < 0.001$). However, none of the male responders (0,0%, n = 0) use solariums, while 3.2% (n = 22) of women do ($p = 0.014$) (Tab. IV).

**Table IV.** Habits or lifestyle choices of all responders

| Lifestyle habits | Answer | n (%) | Gender | | | p | Field of study | | p |
|---|---|---|---|---|---|---|---|---|---|
| | | | Female | Male | Indeterminate sex | | Non-medical | Medical | |
| Smoking, n (%) | No | 847 (81.4%) | 555 (81.6%) | 279 (81.6%) | 13 (68.4%) | 0.343 | 716 (81.0%) | 131 (83.4%) | 0.469 |
| | Yes | 194 (18.6%) | 125 (18.4%) | 63 (18.4%) | 6 (31.6%) | | 168 (19.0%) | 26 (16.6%) | |
| Controlling/ /examining BMI (to be 18.5–24.9 kg/ /$m^2$), n (%) | No | 516 (49.6%) | 312 (45.9%) | 192 (56.1%) | 12 (62.3%) | < 0.001 | 463 (52.4%) | 53 (33.8%) | < 0.001 |
| | Yes | 525 (50.4%) | 368 (54.1%) | 150 (43.9%) | 7 (36.8%) | | 421 (47.6%) | 104 (66.2%) | |
| Healthy eating habits, n (%) | No | 426 (40.9%) | 253 (37.2%) | 164 (48.0%) | 9 (47.4%) | 0.003 | 383 (43.3%) | 43 (27.4%) | < 0.001 |
| | Yes | 615 (59.1%) | 427 (62.8%) | 178 (52.0%) | 10 (52.6%) | | 501 (56.7%) | 114 (72.6%) | |
| Red meat consumption, n (%) | None | 256 (24.6%) | 214 (31.5%) | 32 (9.4%) | 10 (52.6%) | < 0.001 | 213 (24.1%) | 43 (27.4%) | 0.027 |
| | Less than 1/week | 465 (44.7%) | 313 (46.0%) | 145 (42.4%) | 7 (36.8%) | | 384 (43.4%) | 81 (51.6%) | |
| | More than 1/week | 247 (23.7%) | 127 (18.7%) | 119 (34.8%) | 1 (5.3%) | | 219 (24.8%) | 28 (17.8%) | |
| | Daily | 73 (7.0%) | 26 (3.8%) | 46 (13.5%) | 1 (5.3%) | | 68 (7.7%) | 5 (3.2%) | |

→

**Table IV cont.** Habits or lifestyle choices of all responders

| Lifestyle habits | Answer | n (%) | Gender | | | p | Field of study | | p |
|---|---|---|---|---|---|---|---|---|---|
| | | | Female | Male | Indeterminate sex | | Non-medical | Medical | |
| Fruit and vegetable consumption, n (%) | None | 4 (0.4%) | 0 (0.0%) | 4 (1.2%) | 0 (0.0%) | < 0.001 | 4 (0.5%) | 0 (0.0%) | 0.005 |
| | Less than 1/week | 56 (5.4%) | 24 (3.5%) | 30 (8.8%) | 2 (10.5%) | | 55 (6.2%) | 1 (0.6%) | |
| | More than 1/week | 255 (24.5%) | 141 (20.7%) | 109 (31.9%) | 5 (26.3%) | | 224 (25.3%) | 31 (19.7%) | |
| | Daily | 726 (69.7%) | 515 (75.7%) | 199 (58.2%) | 12 (63.2%) | | 601 (68.0%) | 125 (79.6%) | |
| Physical activity, n (%) | None | 52 (5.0%) | 33 (4.9%) | 18 (5.3%) | 1 (5.3%) | 0.182 | 46 (5.2%) | 6 (3.8%) | < 0.001 |
| | Occasionally | 599 (57.5%) | 410 (60.3%) | 179 (52.3%) | 10 (52.6%) | | 531 (60.1%) | 68 (43.3%) | |
| | More than 2 or 3/week | 390 (37.5%) | 237 (34.9%) | 145 (42.4%) | 8 (42.1%) | | 307 (34.7%) | 83 (52.9%) | |
| Alcohol consumption, n (%) | None | 668 (64.2%) | 465 (68.4%) | 191 (55.8%) | 12 (63.2%) | 0.002 | 557 (63.0%) | 111 (70.7%) | 0.411 |
| | 1–2 units per week | 19 (1.8%) | 8 (1.2%) | 11 (3.2%) | 0 (0.0%) | | 17 (1.9%) | 2 (1.3%) | |
| | Less than 5 units per week | 274 (26.3%) | 173 (25.4%) | 96 (28.1%) | 5 (26.3%) | | 240 (27.1%) | 34 (21.7%) | |
| | More than 5 units per week | 58 (5.6%) | 29 (4.3%) | 28 (8.2%) | 1 (5.3%) | | 49 (5.5%) | 9 (5.7%) | |
| | More than 10 units per week | 19 (1.8%) | 3 (0.4%) | 16 (4.7%) | 0 (0.0%) | | 18 (2.0%) | 1 (0.6%) | |
| | More than 3 units daily | 3 (0.3%) | 2 (0.03%) | 0 (0.0%) | 1 (5.3%) | | 3 (0.3%) | 0 (0.0%) | |
| Using UV light protection filters, n (%) | No | 466 (44.8%) | 234 (34.4%) | 223 (65.2%) | 9 (47.4%) | < 0.001 | 405 (45.8%) | 61 (38.9%) | 0.106 |
| | Yes | 575 (55.2%) | 446 (65.6%) | 119 (34.8%) | 10 (52.6%) | | 479 (54.2%) | 96 (61.1%) | |
| Limiting sun exposure between 10am and 4pm during summer months, n (%) | No | 511 (49.1%) | 323 (47.5%) | 182 (53.2%) | 6 (31.6%) | 0.069 | 423 (47.9%) | 88 (56.1%) | 0.058 |
| | Yes | 530 (50.9%) | 357 (52.5%) | 160 (46.8%) | 13 (68.4%) | | 461 (52.1%) | 69 (43.9%) | |
| Checking skin lesions, n (%) | No | 349 (33.5%) | 190 (27.9%) | 152 (44.4%) | 7 (36.8%) | < 0.001 | 321 (36.3%) | 28 (17.8%) | < 0.001 |
| | Yes | 692 (66.5%) | 490 (72.1%) | 190 (55.6%) | 12 (63.2%) | | 563 (63.7%) | 129 (82.2%) | |
| Taking harmful substances in future workplace into consideration, n (%) | No | 529 (50.8%) | 358 (52.6%) | 161 (47.1%) | 10 (52.6%) | 0.240 | 469 (53.1%) | 60 (38.2%) | < 0.001 |
| | Yes | 512 (49.8% | 322 (47.4%) | 181 (52.9%) | 9 (47.4%) | | 415 (46.9%) | 97 (61.8%) | |
| HBV vaccinee, n (%) | No | 536 (51.5%) | 334 (49.1%) | 191 (55.8%) | 11 (57.9%) | 0.108 | 505 (57.1%) | 31 (19.7%) | < 0.001 |
| | Yes | 505 (48.5%) | 346 (50.9%) | 151 (44.2%) | 8 (42.1%) | | 379 (42.9%) | 126 (80.3%) | |
| HPV vaccinee, n (%) | No | 641 (61.6%) | 405 (59.6%) | 224 (65.6%) | 12 (63.2%) | 0.182 | 555 (62.8%) | 86 (54.8%) | 0.057 |
| | Yes | 400 (38.4%) | 275 (40.4%) | 118 (34.5%) | 7 (36.8%) | | 329 (37.2%) | 71 (45.2%) | |
| Planning to vaccinate a child against HBV and HPV, n (%) | No | 157 (15.1%) | 104 (15.3%) | 50 (14.6%) | 3 (15.8%) | 0.957 | 149 (16.9%) | 8 (5.1%) | < 0.001 |
| | Yes | 884 (84.9%) | 576 (84.7%) | 292 (85.4%) | 16 (84.2%) | | 735 (83.1%) | 149 (94.9%) | |

BMI — body mass index; HBV — hepatitis B virus; HPV — human papilloma virus; UV — ultraviolet radiation

### C. Differences in lifestyle habits between MS and NMS

Smoking was reported by 16.6% (n = 26) of MS and 19.0% (n = 168) of NMS, with no statistically significant difference proven between those two groups. Almost two-thirds of MS (66.2%, n = 104) control their BMI to maintain it within the range of 18.5–24.9 kg/m$^2$. However, less than half of NMS (47.6%, n = 421) do so ($p < 0.001$). Most MS (52.9%, n = 83) are physically active 2 to 3 times a week, with an additional 43.3% (n = 68) reporting sporadic activity. For NMS, the reported numbers were 34.7% (n = 307) and 60.1% (n = 531), respectively ($p < 0.001$). Nearly three-quarters (72.6%, n = 114) of MS and 56.7% (n = 501) of NMS report having healthy eating habits ($p < 0.001$).

The majority of responders consume fresh fruits and vegetables daily — 79.6% (n = 125) for MS and 68.0% (n = 601) for NMS ($p < 0.001$). Additionally, 19.7% (n = 31) of MS and 25.3% (n = 224) of NMS consume them more than once per week. The majority of both MS (82.2%, n = 129) and NMS (63.7%, n = 563) check their skin lesions ($p < 0.001$). However, most respondents do not have regular skin lesion checks at a doctor's office — 51.6% (n = 81) for MS and 66.9% (n = 591) for NMS, or they do so irregularly – 42.0% (n = 81) and 27.8% (n = 246) respectively ($p < 0.001$ for comparison of the groups in both of these regards). Over half of MS (61.8%, n = 97) consider the risk of exposure to hazards such as asbestos, benzene, arsenic, or engine exhaust fumes when choosing future career paths, while less than half of NMS do so (46.9%, n = 415) ($p < 0.001$). A minority of NMS report being vaccinated against HBV — 42.9% (n = 379), with 80.3% (n = 126) MS doing so ($p < 0.001$) (Tab. IV).

Testicular self-examinations are performed once per month by 26.9% (n = 84) of NMS compared to 46.2% (n = 18) MS, less than once a month by 23.4% (n = 73) of NMS and 33.3% (n = 13) of MS and never by 49.7% (n = 155) of NMS and 20.5% (n = 8) of MS ($p = 0.002$). Regarding breast self-examination, 10.3% (n = 59) of NMS and 17.9% (n = 21) of MS perform it correctly, which means once a month, 2–3 days after their period. Some of them perform it regardless of the period timing — 19.7% (n = 113) of NMS and 20.5% (n = 24) of MS or less than once a month — 34.8% (n = 200) of NMS and 37.6% (n = 44) of MS. On the other hand, 35.2% (n = 202) of NMS and 23.9% (n = 28) do not perform breast self-examination at all ($p = 0.031$).

### *Embracing screening tests programs and future decisions*

Regarding declarations of participating in screening programs, 86.0% (n = 592) of all responding women already participate or are planning to participate in the cytology screening program, and for mammography, 93.9% (n = 644) are willing to join the program. For the colonoscopy program, it was 66.3% (n = 690) of all students. Willingness to in the future vaccinate their children against HPV and HBV was declared by 84.9% (n = 884) of all participants.

When declaring participating in a screening colonoscopy, 67.1% (n = 456) of women and 64.6% (n = 221) of men are willing to do so. Over 80% of both men (85.4%, n = 292) and women (84.7%, n = 576) would be willing to vaccinate their children against HBV and HPV ($p = 0.957$).

In the mammography screening program, 93.0% (n = 528) of NMS and 98.3% (n = 116) of MS plan to participate ($p = 0.027$). In the cytology program, 85.1% (n = 485) of NMS and 90.7% (n = 107) of MS are participating or intend to participate ($p = 0.111$). In the colorectal cancer screening program, which involves both women and men, 63.9% of NMS and 79.6% of MS plan to participate in the future ($p < 0.001$) (Supp. Tab. VII). The majority of both MS (94.9%) and NMS (83.1%) declare willingness to vaccinate their children against HPV or HBV ($p < 0.001$) (Tab. IV).

## Discussion

This study aimed to assess the awareness of these recommendations among Polish students, and determine what actions should be taken to increase this awareness, disseminate the code and encourage adherence to its guidelines.

It showed that the general awareness of the ECAC was limited. In the study, only 10.7% of responders were familiar with ECAC. We achieved similar results regarding familiarity with the term ECAC compared to the study by D. Ritchie et al., which collected data from eight European countries (Finland, France, The Republic of Ireland, The United Kingdom, Hungary, Poland, Portugal, Spain) [5, 7].

Awareness of the impact of lifestyle on the risk of developing cancer is higher in the population of MS compared to NMS. For almost all factors, a higher percentage of MS indicated more substantial agreement with the statements compared to NMS. Factors like smoking, obesity, sedentary lifestyle, unhealthy eating habits, drinking alcohol, harmful substances in the workplace, not breastfeeding, hormone replacement therapy, HPV and HBV infection show significant differences in agreement between MS and NMS ($p < 0.001$).

Medical students have greater knowledge about biological threats like HBV and HPV infection, which may influence the results obtained in this group regarding the willingness to be vaccinated against HBV and HPV.

Nearly two-thirds of students had no opinion about hormone replacement therapy (HRT) as a cancer risk factor. The young age and lack of need for HRT translate into low knowledge and awareness on this topic.

More than a quarter of MS are able to identify screening tests and the corresponding cancers. Among NMS students awareness is dramatically low. This may be primarily due to the relatively young age of the respondents and insufficient education. That is also related to the availability of screening programs for people older than the student population. In our

study, due to the insufficient age for participation in screening tests, we could only examine the aspiration of embracing them, and the vast majority of both MS and NMS expressed a desire to participate in the future. This means that although awareness of the available tests is low, young people wish to undergo screening to prevent and detect cancer early. After the 4th year of medical studies, awareness is significantly higher. This is likely due to the start of clinical courses in oncology and other subjects that address public health and cancer prevention topics.

A serious and urgent problem appears to be the lack of awareness about self-examinations. According to our study, 33.3% of female responders do not perform breast self-examinations which is consistent with the literature [8]. Among male respondents, almost half do not perform testicular self--examinations. Gutema et al. [9] asked students whether they had performed a testicular self-examination within the past year, receiving a negative response from nearly 90%. According to the authors, this is due to a lack of proper preparation, information and communication with students, and most importantly, a lack of know-how tailored to the students' behaviour model [9].

The respondents, students are a group of young people who is the most subject to all of confusing, misleading and even contradictory information about disease prevention and healthy life rules being presented nowadays in multiple social media and other media streams. In the face of lack of consistency, a professional source of reliable information, based on scientific evidence is priceless [10].

Medical students constitute a specific target group, as research says that the lack of encouragement by family members and physicians is one of the factors that strongly affects patients' will to participate in cancer screening programs [10]. Future physicians, nurses and other health professionals should know the terms of ECAC, and acquire the relevant skills to interest patients in healthy lifestyle.

The benefit of our study lies in providing evidence regarding the awareness of the participants about a healthy lifestyle, as well as their knowledge of risk factors for cancer development. This information can contribute to the promotion and advocacy of measures that enable a reduction in the incidence of cancer, as well as early detection of tumours, among both participants and their families.

### *Limitations*

Due to the voluntary nature of participation, we gathered a very heterogeneous group consisting of students from various fields and cities.

## Conclusions

Knowledge about the European Code Against Cancer (ECAC) within the Polish student community is insufficient. Despite a weak understanding of risk factors, a significant portion of students either utilize or intend to undergo preventive screening tests. This indicates that awareness and knowledge about cancer comes from sources other than ECAC, justifying the need to increase resources for promoting ECAC, and modifying its principles based on ongoing research.

## Article information and declarations

### *Data availability statement*

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

### *Ethics statement*

The research was conducted in accordance with the principles embodied in the Declaration of Helsinki and the Bioethics Committee has confirmed that a formal opinion is unnecessary due to the voluntary nature of the questionnaire.

### *Authors contributions*

M.L., B.A.P.: conceptualization, data curation, investigation, project administration, resources, visualization, writing — original draft preparation, writing — review & editing.
A.Cz.: conceptualization, data curation, formal analysis, methodology, validation, writing — original draft preparation.
D.S.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing — original draft preparation, writing — review & editing.
P.S.: formal analysis, methodology, validation, writing — review & editing; S.N.: supervision, writing — review & editing.

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### *Conflict of interest*

The authors declare no conflict of interest.

### *Supplementary material*

The supplementary materials, including tables and figures, are available online.

**Błażej A. Pilch**
*Immunooncology Students Club, Collegium Medicum*
*University of Warmia and Mazury in Olsztyn, Poland*
*Michała Oczapowskiego 2*
*10–719 Olsztyn, Poland*
*e-mail: blazej.pilch97@gmail.com*

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## References


1. Didkowska J, Barańska K, Miklewska M, et al. Cancer incidence and mortality in Poland in 2023. Nowotwory. Journal of Oncology. 2024; 74(2): 75–93, doi: 10.5603/njo.99065.
2. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024; 74(3): 229–263, doi: 10.3322/caac.21834, indexed in Pubmed: 38572751.
3. Schüz J, Espina C, Villain P, et al. Working Groups of Scientific Experts. European Code against Cancer 4th Edition: 12 ways to reduce your cancer risk. Cancer Epidemiol. 2015; 39 Suppl 1: S1–10, doi: 10.1016/j.canep.2015.05.009, indexed in Pubmed: 26164654.
4. Dyzmann-Sroka A, Nowak A. European Code Against Cancer in practical aspects. Psychoonkologia. 2015; 19(3): 110–115, doi: 10.5114/pson.2015.55120.
5. Espina C, Yared W, Ritchie D, et al. Sustainability and monitoring of the European Code Against Cancer: Recommendations. Cancer Epidemiol. 2021; 72: 101933, doi: 10.1016/j.canep.2021.101933, indexed in Pubmed: 33838462.
6. Karasiewicz M, Chawłowska E, Lipiak A, et al. How to Improve Cancer Prevention Knowledge? A Way to Identify Gaps and Tackle the Limited Availability of Health Education Services in Primary Health Care Using the European Code Against Cancer. Front Public Health. 2022; 10: 878703, doi: 10.3389/fpubh.2022.878703, indexed in Pubmed: 35586014.
7. Ritchie D, Mallafré-Larrosa M, Ferro G, et al. Evaluation of the impact of the European Code against Cancer on awareness and attitudes towards cancer prevention at the population and health promoters' levels. Cancer Epidemiol. 2021; 71(Pt A): 101898, doi: 10.1016/j.canep.2021.101898, indexed in Pubmed: 33611135.
8. Abo Al-Shiekh SS, Ibrahim MA, Alajerami YS. Breast Cancer Knowledge and Practice of Breast Self-Examination among Female University Students, Gaza. ScientificWorldJournal. 2021; 2021: 6640324, doi: 10.1155/2021/6640324, indexed in Pubmed: 34007246.
9. Gutema H, Debela Y, Walle B, et al. Testicular self examination among Bahir Dar University students: application of integrated behavioral model. BMC Cancer. 2018; 18(1): 21, doi: 10.1186/s12885-017-3935-8, indexed in Pubmed: 29301513.
10. Espina C, Herrero R, Sankaranarayanan R, et al. Toward the World Code Against Cancer. J Glob Oncol. 2018; 4: 1–8, doi: 10.1200/JGO.17.00145, indexed in Pubmed: 30241265.

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Rare tumors

# Coordinated medical care program for neurofibromatosis type 1 children and youth in Poland influences the future of their affected parents as well — a single academic reference center experience and national program description

Marek W. Karwacki

*Department of Pediatric Hematology and Oncology, Transplantation Medicine and Pediatrics, Medical University of Warsaw, Poland*
*Coordinated Medical Care Center for NF/RAS Patients, Pediatric Teaching Hospital, Medical University of Warsaw, University Clinical Center, Poland*
*Center of Excellence for Rare and Undiagnosed Diseases, Medical University of Warsaw, Poland*

**Introduction.** Neurofibromatosis type 1 (NF-1) is an inherited neoplastic syndrome. In Poland, most affected adults are unaware of the disease-related risk of cancer.

**Material and methods.** During 36 months of described pilotage, 764 children and youth, and 48.2% of familial cases, were registered.

**Results.** Among parents, 30.4% were unaware of NF-1 diagnosis and 10.8% had any knowledge of NF-1-related risk of malignancy. As a consequence of advised prophylactic examinations, in 6 (1.6%) parents, clinically silent tumors were detected accidentally in preclinical stage: one 1B-breast cancer, one IA malignant melanoma, 2 pheochromocytomas and 2 low-grade CNS gliomas.

**Conclusions.** The early successful prevention of malignancy in professionally counselled NF-1 patients, proven currently, necessitates the urgent extension of prophylaxis and coordinated medical care program to the whole NF-1 population, not only in Poland, but worldwide. Precise knowledge concerning the disease-related medical risks should become a subject of the training of medical professionals regardless of their specialty.

**Keywords:** neurofibromatosis type 1, risk of malignancy, coordinated medical care program, adult

## Introduction

Neurofibromatosis type 1 (NF-1; OMIM #162200) is a hereditary malignancy syndrome [1]. It is one of the most common monogenic diseases worldwide, with an estimated prevalence of 1:2.500 live births [2]. The primary phenotypic presentation of NF-1 includes the "café au lait" skin spots (CALs) observed in varying, but usually high numbers. Multiple benign peripheral nerve sheath tumors (BPNST) of two different kinds, neurofibromas (NFM) and plexiform neurofibromas (PN), are the second hallmark of the disease (Tab. I). The multisystem anomalous phenotype of NF-1 results from pathogenic *Nf1* gene variants, and is inherited as an autosomal dominant trait [2, 3]. The mutated gene is not only responsible for oncogenesis, but in parallel for connective tissue anomalies (bone dysplasia and joint hypermobility, mild cardiac anomalies and multiple aneurysms), behavioral and learning disability

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**Table I.** The 2021 revised diagnostic criteria for neurofibromatosis type 1 (NF-1) [adapted from: Legius, E., Messiaen, L., Wolkenstein, P. et al. Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. Genet Med 23, 1506–1513 (2021). https://doi.org/10.1038/s41436-021-01170-5]

| **A: The diagnostic criteria for NF-1 are met in an individual who does not have a parent diagnosed with NF-1 if two or more of the following are present:** |
|---|
| — **A1:** Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals[1] |
| — **A2:** Freckling in the axillary or inguinal region |
| — **A3:** Two or more neurofibromas of any type or one plexiform neurofibroma |
| — **A4:** Optic pathway glioma |
| — **A5:** Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities defined as bright, patchy nodules imaged by optical coherence tomography or/and near-infrared reflectance imaging |
| — **A6:** A distinctive osseous lesion such as sphenoid dysplasia[2], anterolateral bowing of the tibia, or pseudarthrosis of a long bone |
| — **A7:** A heterozygous pathogenic NF-1 variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells |
| **B: A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of NF-1 if one or more of the criteria in A are present** |

[1]If only café-au-lait macules and freckling are present, the diagnosis is most likely NF-1 but exceptionally the person might have another diagnosis such as Legius syndrome. At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral; [2]Sphenoid wing dysplasia is not a separate criterion in case of an ipsilateral orbital plexiform neurofibroma

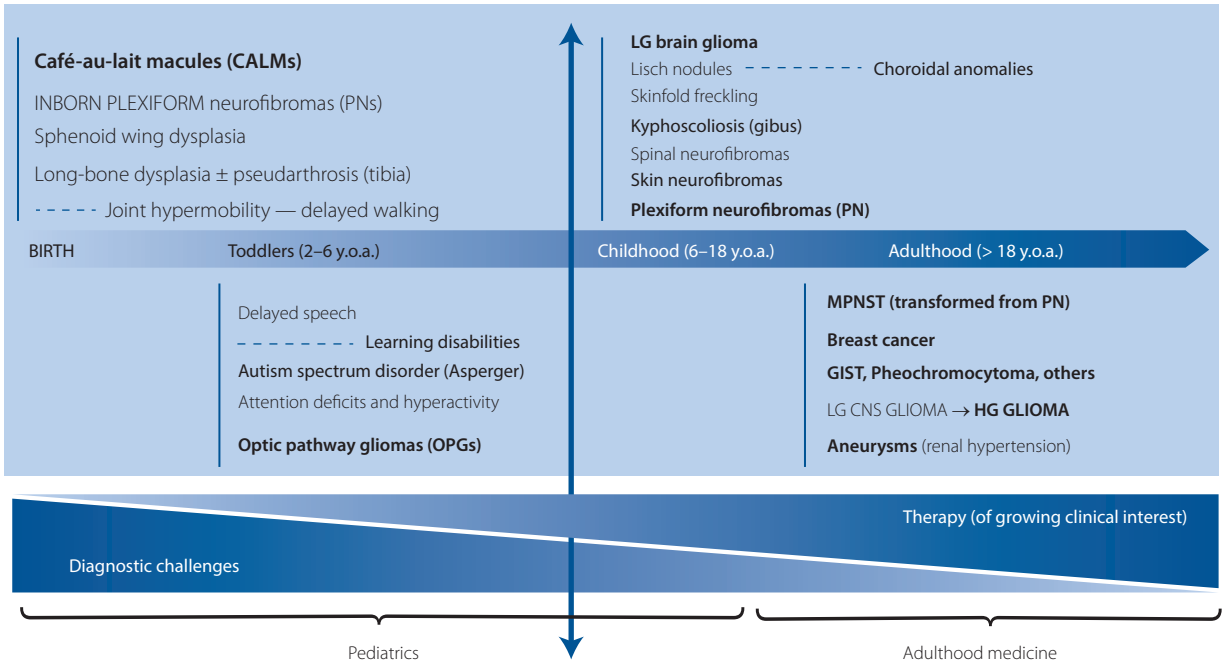


**Figure 1.** Age dependent presentation of neurofibromatosis type 1 (NF-1) symptoms as a diagnostic obstacle: transition from pediatric to adulthood medicine (= from diagnostic to therapeutic problems); (E)RMS — (embryonal) rhabdomyosarcoma; ADHD — attention deficit hyperactivity (-like) disorder; ALL — acute lymphoblastic leukemia; ANLL — acute non-lymphoblastic leukemia; CALs — café-au-lait spots (macules); CNS — central nervous system; FASI — focal areas of signal intensity; GIST — gastrointestinal stromal tumor; JMML — juvenile myelomonocytic leukemia; LG glioma — low grade glioma; MM — malignant melanoma; MPNST — malignant peripheral nerve sheath tumors; MRI — magnetic resonance imaging; NETs — neuroendocrine tumors; NFM — neurofibroma; PhCC — pheochromocytoma; PNF — plexiform neurofibroma; STS — soft tissue sarcoma

and others (Fig. 1) [2–4]. The diagnostic criteria (Tab. I) allowing the accurate clinical diagnosis of NF-1 have been revised recently [4]. The outstanding characteristic of NF-1 comprises: 1) 100% penetrance of gene mutation; 2) rate of spontaneous mutations reaching 50%, and 3) age-dependent (Fig. 1) and extremely variable phenotypic expression without anticipation [4].

The *Nf1* gene belongs to the important regulators in the RAS-MAP-Kinase family of tumor suppressor genes [1]. In otherwise healthy individuals without NF-1, somatic biallelic mutational deactivation of the *Nf1* in malignant cells added up to carcinogenesis and became a critical driver, either in multiple cancers, especially in breast, colorectal, urothelial, lung, ovarian and skin (including melanoma), or in brain and neuroendocrine neoplasia, sarcomas and leukemias [5, 6]. It is assumed that the *Nf1* biallelic mutation may induce therapeutic resistance to chemotherapy, and other targeted therapies in different malignancies [6]. Germinal *Nf1* mutation responsible for NF-1 favors a mutational drive leading to oncogenesis

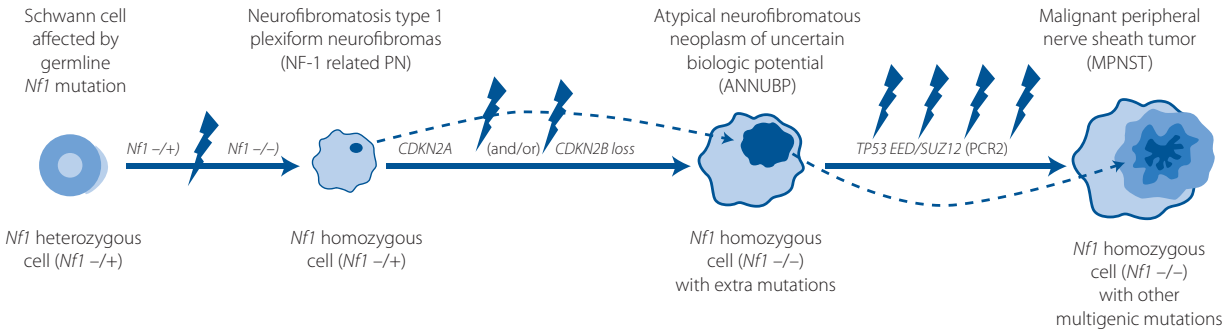


**Figure 2.** Mutational drive stages resulting in malignant transformation of *Nf1*-mutated Schwann cell to plexiform neurofibroma and finally — to malignant peripheral sheath tumor: from germinal Nf1 mutation to benign nerve sheath tumor and finally — multigenic somatic sarcoma cell

**Table II.** Different types of neoplasia more prevalent in neurofibromatosis type 1 (NF-1) patients than in the general population (based on [7])

| Type of tumors and malignancies more common in patients with NF-1 regardless of the age | Type of both benign and malignant tumors occurring at a younger age in NF-1 patients than in the general population | Type of malignancy appearing to be more fatal in NF-1 patients than in the general population |
|---|---|---|
| — Glioma (low- and high-grade)<br>— Sarcoma (many types)<br>— Breast cancer<br>— Endocrine cancers (including pheochromocytoma and neuroendocrine tumors)<br>— Melanoma<br>— Acute lymphoblastic leukemia<br>— Ovarian cancer<br>— Prostate cancer<br>— Meningioma | — Low-grade glioma<br>— High-grade glioma<br>— Malignant peripheral nerve sheath tumors<br>— Breast cancer | — Undifferentiated pleomorphic sarcoma<br>— High-grade glioma<br>— Malignant peripheral nerve sheath tumors<br>— Ovarian cancer<br>— Melanoma |

[1, 7, 8]. For years the increased prevalence of carcinogenesis in general, and concerning specific cancer types in NF-1 patients has become obvious worldwide [1, 7–18]. Apart from cutaneous NFMs, clinically and histologically distinct PN, presented in more than half of NF-1 patients, may arise not only in skin depth, but elsewhere [1–4]. Yet, a risk of the malignant transformation of PN into a malignant peripheral nerve sheath tumor (MPNST) is assumed at 8–15% (Fig. 2). MPNSTs become the most common and the most life-threatening malignancy in NF-1 [4, 7]. The other NF-1-associated neurogenic tumors arise in the central nervous system:

— relatively frequent optic pathway gliomas occurred in approximately 40% of patients, predominantly in toddlers (a prevalence of 11.1% [7]);
— rarely occurring intracranial low-grade gliomas (LGG) with a prevalence of 16.6% are found in approximately 20% of NF-1 patients and, likewise, detected in childhood [7];
— high-grade CNS tumors, mostly gliomas, diagnosed rarely in adulthood (the prevalence of LGG is 1.7%, whereas of glioblastoma multiforme — 1.1% [7]).

Except the neurogenic tumors (Tab. II), leukemias, melanoma and soft tissue sarcomas, gastrointestinal stromal tumors (GIST), and pheochromocytoma (PhCC) were acknowledged as NF-1-associated malignancies [1, 4, 7, 12]. Biallelic somatic mutation of the *Nf1* gene occurs in 10 to 15% of juvenile myelomonocytic leukemia cells [9], but it rarely arises in NF-1 children [10, 11]. The significant risk of breast cancer (BC) in NF-1 (including men) has been recently revealed [13–17]. The other lately described malignancies in NF-1 comprised embryonal rhabdomyosarcoma (ERMS), neuroendocrine tumors other than PhCC, squamous cell lung carcinoma, papillary thyroid carcinoma, and meningioma [1, 4, 7, 12, 18]. It seems that a the prevalence of nonneurofibromatic neoplasia was 41.4%, and usually presents as a single entity (a prevalence of 34.2% in contrast with multiple neoplasia of 7.2%) [7].

Excepting young children in whom the exact diagnosis is challenging, the correct clinical diagnosis of NF-1 based on phenotypic manifestations may be established in > 90% of children at the age of 6–10 years, and is obvious in adulthood [4, 19, 20]. Regrettably, despite the certainty of NF-1 diagnosis in adults, the proper diagnosis is still neglected among the physicians not only in Poland [17], but also elsewhere [4, 19]. As a consequence, the majority of adult NF-1 patients do not receive preventive measures to minimize NF-1-related threats. In particular, awareness of Polish medical professionals concerning the increased risk of cancer in such a population of patients is scant [17]. We have proven, that among Polish NF-1 women, awareness of the NF-1-related BC risk was

**Table III.** Current list of Coordinated Medical Care Centers for NF/RAS Patients (NF/RAS CMCCtrl) in Poland* settled according to original Decree of the Polish Minister of Health issued in June, 2020 [21] (followed by the two further amendments from 2024)

| |
|---|
| **First 4 "pediatric" NF/RAS CMCCtrl settled by the original Decree of the Polish Minister of Health issued in June, 2020** |
| — Poradnia Neurofibromatoz, Instytut Matki i Dziecka w Warszawie<br>— CKOM NF/RAS, Szpital Uniwersytecki Nr 1 im. dr Antoniego Jurasza w Bydgoszczy<br>— CKOM NF/RAS, Uniwersyteckie Centrum Kliniczne GUMed w Gdańsku<br>— CKOM NF/RAS, Uniwersyteckie Centrum Kliniczne WUM w Warszawie |
| **Additional 2 "pediatric" NF/RAS CMCCtrl settled by the third amendment of the original Decree of the Polish Minister of Health (issued in January, 2024)** |
| — CKOM NF/RAS, Uniwersytecki Szpital Dziecięcy w Krakowie<br>— CKOM NF/RAS, Wojewódzki Specjalistyczny Szpital Dziecięcy im. prof. dr Stanisława Popowskiego w Olsztynie |
| **Additional 2 NF/RAS CMCCtrl for adults settled by the fourth amendment of the original Decree of the Polish Minister of Health (issued in December, 2024)** |
| — CKOM NF/RAS, Samodzielny Publiczny Zakład Opieki Zdrowotnej Centralny Szpital Kliniczny Uniwersytetu Medycznego w Łodzi<br>— CKOM NF/RAS, Państwowy Instytut Medyczny Ministerstwa Spraw Wewnętrznych i Administracji w Warszawie |

*For the purpose of the current manuscript and to facilitate the location of centers for not only Polish physicians, the names of the centers are provided in original wording; NF/RAS CMCCtrl (in Polish: CKOM NF/RAS) — neurofibromatoses and related RASopathies Coordinated Medical Care Centers

declared by only 30%, and only 21% received this important information from medical professionals [17].

Age dependent and unpredictable course of the disease in a defined patient and the expecting multiorgan morbidity together with weak awareness of disease complications among adult patients (youth and parents) warrant the specific systemic organization of multispecialty care for patients suffering from NF-1 which is focused on the age-related characteristics of their health problems. In response to medical and NF-1 society needs, the piloting of a comprehensive coordinated medical care program for patients with neurofibromatoses and related RASopathies (NF/RAS-CCMC) was introduced to the National Health System in Poland by the Decree of the Polish Minister of Health (MOH) in June 2020 [20] (with further amendments).

As mentioned in the above amendments, the purposes of the 5.5-year pilot program, which will continue until the end of 2025, were:

1) the official settlement of 6 Centers of Coordinated Medical Care for NF/RAS Patients (NF/RAS CMCCtrl) in Poland (Tab. III);
2) the evaluation of program effectiveness with regard to general health system cost reduction, and the improvement of disease recognition and the prevention of its complications;
3) enhancement of coordinated medical care for the whole population of NF-1 patients, if the pilot program meets the expectations of healthcare system authorities.

The mainstay of the program is professional supervision of patients' health complaints based on regular once-yearly visits at the Center and all year-round health surveillance based on telemedical contact (Fig. 2, Tab. IV). It comprises the patient's examinations, necessary imaging and laboratory tests and, if required, specialist consultations to address current or longitudinal patient complaints. In case of emerging symptoms, the NF/RAS CMCCtrl is obliged to organize an urgent visit or hospitalization, and implement the necessary examinations as well as treatment, if required. Thus, NF-1 patients included into the program are protected against unnecessary and frequently repeated consultations and imaging, but receive adequate and comprehensive care instead (Tab. IV). Apart from the main goals of the program (i.e., the improvement of prophylactic measure efficacy and general health status of the NF-1 population in Poland), one of the secondary aims of patient-oriented, coordinated care is to avoid the so-called "diagnostic odyssey" of the patients, when they were continuously searching for the proper diagnosis and consulted by many specialists without conclusion in the past. The additional advantage of the program is to free them from costly, unnecessary, and usually repeated examinations and medical consultations, along with occasionally harmful medical procedures [21]. The prevention of unnecessary "over-diagnosing" improves the sense of well-being and psychological status of the patients and their families and improve their quality of life due to particular savings in every day expenses, lost days at work and at schools, etc. (Tab. IV). The program was settled in accordance with the Polish standards of care for NF-1 patients [21] (Fig. 3 and 4).

Regrettably, beside unique initiatives undertaken by adult clinical oncologists [22], neither specialized care for adult patients with NF-1 has been established in Poland so far, nor have adult patients been properly informed about the possible risk of health- or life-threatening symptoms related to NF-1 [17]. The standard of care for adult patients suffering from NF-1 [19] is still an enigma in Poland. Thus, the obligatory responsibility of each NF/RAS CMCCtrl includes mandatory clinical and genetic counselling provided not only to a child diagnosed with NF-1 in the Center for the first time but to every symptomatic parent as well, who used to be often unaware of his/her disease. Such counselling, concerning precise information about

**Table IV.** The Polish system of Coordinated Medical Care for Patients suffering from neurofibromatosis type 1 (NF-1): benefits and components of the system

| | |
|---|---|
| **THE SYSTEM:**<br>PREVENTIVE measure instead of aggressive medical action | — The mainstay of the program is multispecialty SUPERVISION of the patients' health complaints COORDINATED by program coordinator („NF-ologist") based on the regular once-yearly visits at the Center and all year-round health surveillance established due to the telemedical contact<br>• The patronage visit comprises the necessary imaging as well as physical examinations and, if required, specialist consultations to address current or longitudinal patient's complaints<br>— In case of EMERGING SYMPTOMS discovered either by the patient or caregiver or the patient's physician(s), the Center is obliged to organize an urgent visit or hospitalization and implement necessary examinations and consultations ± treatment<br>— Thus, NF-1 patients included into the program are protected against unnecessary and frequently repeated consultations and imaging, but receive adequate and comprehensive care instead<br>— The secondary cardinal aims of the patient-oriented, coordinated care is to avoid the so called "diagnostic odyssey" of the patients and to free them from costly and unnecessary, usually repeated examinations and medical consultations, and sometimes harmful medical procedures as well |
| | **BENEFITS:**<br>— Ambulatory based system (low costs)<br>— All-in-one bases (multidisciplinary, comprehensive, multipotential patient's oriented care, provided by the medical staff experienced in NF health related problems) |
| **THE CENTER:**<br>as simple as possible | — Servs as a center of CLINICAL EXCELLENCE in NF's (to patients, GPs, other specialists and general community)<br>— A SUBSIDIARY of PEDIATRIC HEMATOLOGY/ONCOLOGY WARD<br>• WHY?: *everyday experience in multidisciplinary care coordinated by pediatric oncologist …*<br>• *… Nf1 derived BENIGN TUMORS (PNs) and malignancies are the most life troublesome symptoms*<br>— THE STAFF: medical coordinators (at least 2/ctr!), nurses, assistant, basic office environment<br>— METHOD of CONTACTS/MEDICAL SURVEILLANCE: telemedical communicator and e-mail connections<br>— RESPONSIBILITY for contacts with parental organization, medical and patients' education systems (e.g. physicians' postgraduate training) and mass media |
| | **BENEFITS:**<br>— reduction of unnecessary costs of needless examinations and consultations<br>— rationalization/minimalization of health care system costs (meaningless) |
| **NF COORDINATOR:**<br>responsibilities | — PATIENT-oriented, PLANNED, LONGITUDINAL care for child diagnosed with NF/RAS<br>• Update concerning in-between period<br>• Assessment of current ailments, developmental or educational progress, psycho-social problems, comprehensive physical growth<br>• Planning of rational imaging (e.g. USG, MR*), biochemistry, hormonal screening & hematology<br>• Planning and realization of in-house or external medical & psychological/educational consultations<br>• Recapitulation of pt's health status and planning the future medical activities and next visit<br>• „Permanent medical supervision" by e-mail correspondence in-between |
| **NF COORDINATOR:**<br>Co-responsibilities | — Expertise consultations for General Practitioners and other specialists engaged in patient's care<br>— Differential diagnosis of a child with multiple CALs (no less than 4)<br>— Close cooperation with parental organization ("NF Polska Alba Julia" Society)<br>— Education and health promotion concerning NF/RAS towards medical society, pre- and postgraduate medical training, as well as in general community |
| **The patient:**<br>Who is a beneficiary of the coordinated care? | — Child diagnosed with NF-1 or related RASopathy *(Legius s., segmental or spinal Neurofibromatoses, allelic forms of NF-1, e.g. Watson or Neurofibromatosis-Noonan syndrome, etc.)*<br>— Child highly suspected of NF/RAS *(e.g. > 6 CALs at age 2. or > 10 at age 3)*<br>— Child with multiple CALs (*at least 4*) and no other distinguished signs & symptoms of other diseases (*for differential diagnosis or confirmation of oligosymptomatic or „atypical" NF/RAS*)<br>— Child diagnosed with *Nf2*-, *LZTR1*- and *SMARCB1*-related and other Schwannomatoses |

CALs — Café au lait spots; MR — magnetic resonance imaging; NF/RAS — Neurofibromatoses and related RASopathies; USG — ultrasound examination

the disease-related risks of genuine malignancy and other NF-1 related complications, is of particular importance for NF-1 women in whom menopause may be accelerated. Obviously, the Hormone Replacement Therapy usually recommended to healthy postmenopausal woman is contraindicated in those burdened with NF-1 because of an increased risk of BC. All youth and adult NF-1 patients, including NF-1 child-affected parents, are also advised on the necessary examinations required to reveal possible NF-1 complications which mostly come to light in adulthood.

## Material and methods

Previously published discovery [17] that a meaningful group of adults suffered from NF-1 lived not only without awareness of the disease threats, but yet without the proper diagnosis in Poland, was the reason why we decided to summaries the additional benefits of the NF/RAS-CCMC in Poland, disclose in the analysis of parental behavior toward the information concerning the NF-1 risk in adulthood.

Between October 1st, 2020 when the pilotage officially started, and December 31st, 2023 (39 months), 764 newly

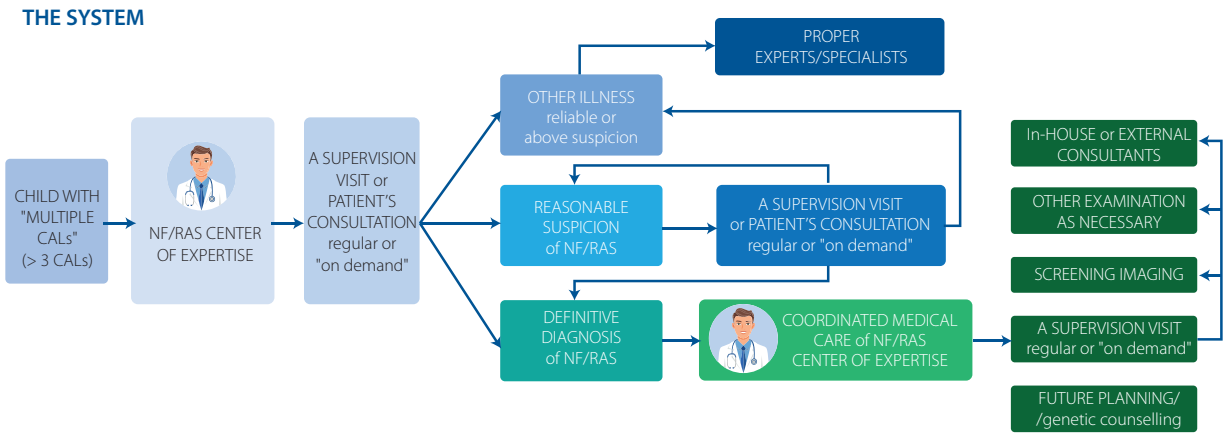


**Figure 3.** The Polish system of Coordinated Medical Care for Patients suffering from neurofibromatosis type 1 [and more widely: from neurofibromatoses and related RASopathies (NF/RAS)]; CALs — café au lait spots; NF-1 — neurofibromatosis type 1

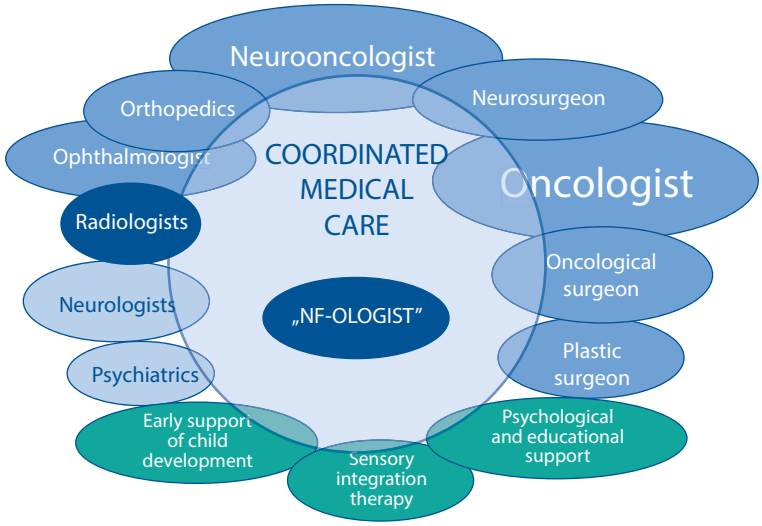


**Figure 4.** The Polish system of Coordinated Medical Care for Patients suffering from neurofibromatosis type 1: patient's oriented, multispecialty, comprehensive and coordinated care (the role of coordinating "NF-specialists")

diagnosed patients aged up to 30 with confirmed NF-1 diagnosis were included into the coordinated medical care program in the NF/RAS CMCCtrl of the Medical University of Warsaw (MUW). Patient characteristics are summarized in Figure 3. The aim of our investigation, which is the subject of the current publication, concerning parents (but not children), who received NF-1-oriented counselling, regarding the necessary examinations and medical surveillance at their child's first visit to the MUW NF/RAS CMCCtrl.

## Results

As regards the newly diagnosed group of 764 patient with NF-1, 396 of them (51.8%) were diagnosed as a sporadic mutation case and 46 (6.1%) were older than 18 years of age. A total of 368 patients had an affected parent (48.2% of familial cases) (Fig. 5). In 112 families (30.4%), a full-blown affected parent was informed about the definite diagnosis for the first time in our Center when the diagnosis was established and confirmed in his/her child. Surprisingly, but not unexpectedly, this was in accordance with our previously published observation [17]. Noteworthy, amid those 368 affected parents, only 40 (10.8%) had any knowledge concerning the risk of malignancy and the methods of possible cancer risk screening and prevention. As described above, all those newly diagnosed patients (i.e., parents) were recommended to undergo all the necessary examinations: either regular screening advised to asymptomatic parents or their extended investigation focused on an unexpected or significant intensification of existing symptoms complicating their course of NF-1, or in case of serious medical issues arising in them *de novo*. All but 26 (26/368; 7.1%) accepted the information provided by the Center's physician, and declared that they would apply advised preventive modalities.

As a consequence, in 6 NF-1 parents (6/368; 1.6%; 2 males and 4 females), some malignancies were diagnosed

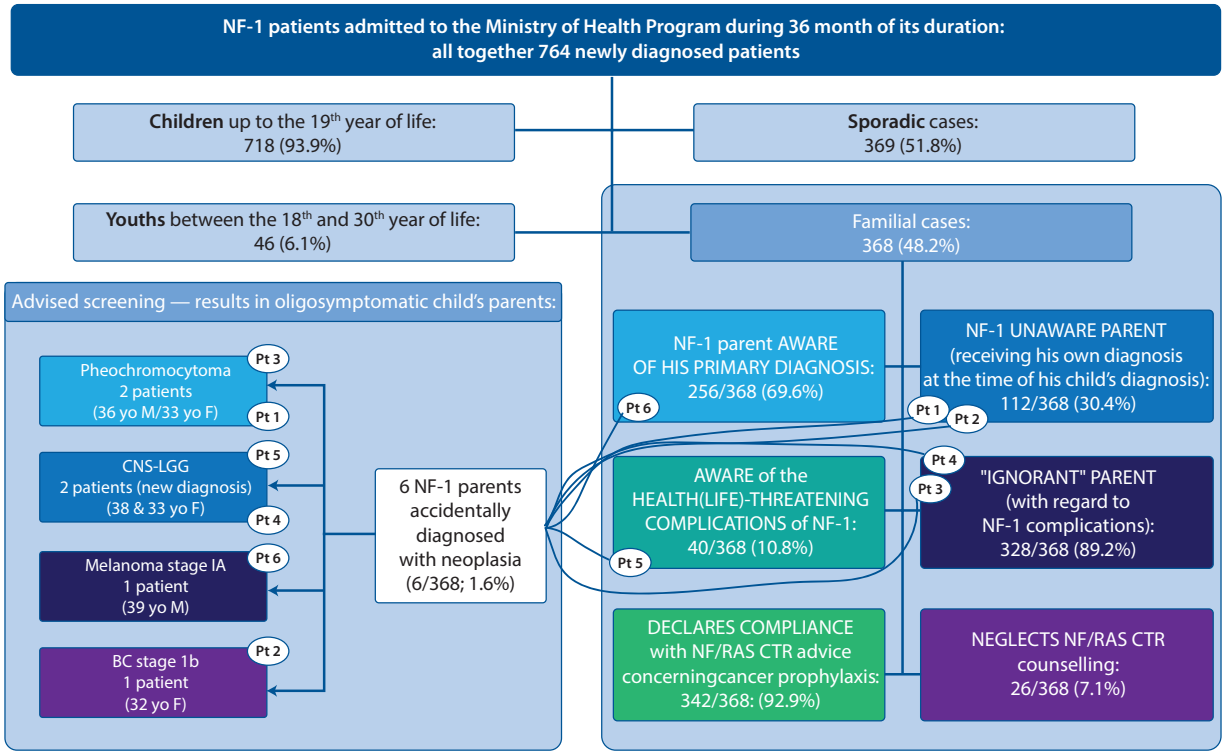


**Figure 5.** Characteristics of the objective group of patients suffering from neurofibromatosis type 1 (NF-1) and their parents; BC — breast cancer; CNS-LGG — central nervous system low grade glioma; NF/RAS Ctr — neurofibromatoses and related RASopathies Coordinated Medical Care Centers

accidentally in preclinical, oligosymptomatic stage due to the counselling advised at the first visit at the Center by the pre-emptive imaging.

Three of them were operated on immediately after they underwent the so-called preventive ultrasound recommended during the first visit in our NF/RAS CMCCtrl, which revealed a *de novo* tumor in the examined region. Abdominal pheochromocytomas were confirmed histologically and removed radically in the presymptomatic period in 2 patients (a male, 36, and a female, 33 years old). The surgical procedure ended the treatment process entirely. One of them had the primary diagnosis of NF-1 established simultaneously with her child's diagnosis (the mother lived for 33 years unaware of the disease). The third woman (32 years old), unaware of her NF-1 diagnosis as well, an accidentally discovered breast lump "suspicious" of malignant in advised ultrasound examination, one among existing 2 other benign neurofibromas observed previously inside the breast, was confirmed in breast magnetic resonance as probably malignant. Finally she was diagnosed with clinical stage 1B BC and received adequate care in a dedicated BC Unit, established by her regional department of adult oncology. In a further 2 cases (a 38- and 33-year-old female suffering from progressive migraine), the newly discovered LGG was confirmed in a post-biopsy histopathological and molecular examination. In the last one (a 39-year-old male) clinical stage IA malignant melanoma was confirmed after the radical excision of an atypical naevus, disclosed in a dermoscopy examination done prophylactically by an oncologist.

## Discussion

The research confirming the lack of unawareness of increased BC risk among Polish women suffering from NF-1 is currently a published fact [17]: 68% of surveyed women had not received such information at all, whereas only 23% had received professional counselling which was mostly provided by NF center physicians. The oldest, previously unwitting woman, received a precise diagnosis of NF-1 from oncologists during the 62nd year of her life. At the same time, she was informed about the BC diagnosis. This publication indirectly confirmed that the awareness of Polish adult NF-1 patients concerning their inherited disease is limited, and that their knowledge with respect to the necessity of active medical supervision regarding primary disease health complication is a must. Despite the definite limitations of the Polish National Health Fund [17], patients' responsibility for their own well-being should drive them to seek medical consultation — not only in case of fatal complications, but in advance, as a prophylactic measure. Regardless of the mild or insignificant intellectual limitations which may sometimes play a role in the case of NF-1, knowledge concerning the possible complications of the course of NF-1 is currently easily available due to widespread internet access and the various possibilities of information exchange. However, awareness of the precise basic diagnosis constitutes

the fundamental basis for such active patient's selfcare. Albeit, this is limited in Poland, as some physicians, including general practitioners, disregard even obvious symptoms of NF-1 in patients [17]. The ignorance of NF-1-related risks may result in prolonging the precise diagnosis and prolonged maltreatment. The literature search done by an author revealed no other than cited [17] publications concerning health problems resulting from the lack of awareness of NF-1-related complications. However, the problem was discussed widely in patients' and medical societies, especially during NF-1 parental organization's meetings held not only in Poland, but in other countries as well (e.g. during global Neurofibromatoses Congresses organized on regular yearly bases in US and Europe).

Therefore, the lack of an established and comprehensive program of care for adults suffering from NF-1 is our national challenge, and all initiatives taken currently by "adult medicine specialists" [19, 22] are welcome both by the patients and the nongovernmental organizations representing their interests in Poland. As described above, the fundamental age--related restrictions limiting the access of adult NF-1 patients to coordinated medical care programs is related to the fact that all four centers responsible for NF/RAS comprehensive program in Poland were established on a pediatric academic oncology departments basis. Fortunately, 3 of them are a part of the multispecialty structure of Medical University Clinical Centers, gathering highly specialized medical academic departments for children AND adults. Thus, the NF/RAS Centers registered by parental Medical Universities in Poland as an integrated part of their structures are able to provide the highest standards of care for NF-1 patients (and other neurofibromatoses) regardless of age. Hence, the only action advice for the Polish Ministry of Health (and generally — healthcare system authorities) is to spread the legal responsibility of NF/ /RAS CMCCtrl from pediatric-only to pediatric and adult care for NF-1 patients. The idea may be widened and include other healthcare systems without appropriate care for NF-1 and, more widely, other rare disorders in general.

As described above and in the previous publication [17], during the anamneses the MUW NF/RAS CMCCtrl staff frequently noted the ignorance of the health risks related to NF-1. This may be due to the common belief of medical professionals that NF-1 is a disease slightly limiting life expectancy [23–26]. The life expectancy limitation of 8 to 15 years in comparison with the general population determined by the quoted epidemiology studies seems to justify this general belief. Regrettably, NF-1 is still a disorder of a significantly increased risk of various health complications related to the tissue and organ consequences of *Nf1* mutation. In our practice, which is a mainstay of MUW-NF/ /RAS CMCCtrl activity, the affected parents of primarily diagnosed children always receive written information concerning the NF-1-related complications occurring particularly in adulthood, and the screening modalities necessary to diagnose them, during the first admission to the Center or at the time of disease confirmation in the child (or/and the affected parent) at the latest. In this context, the negligible percentage of NF-1 adults aware of their disease hazards is relevant (app. 10% as disclosed above), and necessitates further action to improve adult NF-1 care in Poland. It may be applicable to other countries all over the world as well, where the access of all patients to a NF-1 screening program is still limited.

Finally, as no NF-1 patient registry has been developed in Poland yet and the only measurable epidemiological data available in Poland refer to the incidence and mortality related to BC, but not to other malignancies of risk in NF-1 patients, with reference to the presented results we claim that a preventive oncological patient's health problems oriented program (and more widely: concentrated on the other ailments related to NF-1 as well) is worth being introduced legally for the whole population of NF-1 patients, not only children. The simplified proof which might supported this claim, may result from the described case of a young woman affected by subclinical BC, hidden among other neurofibromas inside the breast, disclosed as early as at her 32$^{nd}$ year of age.

Despite favorable mortality trends since the 1990s in Europe [27], Poland is the only country where the BC mortality rate is currently increasing [28]. The disease progresses to an advanced stage in 30% of women with BC in Poland, and in 5–10% of patients it is diagnosed when it has already metastasized to other organs [29]. This results mostly from the fact that Polish women disregard the need for preventive examinations (not published data of the Polish National Health Fund[1] of 2021) and the fact that the Population Program for Early Detection of Breast Cancer targets women aged 50 to 69 and women with proven genetic predispositions to BC. The test assessing the genetic predisposition to BC in Poland does not include the *Nf1* gene, which goes against widely accepted recommendations [30]. As regards other rare tumors (e.g., pheochromocytoma), no preventive measures or activity have been performed in Poland at all. In this respect, the 3 young patients with NF-1 referred for preventive ultrasonography after MUW NF/RAS CMCCtrl counselling, would not have a growing tumor diagnosed early enough at the presymptomatic stage of the disease, to protect the patient's health or even life. The published results constitute indirect, but significant, evidence, that precise information provided to the persons at risk is the responsibility of the NF-1 care programs, especially in countries with limited access to NF-1 patient-oriented care.

## Conclusions

The immediate but unexpected result of the implementation of a coordinated medical care program for NF-1 children and youth in Poland is worth being propagated not only in the country, but worldwide. Early successful prevention of malignancy

[1]Discussed in *https://www.euractiv.com/section/diabetes-cancer-hepatitis/news/fighting-metastatic-breast-cancer-is-a-race-against-time-in-poland/, 2021*

or its complications in professionally counselled NF-1 parents, as demonstrated in the presented 6 cases provided with adequate knowledge at the right time, is the reason why the extension of the prophylaxis should be considered across the whole NF-1 population; the coordinated medical care program should be available for them with no exceptions. Finally, it is advised that with regard to NF-1 and its high prevalence among rare diseases, precise knowledge concerning certain malignancies as well as other NF-1 related medical risks should become the subject of training of medical professionals regardless of their specialty.

## Article information and declarations

### Data availability statement

Not applicable. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Ethics statement

According to Polish Law, ethics approval was not required for this kind of research and publication. All participants with neurofibromatosis type 1 provided consent/assent to participate in the focus group of patients in our Institution, but they were not obliged to sign the consent to participate in the study.

### Authors contributions

Marek W. Karwacki — conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, supervision, validation, visualization, writing — original draft preparation, writing — review & editing.


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### Conflict of interest

The author declares no conflict of interest.

### Supplementary material

None.


**Marek W. Karwacki**
*Department of Pediatric Hematology and Oncology, Transplantation Medicine and Pediatrics*
*Medical University of Warsaw*
*Żwirki i Wigury 63a*
*02–091 Warsaw, Poland*
*e-mail: mwkarwacki@gmail.com*



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## References


1. Uusitalo E, Rantanen M, Kallionpää RA, et al. Distinctive Cancer Associations in Patients With Neurofibromatosis Type 1. J Clin Oncol. 2016; 34(17): 1978–1986, doi: 10.1200/JCO.2015.65.3576, indexed in Pubmed: 26926675.
2. Pasmant E, Vidaud M, Vidaud D, et al. Neurofibromatosis type 1: from genotype to phenotype. J Med Genet. 2012; 49(8): 483–489, doi: 10.1136/jmedgenet-2012-100978, indexed in Pubmed: 22889851.
3. Sabbagh A, Pasmant E, Imbard A, et al. NF1 molecular characterization and neurofibromatosis type I genotype-phenotype correlation: the French experience. Hum Mutat. 2013; 34(11): 1510–1518, doi: 10.1002/humu.22392, indexed in Pubmed: 23913538.
4. Legius E, Messiaen L, Wolkenstein P, et al. International Consensus Group on Neurofibromatosis Diagnostic Criteria (I-NF-DC). Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. Genet Med. 2021; 23(8): 1506–1513, doi: 10.1038/s41436-021-01170-5, indexed in Pubmed: 34012067.
5. Philpott C, Tovell H, Frayling IM, et al. The NF1 somatic mutational landscape in sporadic human cancers. Hum Genomics. 2017; 11(1): 13, doi: 10.1186/s40246-017-0109-3, indexed in Pubmed: 28637487.
6. Tao J, Sun D, Dong L, et al. Advancement in research and therapy of mutant malignant tumors. Cancer Cell Int. 2020; 20: 492, doi: 10.1186/s12935-020-01570-8, indexed in Pubmed: 33061844.
7. Landry JP, Schertz KL, Chiang YJ, et al. Comparison of Cancer Prevalence in Patients With Neurofibromatosis Type 1 at an Academic Cancer Center vs in the General Population From 1985 to 2020. JAMA Netw Open. 2021; 4(3): e210945, doi: 10.1001/jamanetworkopen.2021.0945, indexed in Pubmed: 33734413.
8. Well L, Döbel K, Kluwe L, et al. Genotype-phenotype correlation in neurofibromatosis type-1: NF1 whole gene deletions lead to high tumor-burden and increased tumor-growth. PLoS Genet. 2021; 17(5): e1009517, doi: 10.1371/journal.pgen.1009517, indexed in Pubmed: 33951044.
9. Online Mendelian Inheritance in Man: # 607785 JMML.
10. Liy-Wong C, Mohammed J, Carleton A, et al. The relationship between neurofibromatosis type 1, juvenile xanthogranuloma, and malignancy: A retrospective case-control study. J Am Acad Dermatol. 2017; 76(6): 1084–1087, doi: 10.1016/j.jaad.2016.12.012, indexed in Pubmed: 28189268.
11. Bergqvist C, Hemery F, Jannic A, et al. Lymphoproliferative malignancies in patients with neurofibromatosis 1. Orphanet J Rare Dis. 2021; 16(1): 230, doi: 10.1186/s13023-021-01856-8, indexed in Pubmed: 34011343.
12. Alkhayyat M, Saleh MA, Coronado W, et al. Epidemiology of neuroendocrine tumors of the appendix in the USA: a population-based national study (2014-2019). Ann Gastroenterol. 2021; 34(5): 713–720, doi: 10.20524/aog.2021.0643, indexed in Pubmed: 34475743.
13. Uusitalo E, Kallionpää R, Kurki S, et al. Breast cancer in neurofibromatosis type 1: overrepresentation of unfavourable prognostic factors. Br J Cancer. 2016; 116(2): 211–217, doi: 10.1038/bjc.2016.403, indexed in Pubmed: 27931045.
14. Frayling I, Mautner VF, Minkelen Rv, et al. Breast cancer risk in neurofibromatosis type 1 is a function of the type of *NF1* gene mutation: a new genotype-phenotype correlation. J Med Genet. 2018; 56(4): 209–219, doi: 10.1136/jmedgenet-2018-105599, indexed in Pubmed: 30530636.
15. Evans DG, Kallionpää RA, Clementi M, et al. Breast cancer in neurofibromatosis 1: survival and risk of contralateral breast cancer in a five country cohort study. Genet Med. 2020; 22(2): 398–406, doi: 10.1038/s41436-019-0651-6, indexed in Pubmed: 31495828.
16. Gensini F, Sestini R, De Luca A, et al. Early-onset malignant phyllodes breast tumor in a patient with germline pathogenic variants in NF1 and BRCA1 genes. Fam Cancer. 2021; 20(3): 195–199, doi: 10.1007/s10689-020-00217-x, indexed in Pubmed: 33210232.
17. Karwacki MW. Breast cancer risk (un)awareness among women suffering from neurofibromatosis type 1 in Poland. Contemp Oncol (Pozn). 2020; 24(2): 140–144, doi: 10.5114/wo.2020.97637, indexed in Pubmed: 32774141.
18. Evans DG, Howard E, Giblin C, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A. 2010; 152A(2): 327–332, doi: 10.1002/ajmg.a.33139, indexed in Pubmed: 20082463.

19. Stewart DR, Korf BR, Nathanson KL, et al. Care of adults with neurofibromatosis type 1: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2018; 20(7): 671–682, doi: 10.1038/gim.2018.28, indexed in Pubmed: 30006586.
20. Rozporządzenie Ministra Zdrowia z dnia 15 czerwca 2020 r. w sprawie programu pilotażowego w zakresie koordynowanej opieki medycznej nad chorymi z neurofibromatozami oraz pokrewnymi im rasopatiami. Dziennik Ustaw RP nr 2020.1185 [Journal of Laws of the Republic of Poland, Decree of Ministry of Health no. 2020.1185] 2020.
21. Karwacki MW, Wysocki M, Perek-Polnik M, et al. Coordinated medical care for children with neurofibromatosis type 1 and related RASopathies in Poland. Arch Med Sci. 2021; 17(5): 1221–1231, doi: 10.5114/aoms.2019.85143, indexed in Pubmed: 34522251.
22. Rutkowski P, Raciborska A, Szumera-Ciećkiewicz A, et al. Recommendations of the Polish Sarcoma Group on diagnostic-therapeutic procedures and control in patients with type 1 neurofibromatosis (NF1) and the associated malignant neoplasm of peripheral nerve sheaths. Nowotwory. Journal of Oncology. 2022; 72(2): 106–128, doi: 10.5603/njo.2022.0018.
23. Zöller M, Rembeck B, Akesson HO, et al. Life expectancy, mortality and prognostic factors in neurofibromatosis type 1. A twelve-year follow-up of an epidemiological study in Göteborg, Sweden. Acta Derm Venereol. 1995; 75(2): 136–140, doi: 10.2340/0001555575136140, indexed in Pubmed: 7604643.
24. McGaughran JM, Harris DI, Donnai D, et al. A clinical study of type 1 neurofibromatosis in north west England. J Med Genet. 1999; 36(3): 197–203, indexed in Pubmed: 10204844.
25. Bergqvist C, Servy A, Valeyrie-Allanore L, et al. NF France Network. Neurofibromatosis 1 French national guidelines based on an extensive literature review since 1966. Orphanet J Rare Dis. 2020; 15(1): 37, doi: 10.1186/s13023-020-1310-3, indexed in Pubmed: 32014052.
26. Wilding A, Ingham SL, Lalloo F, et al. Life expectancy in hereditary cancer predisposing diseases: an observational study. J Med Genet. 2012; 49(4): 264–269, doi: 10.1136/jmedgenet-2011-100562, indexed in Pubmed: 22362873.
27. Malvezzi M, Carioli G, Bertuccio P, et al. European cancer mortality predictions for the year 2019 with focus on breast cancer. Ann Oncol. 2019; 30(5): 781–787, doi: 10.1093/annonc/mdz051, indexed in Pubmed: 30887043.
28. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019; 144(8): 1941–1953, doi: 10.1002/ijc.31937, indexed in Pubmed: 30350310.
29. Jasiura A, Dera I, Szlachcic K, et al. Breast cancer screening programmes in selected European countries and Poland. Journal of Education, Health and Sport. 2021; 11(7): 11–21, doi: 10.12775/34598.
30. Hu C, Hart SN, Gnanaolivu R, et al. A Population-Based Study of Genes Previously Implicated in Breast Cancer. N Engl J Med. 2021; 384(5): 440–451, doi: 10.1056/NEJMoa2005936, indexed in Pubmed: 33471974.

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Review article

Tumor pathology

# Endoscopic ultrasound-guided fine needle aspiration biopsy — diagnostic principles and workup

Małgorzata Lenarcik[1, 2], Magdalena Misiak-Gałązka[2, 3], Andrzej Mróz[2, 4]

[1]*Department of Gastroenterology, Hepatology and Clinical Oncology, Centre of Postgraduate Medical Education, Warsaw, Poland*
[2]*Department of Pathology, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[3]*Maria Sklodowska-Curie Medical Academy, Warsaw, Poland. Evimed Medical Center Ltd.*
[4]*Department of Pathomorphology, Centre of Postgraduate Medical Education, Warsaw, Poland*

Endoscopic ultrasound-guided fine needle aspiration biopsy (EUS-FNAB) is a well-recognized diagnostic tool of high sensitivity (60–95%) and specificity (85–100%) for diagnosing solid, cystic, and solid-cystic lesions in the gastrointestinal tract (esophagus, stomach, and intestines) or pancreas and biliary tract. The specificity may be lower though for lesions of smaller size or of difficult location.

The quality of received tissue increases with the endoscopist's experience and proper application of the technique and the needles (e.g. vacuum aspiration); the key point for the diagnosis is high level cytomorphologic analysis performed by an experienced pathologist.

**Keywords:** EUS-FNAB, cytomorphology, diagnostic category, diagnostic workup, immunohistochemistry, EUS-FNAB technique

## Introduction

Endoscopic ultrasound-guided fine needle aspiration biopsy (EUS-FNAB) is an ultrasonography-based endoscopic method enabling the assessment of the gastrointestinal wall and surrounding structures with the possibility of harvesting tissue biopsy for histopathological expertise. The aim of this article is to present the diagnostic utility of endoscopic ultrasound-guided fine needle aspiration biopsy (EUS-FNAB) based on integrated clinicopathological cooperation in terms of the diagnostic of the tumors/lesion in the gastrointestinal tract.

## EUS-FNAB technique

The endoscope (echoendoscope) with its terminal ultrasonographic head is used for performing endoscopic ultrasound (EUS). After the echoendoscope's introduction, the EUS_head is placed against the wall of gastrointestinal tract and the surrounding structures are visualized within the range of several centimeters.

These include abnormalities of the esophageal, gastric, duodenal and intestinal walls, lymph nodes of the posterior mediastinum, perigastric and periduodenal regions as well as in the pancreas or biliary tract and perisigmoid and perirectal regions. The most prevalent indications for EUS-FNAB are tumors of the pancreas and biliary tract, submucosal tumors of the esophagus, stomach, and duodenum as well as enlarged lymph nodes of the gastrointestinal tract.

The special needle is introduced via the biopsy channel of the echoendoscope. This needle is visible on the US scan after passing the channel and injecting the lesion, enabling the control of its position (Fig. 1 — needle in the tumor). The tissue is harvested by the movements of the needle as well as creating the sub pressure by connecting the vacuum

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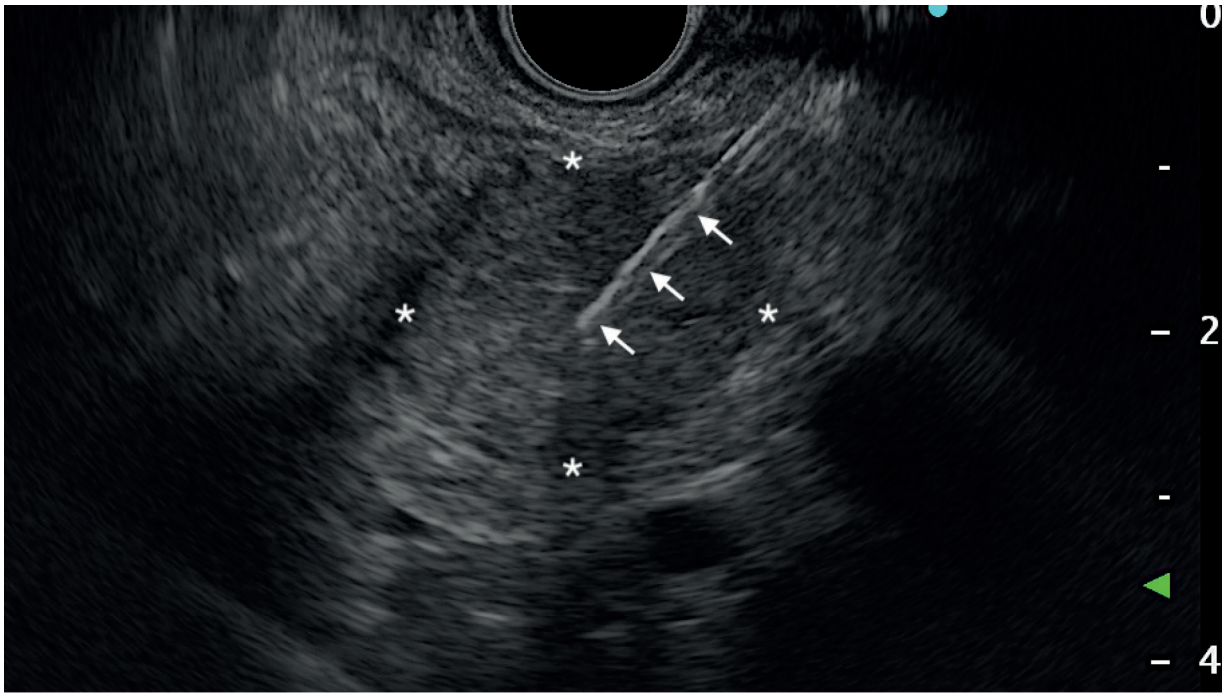

**Figure 1.** Endoscopic ultrasound (EUS) — biopsy needle (arrows) in 20 mm pancreatic lesion (asterisks)

syringe. The material is expelled from the needle by delivering a stream of air or saline from the syringe. This material is assessed macroscopically in terms of the presence of fragments macroscopic on-site evaluation (MOSE) and fixed for further histological and/or cytological examinations (Fig. 2 — macroscopic evaluation). Several (2 to 4) passings are performed according to the MOSE.

The EUS needles are usually 0,5 mm to 1,1 mm in diameter (25 to 19 gauge), with 22 gauge needles mostly used (0,7 mm). Nowadays the standard of use are fine needle biopsy (FNB) type needles which replaced the previously used fine needle aspiration (FNA) type. The FNB needles have a special cut blade which allows the harvesting of tissue fragments for histological assessment. (Fig. 3 — the needle tip in the lesion). The biopsies performed with FNB needles are bigger, richer in tumor tissue, preserved histopathological pattern of the lesion and are of greater histological assessment value than those made with FNA needles. This increases the diagnostic yield as well as the sensitivity and specificity of the biopsies [1–6].

The endoscopic ultrasound-guided fine needle aspiration biopsy technique results in diagnostic tissue acquisition in 95% of pancreatic tumors, submucosal tumors, and enlarged lymph nodes, with 90% of the cases containing the tissue fragment. Sensitivity surpasses 90% and the specificity reaches 100% [7, 8]. The complications of the procedure are rare and include acute pancreatitis of mostly indolent course (< 1%), hemorrhage (< 0.7%), infection (< 1%) or endoscopy related perforation (< 0.1%) [9].

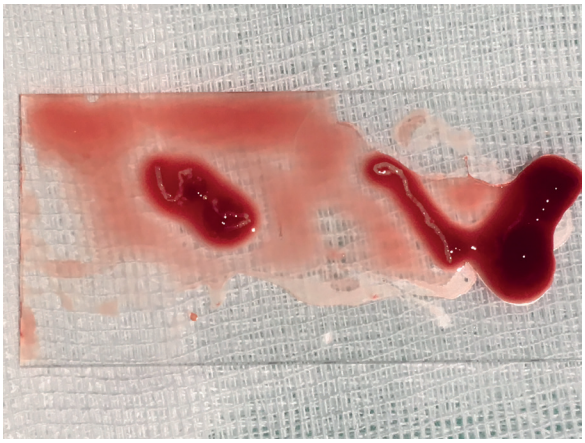

**Figure 2.** Macroscopic on-site evaluation (MOSE). Tissue of pancreatic lesion, blood, and clots are visible. A 22G biopsy needle was used

The differential diagnosis of endosonography-detected lesions requires clinical data correlation, biochemical analysis of cystic lesion content, and meticulous cytohistological assessment of the acquired tissue with immunohistochemical and/or histochemical stainings. This complex strategy increases the sensitivity and specificity of histopathological studies, reflecting in high quality diagnosis and proper therapeutical choice (Tab. I).

Individual approach is advised in each clinical case based on the principles of good clinical practice (GCP) and classifications/recommendations of scientific societies in endosonography [10].

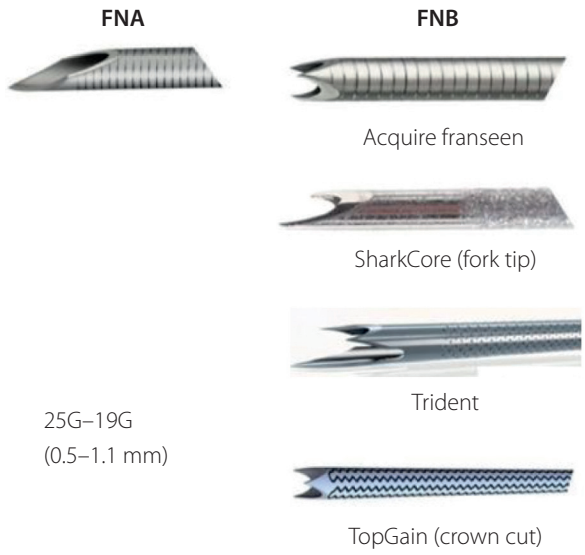


**Figure 3.** Types of needles; FNA — fine-needle aspiration; FNB — fine--needle biopsy

## Cytology (EUS-FNAB) — diagnostic workup

The diagnostic quality of EUS-FNAB materials is influenced by the EUS technique and the endoscopist's experience. The preliminary real-time assessment of the harvested samples may be performed with rapid on-site evaluation (ROSE) during the EUS-FNAB procedure. ROSE improves the quality of samples, decreases the number of passes optimizing diagnostic time slots and qualifying samples for further examinations (histochemistry, immunohistochemistry, flow cytometry or molecular studies) [10, 11]. Based on the type of lesion, the biopsy material can be fixed in 95–96% ethyl alcohol or cytofix for cytology smears or in 10% pH 7,2–7,4 room temperature (20–25°C) buffered formalin for cytohistology. It is of importance that the amount of the fixative should outnumber the amount of the material by at least a factor of 10. The time of fixation should be between 6 and 24 hours. Then the biopsies are routinely proceeded to be embedded in paraffin blocks and cut into 4 µm thick layers to be hematoxylin and eosin (H&E) stained. Endoscopic ultrasound-guided fine needle aspiration biopsy materials enable diagnosis of the type of the neoplasm, the source of the metastasis as well as predictive factors for personalized therapy. The experience of the pathologist and the ability to interpret the results of results of histochemical and immunohistochemical stains and genetic studies in light of the histopathological picture are crucial for making credible diagnosis (Fig. 4).

The principle of immunohistochemistry is to identify specific proteins (antigens) in cells and tissues, which are highlighted by a color reaction and then examined under the microscope in the context of the tissue. There are several hundred markers to establish the differentiation of the neoplasm, stratify the risk or qualify patients for molecular studies or personalized therapies. The immunohistochemistry staining is performed on paraffin embedded tissue using mostly ready to use kits in automatized stainers. The staining is assessed as to its intensity and localization (nuclear, membranous, cytoplasmatic etc.).

## Differential diagnosis

Cystic *vs.* solid-cystic lesions: the cystic lesion can be present in different parts of the gastrointestinal tract, including the pancreas. The main objective is to identify the cystic lesion producing mucus. Intraductal papillary mucinous neoplasms (IPMN) are cystic lesions of the main pancreatic ducts that produce mucus and carry a risk of malignancy. In contrast, mucinous cystic neoplasms (MCN) are cystic lesions that also produce mucus but are not connected to the main pancreatic ducts, and they too have malignant potential.

The cytomorphologic features of IPMN and MCN include mucus, proliferating papillary epithelial structures with possible dysplasia, and ovarian-like stroma in MCN. The histochemistry staining is used for mucus detection and high levels of carcinoembryonic antigen (CEA) confirm diagnosis [12, 13].

Solid-cystic and solid epithelioid mass in gastrointestinal tract (GI) and pancreatobiliary tract: include cytokeratins (pan CK) positive and vimentin negative neoplasms of various histopathology and differentiation. Endoscopic ultrasound-guided

**Table I.** Morphology of endoscopic ultrasound (EUS) detected lesions — diagnostic techniques

| EUS | EUS-FNAB | Fluid analysis | Technique IHC, HC | Histopathology/results |
|---|---|---|---|---|
| Solid lesions, epithelial | Required | No indication | Valuable, required (nen, nec) | Epithelioid tumors of GI/adenoma, LG-IEN or HG-IEN, NEN, NEC, carcinoma |
| Solid lesion, mesenchymal | Required | No indication | Required | Mesenchymal tumors of GI/benign, border-line or malignant |
| Solid cystic lesions | Required | Valuable | Required | IPMN, malignant mucinous cystic neoplasm, cystic ductal carcinoma, NEN, SPN |
| Cystic lesion (micro-macrocystic) | Required | Valuable | Valuable | Brunch duct IPMN, serous cystic neoplasm, mucinous cystic neoplasm, pseudocyst |
| Unilocular cyst | No indication | Required | ---- | Pseudocyst |

EUS — endoscopic ultrasound; EUS-FNAB — endoscopic ultrasound-guided fine needle aspiration biopsy; GI — gastrointestinal tract; HC — histochemistry; HG-IEN — high grade intraepithelial neoplasia; IHC — immunohistochemistry; IPMN — intraductal papillary mucinous neoplasm; LG-IEN — low grade intraepithelial neoplasia; NEC — neuroendocrine carcinoma; NEN — neuroendocrine neoplasm; SPN — solid pseudopapillary tumor

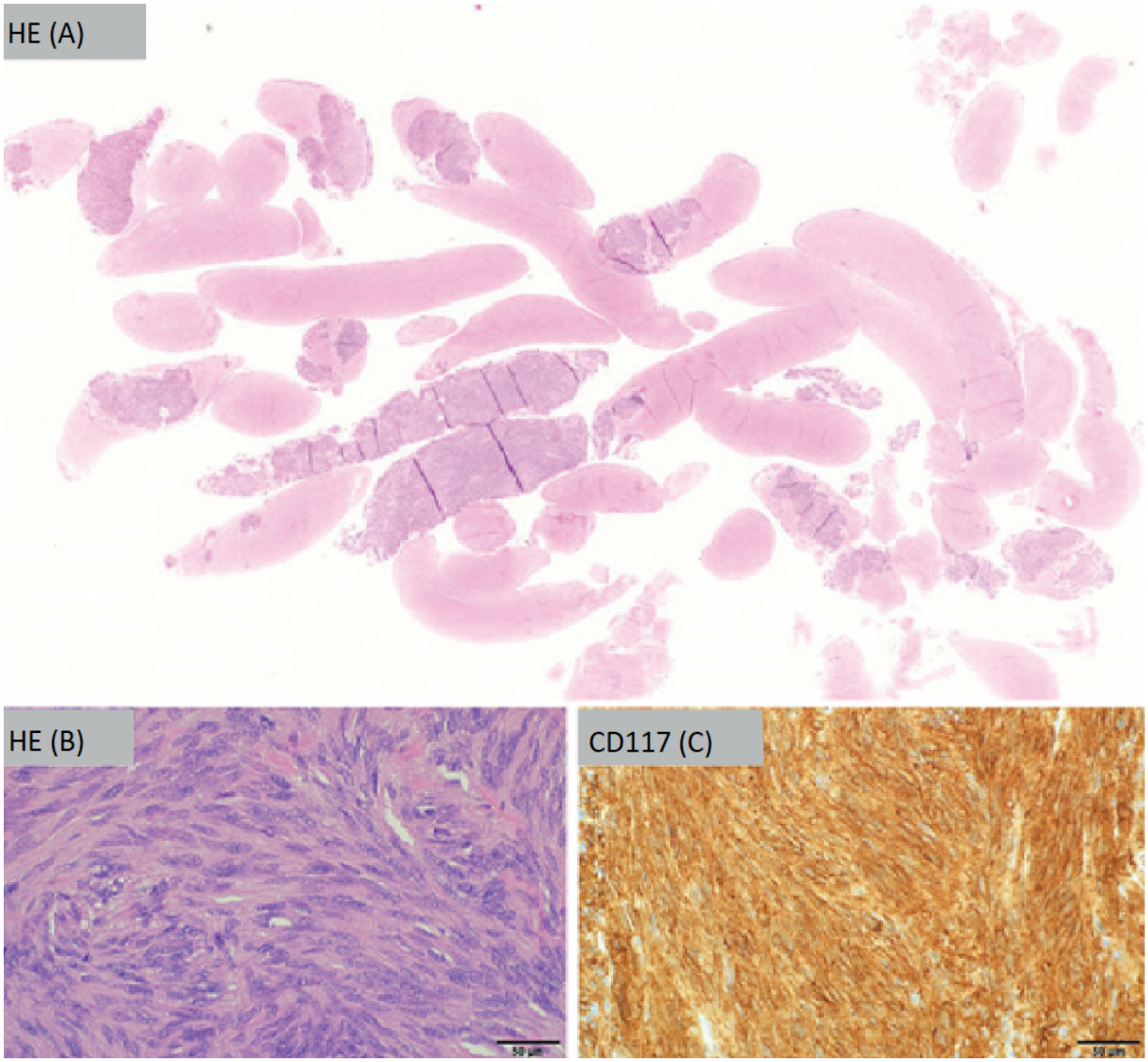


**Figure 4.** Endoscopic ultrasound-guided fine needle aspiration biopsy (EUS-FNAB) derived material from a gastric tumor diagnosed as gastrointestinal stromal tumor (GIST); **A.** Hematoxylin and eosin (H & E) staining, magnification 20×; **B.** H & E staining, magnification 400×, showing spindle cell morphology; **C.** CD117 immunohistochemistry, positive staining (brown deposits localized in the plasma membrane or cytoplasm of GIST cells), magnification 400×

fine needle aspiration biopsies are utilized to assess invasiveness of glandular proliferations [intraepthelial neoplasia (IEN), IEN/dysplasia *vs.* carcinoma] or establish the source of metastases.

Adenocarcinoma in situ (AIS) cells are moderately polymorphic with nucleoli, mucus filled cytoplasm arranged in glands or small papillary formations. It is of most importance to differentiate IEN form reactive atypia usually present in the healing phase of inflammatory bowel diseases (IBD), pancreatitis or after endoscopic retrograde cholangiopancreatography (ERCP).

Endoscopic ultrasound-guided fine needle aspiration biopsy adenocarcinoma cells are highly polymorphic with hyperchromatic, enlarged nuclei, and mitotic activity. The cells form glandular structures or are dispersed, the background can be necrotic and inflamed. In histopathology, atypical glands are found in desmoplastic stroma. Immunohistochemistry helps to establish the origin of the cancer e.g. CK7+, CK20– for stomach, CK7–, CK20+ for large bowel or MUC4+ for pancreas [12, 13].

Neuroendocrine tumors (GEP-NET) derive from neuroendocrine cells in different parts of the gastrointestinal tract (jejunum, ileum, pancreas, stomach, large bowel, and appendix). They are classified and staged according to localization and histological grade. Endoscopic ultrasound-guided fine needle aspiration biopsy is employed for the diagnosis and monitoring of patients with neuroendocrine tumors. The neuroendocrine cells obtained through EUS-FNAB typically exhibit a uniform appearance, with round or oval nuclei containing "salt-and-pepper" chromatin. The cytoplasm of the cells may be eosinophilic, the cells are arranged in nests, stripes or rosettes. Immunohistochemistry demonstrates the expression of neuroendocrine markers such as chromogranin A, synaptophysin,

INSM1, and the Ki67 proliferation index, all of which are essential for the diagnosis and classification of GEP-NET (gastroenteropancreatic neuroendocrine tumor) family neoplasms [13, 14].

Solid mesenchymal mass in GI and pancreatobiliary tract: there are a wide range of various benign and malignant neoplasms which are vimentin positive and cytokeratins (pan CK) negative on immunohistochemistry. The most prevalent tumor in this group is gastrointestinal stromal tumor (GIST), others include leiomyoma, leiomyosarcoma, schwannoma, lipoma, desmoid tumor. Endoscopic ultrasound-guided fine needle aspiration biopsy diagnosis is relies on cytology, where the cells are typically elongated, spindle-shaped, and arranged in small nests, and primarily on histopathology, which provides the histopathological features and variants (including spindle cell, epithelioid, myxoid, or pleomorphic patterns) can be correlated with additional IHC stains like DOG1 and CD117 for GISTs, SMA and desmin of myomatous tumors, S100 for schwannoma and STAT6 for solitary fibrous tumor [15, 16].

## Summary

Classifications of malignancy for gastrointestinal tumors diagnosed on EUS-FNAB are complicated and require the proper application of several factors. The are several systems like the World Health Organization (WHO) for epithelioid lesions (cancer), Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) for mesenchymal tumors, Fletcher's Risk Stratification System for GIST or Papanicolaou for pancreatobilliary mass are the bases for risk factor stratification and administration of optimal therapies [17, 18].

Cytological diagnosis based on EUS-FNAB for GI and pancreatobilliary tumors can be grouped in several categories:

- positive for malignancy: unequivocal cytomorphological features of malignancy. This category includes primary and secondary cancers, solid pseudopapillary neoplasm of the pancreas, neuroendocrine carcinomas, lymphomas, sarcomas;
- suspicious for malignancy: features suggestive of malignancy both in cytological and histopathological aspects but no definitive diagnosis can be made due to the paucity of the tissue or concomitant inflammatory-reactive changes. These cases should be consulted by an expert gastropathologist and if still nonconclusive, the biopsy should be repeated with the ROSE technique for a prompt assessment of the quality of the sample;
- atypia of uncertain significance (AUS): atypical cells, identify for malignancy, usually due to paucity of the cells or tissue with concomitant inflammation and necrosis (inflammatory bowel diseases, primary sclerosing cholangitis, stents, stones). It is required to make another attempt of obtaining representative material (preferably with the ROSE technique);
- benign the samples are adequate as to the cellularity and the representativeness, no atypia or dysplasia found. This category includes: nonneoplastic lesions (heterotopic lesions, accessory spleen, foci of endometriosis, inflammatory pseudotumors) and benign tumors (serous cystic neoplasm, leiomyomas, lymphangiomas, schwannomas, lipomas;
- nondiagnostic: aspirates with a paucity of cells or non-representative samples containing only normal gastric or intestinal epithelium. There is no consensus on the minimum number of cells required for a definitive diagnosis; acellular aspirates or those containing only mucus do not fall into this category, as they may still provide diagnostic value and should be correlated with radiological and clinical data (e.g., IPMN).

## Conclusions

Endoscopic ultrasound-guided fine needle aspiration biopsy is a safe, minimally invasive method for cytological and histopathological diagnosis of GI and pancreatobilliary lesions. This technique requires close cooperation between endoscopists, radiologists, and pathologists. In many cases precise diagnosis can be made; prognostic and predictive factors can also be established.

**Małgorzata Lenarcik**
*Department of Pathology*
*Maria Sklodowska-Curie National Research Institute of Oncology*
*Roentgena 5*
*02–871 Warsaw, Poland*
*e-mail:* ml@lenar.pl

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### *Authors contributions*

Małgorzata Lenarcik — conceptualization, methodology, formal analysis, resources, writing — original draft preparation, writing — review & editing.
Magdalena Misiak-Gałązka — visualization, writing — review & editing.
Andrzej Mróz — formal analysis, visualization, writing — review & editing.

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### *Conflict of interest*

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### *Supplementary material*

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## References


1. Bang JiY, Hebert-Magee S, Navaneethan U, et al. EUS-guided fine needle biopsy of pancreatic masses can yield true histology. Gut. 2018; 67(12): 2081–2084, doi: 10.1136/gutjnl-2017-315154, indexed in Pubmed: 28988195.
2. Bang JiY, Navaneethan U, Hasan MK, et al. Endoscopic Ultrasound-guided Specimen Collection and Evaluation Techniques Affect Diagnostic Accuracy. Clin Gastroenterol Hepatol. 2018; 16(11): 1820–1828.e4, doi: 10.1016/j.cgh.2018.03.004, indexed in Pubmed: 29535060.
3. Gkolfakis P, Crinò SF, Tziatzios G, et al. Comparative diagnostic performance of end-cutting fine-needle biopsy needles for EUS tissue sampling of solid pancreatic masses: a network meta-analysis. Gastrointest Endosc. 2022; 95(6): 1067–1077.e15, doi: 10.1016/j.gie.2022.01.019, indexed in Pubmed: 35124072.
4. Chen YI, Chatterjee A, Berger R, et al. EUS-guided fine needle biopsy alone vs. EUS-guided fine needle aspiration with rapid on-site evaluation of cytopathology in pancreatic lesions: a multicenter randomized trial. Endoscopy. 2021; 54(1): 4–12, doi: 10.1055/a-1375-9775, indexed in Pubmed: 33506455.
5. Facciorusso A, Sunny SP, Del Prete V, et al. Comparison between fine-needle biopsy and fine-needle aspiration for EUS-guided sampling of subepithelial lesions: a meta-analysis. Gastrointest Endosc. 2020; 91(1): 14–22.e2, doi: 10.1016/j.gie.2019.07.018, indexed in Pubmed: 31374187.
6. Facciorusso A, Crinò SF, Gkolfakis P, et al. Endoscopic ultrasound fine-needle biopsy vs fine-needle aspiration for lymph nodes tissue acquisition: a systematic review and meta-analysis. Gastroenterol Rep (Oxf). 2022; 10: goac062, doi: 10.1093/gastro/goac062, indexed in Pubmed: 36340808.
7. Facciorusso A, Del Prete V, Antonino M, et al. Diagnostic yield of Franseen and Fork-Tip biopsy needles for endoscopic ultrasound-guided tissue acquisition: a meta-analysis. Endosc Int Open. 2019; 7(10): E1221–E1230, doi: 10.1055/a-0982-2997, indexed in Pubmed: 31579703.
8. Crinò S, Mitri RDi, Nguyen N, et al. Endoscopic Ultrasound–guided Fine-needle Biopsy With or Without Rapid On-site Evaluation for Diagnosis of Solid Pancreatic Lesions: A Randomized Controlled Non-Inferiority Trial. Gastroenterology. 2021; 161(3): 899–909.e5, doi: 10.1053/j.gastro.2021.06.005.
9. Forbes N, Coelho-Prabhu N, Al-Haddad MA, et al. ASGE Standards of Practice Committee. Adverse events associated with EUS and EUS-guided procedures. Gastrointest Endosc. 2022; 95(1): 16–26.e2, doi: 10.1016/j.gie.2021.09.009, indexed in Pubmed: 34711402.
10. Polkowski M, Jenssen C, Kaye P, et al. Technical aspects of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Technical Guideline - March 2017. Endoscopy. 2017; 49(10): 989–1006, doi: 10.1055/s-0043-119219, indexed in Pubmed: 28898917.
11. Yang F, Liu E, Sun S. Rapid on-site evaluation (ROSE) with EUS-FNA: The ROSE looks beautiful. Endosc Ultrasound. 2019; 8(5): 283–287, doi: 10.4103/eus.eus_65_19, indexed in Pubmed: 31603143.
12. Centeno BA. Diagnostic cytology of the biliary tract and ancreas. In: Odze RD, Goldblum JR. ed. Surgical pathology of the GI tract, liver, biliary tract, and pancreas. 3rd ed. Saunders, Philadelphia 2015: 950–979.
13. International Academy of Cytology-International Agency for Research on Cancer-World Health Organization Joint Editorial Board. WHO Reporting System for Pancreaticobiliary Cytopathology. vol. 2. 1st ed. International Agency for Research on Cancer 2022.
14. Adsay NV, Klimstra DS. Chater 29. In: Odze RD, Goldblum JR. ed. Surgical pathology of the GI tract, liver, biliary tract, and pancreas. 3rd ed. Saunders, Philadelphia 2015: 803–820.
15. Matthew R, Lindberg MD. Section 18, Tumor of the gastrointestinal tract. In: Lindberg LG. ed. Diagnostic pathology: Soft tissue tumors. 2nd ed. Saunders, Philadelphia 2016: 730–769.
16. Rubin B, Hornick J. Mesenchymal Tumors of the Gastrointestinal Tract. Practical Soft Tissue Pathology: A Diagnostic Approach. 2013: 437–473, doi: 10.1016/b978-1-4160-5455-9.00016-8.
17. Layfield LJ, Pitman MB, DeMay RM, et al. Pancreaticobiliary tract cytology: Journey toward„Bethesda" style guidelines from the Papanicolaou Society of Cytopathology. Cytojournal. 2014; 11: 18, doi: 10.4103/1742-6413.134441, indexed in Pubmed: 25071860.
18. Pitman MB. The World Health Organization Reporting System for Pancreaticobiliary Cytopathology. Arch Pathol Lab Med. 2024 [Epub ahead of print], doi: 10.5858/arpa.2023-0411-RA, indexed in Pubmed: 38190275.

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Review article

Radiotherapy

# Combined CONVentional with HYPOfractionated regimen (CONV-HYPO) alternative instead of conventionally fractionated radiotherapy to improve treatment outcomes

Bogusław Maciejewski[1], Małgorzata Kraszkiewicz[2], Piotr Wojcierszek[2], Jean-Pierre Gerard[3]

[1]*Department of Radiotherapy, Maria Skłodowska-Curie National Research Institute of Oncology, branch Gliwice, Poland*
[2]*Department of Brachytherapy, Maria Skłodowska-Curie National Research Institute of Oncology, branch Gliwice, Poland*
[3]*Department of Radiation Oncology, Centre Antoine-Lacassagne, Cote d'Azur University, Nice, France*

For years, the process of accelerated repopulation recognized as a dominant factor for radiotherapy failures has been deduced rather than proved by direct clinical data. It sounds logical and that towards the end of fractionated radiotherapy residual tumor cells likely become hypoxic and resistant to conventional dose fractions. Therefore, total doses higher than 63–65 Gy are likely wasted and useless, at least for locally advanced cancers. Thus, the last few 2.0 Gy fractions should be replaced with a few large 5–10 Gy fractions. The CONV-HYPO concept is presented and discussed in detail. For years, the CONV-HYPO has mainly been explored to treat rectal cancer, and the Papillon 50 kV unit has been most often used as a HYPO contact therapy. Recently, high dose rate (HDR) brachytherapy has become a plausible alternative due to the precise equipment entering to the market. This method is presented in detail. The CONV part of 45 Gy in 25 fractions combined with Capecitabine is followed by the three-step HYPO-HDR BRT procedure consisting of 3 × 8 Gy, 3 × 10 Gy, and if it is well tolerated, then can be followed by the last step of 3 × 12 Gy. This protocol is now used in Gliwice. However, rectal cancer is not the only target for the CONV-HYPO, as it can also be effectively used to treat H&N, lung, esophageal, liver, pancreatic, prostate cancers, and soft tissue sarcomas as well.

**Keywords:** hypoxic tumor cells, ineffective conventional irradiation, CONV-HYPO concept, rectal cancer, Gliwice protocol

## Why conventionally fractionated radiotherapy should be abandoned?

Results of about 850 head and neck cancer patients treated by radiotherapy alone were analyzed in 1990, showing a steep increase in the total dose with extension of the overall treatment time. This tendency was interpreted as the result of accelerated population of tumor clonogens, which may counterbalance cell kill effect of even 1.4–1.6 Gy/day [1]. Repopulation potency has been considered as a dominant factor for radiotherapy failure. It is not easy to debunk such a belief that was advocated for over 30 years. However, it was indirectly deduced only, but not proven by direct clinical data. Nowadays, it looks that *"repopulation concept"* has ignored radiobiological principles and in fact it does not seem entirely reliable and true.

It has been generally accepted as a rule that the biological effects of the fraction's dose is generally counted as a constant rate of the cells killed during fractionated irradiation. However, as a matter of fact, radiation effects relate to the number

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of the tumor cells killed, which are not constant but markedly decrease towards the end of treatment. For example, if a tumor contains 1 billion cells ($10^9$), then after 10 conventional fractions (20 Gy) about 980 million cells will survive, which may still repopulate to neutralize a part of each consecutive fraction's dose. But after 30 fractions of 2 Gy, only $10^1$–$10^2$ cells will survive.

It seems radiobiologically unreliable that when the number of tumor cells gets smaller and smaller after 30–35 fractions — even if they remain euoxic (but they do not) — they still will have enough potential to repopulate faster and faster than after 10–15 fractions, unless their cell cycle turnover time would is shortened by a factor of 15–20, what never happens. A plausible alternative hypothesis might be that residual tumor cells are hypoxic (continued irradiation also causes deterioration in the vascular network and oxygen supply) and dominate during the delivery of the last few dose fractions, which are too small to overcome their radioresistance to kill them all.

Hypoxic cancer cells are about 2.5–3 times more radioresistant than euoxic cells. It suggests that towards the end of irradiation, hypoxic cells likely *"ignore"* the last 5–6 fractions of 2 Gy (Fig. 1). Even if sublethal damage occurs within these cells, intracellular mechanisms can efficiently repair such damage. Therefore, the last few conventional fractions are likely ineffective; there is, in fact, no reason to escalate the total dose for locally advanced tumors to improve their clinical outcome.

Disappointing results of many altered fractionation trials (~ 6% therapeutic gain) which have been carried out for over 25 years [2] are convincing arguments for increasing importance of hypoxic tumor cells (which they dominate) during the few last fractions, the more so because fraction doses in these trials were within the narrow range of 1.15 to 2.0 Gy. It suggest that

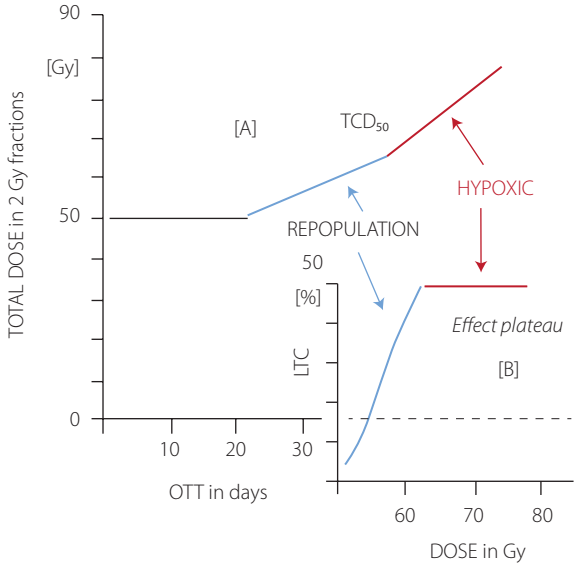


**Figure 1.** Dose-time relationship for head and neck (H&N) cancer corrected for repopulation and hypoxic — based on data from [1]; LTC — local tumor control; OTT — overall treatment time; TCD — total cure dose

any increase in a conventionally fractionated total dose above 63–65 Gy is likely wasted and clinically useless, at least for locally advanced cancers. Finally, if radiation oncologists expect substantial improvements in the therapeutic benefit, one should bear in mind that there is no longer room for conventional 2 Gy radiotherapy, if optimal local tumor control is expected.

## CONV-HYPO dose fractionation — a promising concept

Stereotactic hypofractionated radiotherapy (SHRT) has been offered as a very promising perspective for the use of high-dose fractions in radical radiotherapy with unexpectedly high permanent local tumor control (LTC) of 85–95%, however mainly for small (< 5 cm in diameter) primary tumors [3, 4]. Sophisticated equipment (CyberKnife) and techniques, [volumetric modulated arc therapy (VMAT)] have made such therapy a plausible alternative to conventional irradiation.

It is more than likely that the residual number of tumor cells which survived previous fractions is low, about $10^2$–$10^{2.5}$ cells, and they are undoubtedly hypoxic and radioresistant to conventional 2 Gy fractions. Thus, the last 5–6 conventional dose fractions delivered to locally advanced tumors are wasted (average LTC lower than 50%) since conventional dose intensity (DI) is too low (1.43 Gy/day) to overcome cell's hypoxia. The DI increases to effective 2.6–10.0 Gy/day by using the last 4–6 large fractions. Such combined radiotherapy termed as combined CONVentional with HYPOfractionated regimen (CONV-HYPO) (Fig. 2A, B) includes conventional 45–50 Gy delivered in 25 fractions, followed by 5–6 high fractions of 5–6 Gy or 3 fractions of 10 Gy. The CONV part can be intensified by concurrent chemotherapy to enhance cell kill effects (Fig. 2B). External 5–6 stereotactic hypofractions can easily be given using brachytherapy. Figure 3A shows that 2 Gy fractions of conventional radiotherapy (RT) alone result in successive tumor deceleration, partly neutralized by clonogenic cell repopulation after week 2–3 of treatment. However, when finally $10^1$–$10^2$ cells will survive they are hypoxic, and radioresistant, and they do not respond to 2 Gy fractions (horizontal *"effect plateau"* on Fig. 3A), since the overall biologically effective dose (BED) is low, not higher than ~ 73 izoGy.

Among various altered fractionation schedules tested in clinical trials, Kian Ang [5] proposed a so-called *"concomitant boost"* using conventional fractions given once-a-day during the first few weeks followed by twice-a-day doses of 1.8 Gy and 1.5 Gy during the last two and half weeks. The results showed far from impressive improvements of the LTC, since all fraction doses were below 2 Gy.

The CONV-HYPO alternative consists of two parts (Fig. 2). The first one is just conventional fractionation of 45–50 Gy in 25 fractions, which have the task to eradicate microscopic spread of cancer cells beyond the gross tumor mass, and to produce a partial regression of the primary tumor. The HYPO part is realized by using a few large fractions of external irradiation

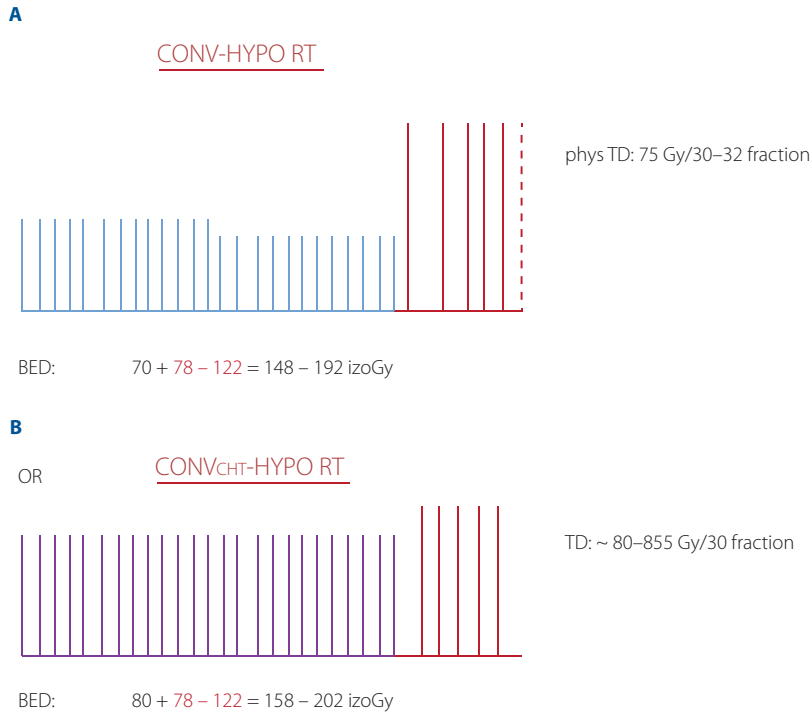


**Figure 2.** Combined CONVentional with HYPOfractionated regimen (CONV-HYPO) fractionation pattern; **A**. Radiotherapy alone, lower dose fractions after 25 Gy theoretically illustrates lowered dose fractions due to neutralizing effect of repopulation; **B.** Combined chemoradiation of the past (CONV). Total biologically effective dose (BED) doses are calculated using α/β value of 6 Gy; CHT — chemotherapy; RT — radiotherapy; TD — total physical dose

or of brachytherapy with hypofractionations of 3 × 10 Gy or 5 × 6–7 Gy, focused on the residual tumor GTV, to eliminate the surviving, mainly hypoxic cells. Although the DI of the first part is low (1.43 Gy/day), the DI of the second part is very high (8–10 Gy/day) which can effectively eliminate residual resistant hypoxic cells. Such a combination of the two different parts of irradiation vary in their biological potential, even if its physical total doses do not differ very much. Although the degree of biological power of the DI during of the first part is about 7-times lower than the second, it is still effective enough to sterilize euoxic tumor clonogens, mainly those localized beyond the gross tumor mass, but it is ineffective in eradicating residual hypoxic cells, which become the target for the HYPO part.

The biological effect is not linearly related to the radiation dose [6–8], and its relationship becomes increasingly supra--linear as the dose increases. Thus, in terms of the cell kill, doses of 3 × 10 Gy are much more effective than the same total dose delivered in 15 fractions of 2 Gy. Due to highly conformal radiotherapy, the total dose that may be given to the tumor is not in fact entirely and always limited by the tolerance of the adjacent normal tissues [8] since the residual tumor volume is very small. Nevertheless, the HYPO total cure dose (TCD) should be weighted as optimal for tumor control, and in the same level, as maximal tolerance doses ($TTD_{max}$).

The Linear-Quadratic formula (L-Q) has been used to count biologically effective doses [8], since an α/β ratio represents the sensitivity of the tumor or critical normal tissues to change in dose per fraction (it has nothing to do with its intrinsic radiosensitivity).

Dale [6] used an α/β formula to count the effective biologically equivalent dose if given in 2 Gy fractions ($EQD_{2.0}$). The $EQD_{2.0}$ quite well represents fraction doses lower than 5 Gy but not large HYPO fractions, since it underestimates the real value of the biological dose. Fowler, Joiner and van der Kogel [7, 8] have suggested to use the following biological effective (BED) dose formula which gives reliable estimates:

$$BED = TD\ (1 + di / \alpha/\beta),$$

where TD is the total physical dose, and di — the dose per fraction. For tumors, an α/β value is in the range of 10–25 Gy (usually 10 Gy) suggests that the tumor cells for the size of the dose per fraction is not very important, whereas for normal tissues since the α/β ratio is usually in the range of 2–5 Gy (highly sensitive to change in the dose per fraction). Therefore it is essential to count the BED value of the HYPO part for critical normal tissues surrounding the tumor because the BED for the CONV part does not change a lot (Tab. I). Moreover, $D_{10}$ (dose reducing the cell number by 1 log, i.e. $10^9$ to $10^8$, or $10^3$ to $10^2$) for the HYPO and the CONV differ significantly (about 3.5 Gy *vs.* 7 Gy). For example, 36 Gy in 4–6 fractions will reduce cell survival from $10^9$ cells to $10^{-1}$ since $10 \times D_{10}$ (36 Gy : 3.5 Gy) decelerates the cell number by 10 logs whereas the same total

dose given in 2.0 Gy fractions (36 Gy : 7 Gy = 5 × $D_{10}$) will reduce the cell number by only 5 logs, e.g. from $10^9$ to $10^4$, and therefore it will not produce any LTC. It argues against normalization of the HYPO total dose to be biologically equivalent if is given in 2.0 Gy fractionations and therefore advantage of the BED formula is much more reliable.

Theoretical cell survival curves (Fig. 3) show that when cancer cell deceleration after conventional dose fractionation reaches a level of about $10^3$–$10^2$ cells (Fig. 3A) one cannot expect the LTC higher than 50% if the irradiation continues, since the residual cancer cells are likely hypoxic and therefore they do not respond to the successive 2 Gy fractions. The first CONV part with 45–50 Gy in 25 fractions (Fig. 3B) can easily eradicate the microspread of cancer cells [for example 7 × $D_{10}$ (7 × 7 Gy) will reduce cell number from e.g. $10^6$ (microcellular lesion) to $10^{-1}$ cell, what would result in about 90% LTC of such micro lesions]. Moreover, the HYPO part with a few large fractions (SHRT or BRACHY can effectively eliminate residual hypoxic cancer cells (Fig. 3B) and furthermore, in some cases it may also offer some organ preservation — important for the patient's continued quality of life.

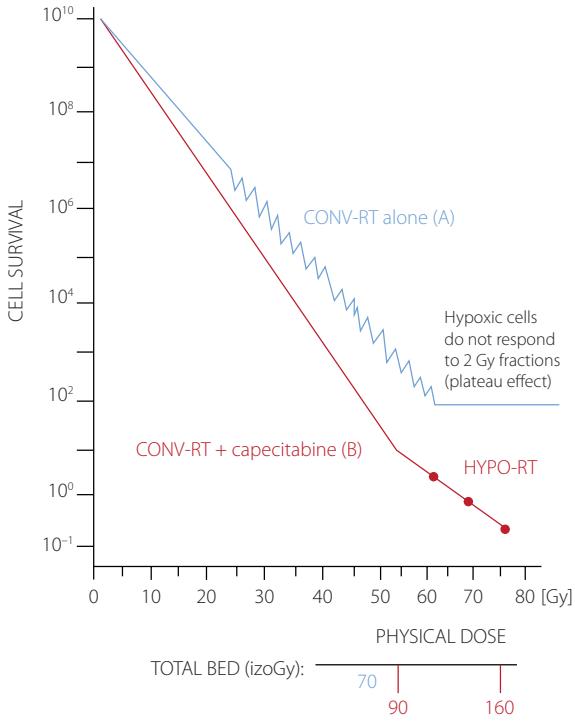


**Figure 3.** Tumor cell survival curve for (**A**) classical conventional radiotherapy (RT) alone (blue line), (**B**) combined CONVentional with HYPOfractionated regimen (CONV-HYPO) schedule (red line). Horizontal part of the curve A means no response to the escalated doses above 60–65 Gy (due to domination of hypoxic cells); BED — biologically effective dose

## CONV-HYPO for rectal cancer

The CONV-HYPO is an approach of the dose fractionation which is an effective alternative to conventional radiotherapy for various tumor types and localization. For head and neck, lung, liver, prostate, kidney, bladder cancers, and various sarcomas the SHRT can also be used as a HYPO module. For bronchial esophageal, and rectal cancers, the HYPO-brachytherapy offers an optimal dose distribution in the tumor volume (GTV) and more effective protection of the epithelium of the tube-like organs and the preservation of their function. For the last 50 years the rectal cancer has been the most often object of the CONV-HYPO to preserve the rectal sphincter. In 1975, Papillon, as a pioneer introduced the contact 50 kV X-ray radiotherapy for early pollypoid rectal cancer [9]. At 5 years the surgery-free survival with good bowel function was about 83%. The Lyon R 96–02 phase III trial showed that X-ray contact therapy combined with external radiotherapy improves sphincter preservation in patients with $cT_2$–$T_3$ cancer of the distal-middle rectum and it resulted in a high 10-year local tumor control (Fig. 4). Renaissance of contact X-ray therapy has begun around 2009 when a new 50 kV machine called Papillon 50$^{TM}$ was manufactured, and around 2018, 11 Papillon systems were installed mainly in the UK and in France [10]. Over 1000 rectal cancer patients have been already treated with contact X-ray therapy combined with chemoradiotherapy. Gérard is one of a few European radiation oncologists with enormous experience in the use Papillon 50$^{TM}$ therapy for $T_2$–$T_3N_{0-1}$ rectal cancer [11–17]. Recently, the GEC ESTRO ACROP has issued consensus recommendations for contact brachytherapy for rectal cancer [18].

Papillon 50 kV approach is a contact radiotherapy and the dose is planned on the surface of the tumor, which results in gradual deceleration of the superficial tumor cells, layer by layer (X-rays beam has the RBE value of 1.4–1.8 compared to 1.0 for high energy photons). Based on to the inverse square law, the penetration (percentage of depth dose) is higher using contact X-ray than for high dose-rate brachytherapy.

**Table I.** Biologically effective doses (BED) estimated for the combined CONVentional with HYPOfractionated regimen (CONV-HYPO) for rectal cancer as tolerance doses (using α/β value = 6 Gy)

| STEP | CONV Fx schedule | BED CONV Fx | HYPO Fx schedule | BED HYPO Fx | HYPO Fx BED relative to 15 × 2 Gy (1.0) | TOTAL BED |
|---|---|---|---|---|---|---|
| I | 45–50 Gy/25 fx | 61.2–70 izoGy | 3 × 8 Gy | 78 izoGy | 1.9 | 139.2–148 izoGy |
| II | –II– | –II– | 3 × 10 Gy | 90 izoGy | 2.1 | 151–160 izoGy |
| III | –II– | –II– | 3 × 12 Gy | 122.4 izoGy | 2.9 | 183.6–192 izoGy |

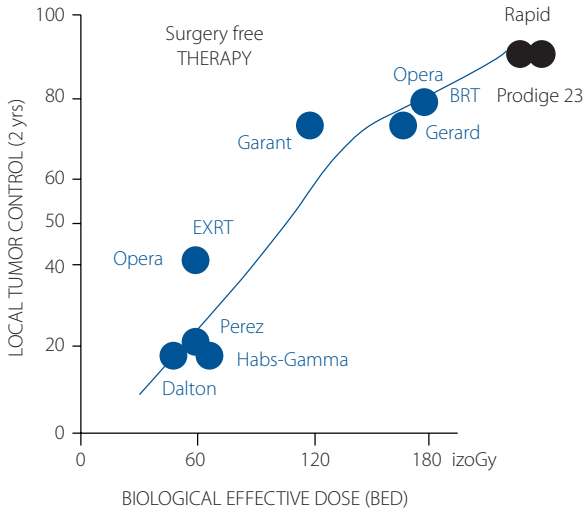


**Figure 4.** LTC-DOSE escalation relationship for the combined conventional with HYPO fractionated regimen (CONV-HYPO ± chemotherapy) for surgery – free rectal cancer (adapted from Gerard et al. [15]), the EQD doses calculated by Appelt [19] are converted into biologically effective dose (BED) using α/β value of 6 Gy; BRT — brachytherapy; EXRT — external irradiation

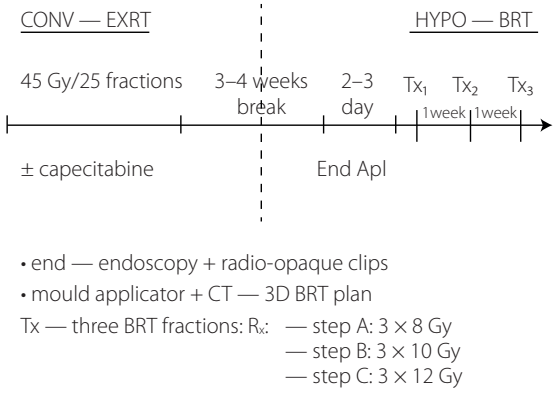


**Figure 5.** Work flow of CONVentional with HYPOfractionated regimen brachytherapy [CONV-HYPO (BRT)] — Gliwice protocol for surgery-free therapy of rectal cancer patients; CT — computed tomography; EXRT — external irradiation

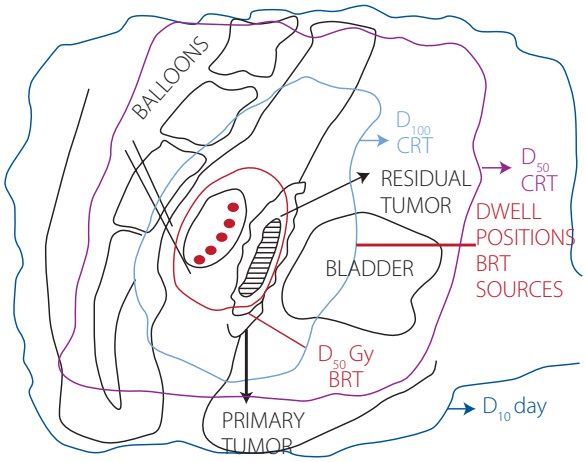


**Figure 6.** Example of dose distribution of the CONVentional (CONV) combined with high-dose HYPOfractionated brachytherapy (HYPO BRT) planned by Kraszkiewicz and Wojcieszek for local rectal cancer. The step 2–10 Gy is planned for BRT; CRT — conventional RT

The Papillon 50 kV therapy is limited to $T_1$, $T_{2-3}$ $N_0$ tumors (≤ 4 cm in diameter) localized in the distal and middle part of the rectum, which must be accessible to the rectal application of the X-ray tube. Contact X-ray therapy has sometimes been given first, followed by chemoradiation (with Capecitabine) and provided the 3–5 year local tumor control (Fig. 4) and overall survival close to 85% [15, 17].

Alternative to the Papillon 50 kV is a high-dose rate endorectal brachytherapy (HDR BRT) with the use of high quality imaging for tumor visualization, and the 3D-treatment conformal planning [19–21]. Since 2005, due to the development of the intracavitary mould applicator (Nucletron), the HYPO-HDR BRT (high dose brachytherapy) has become a useful alternative to contact 50 kV therapy. By contrast with HYPO — 50 kV technique with the planned dose on the tumor surface, decreasing along with the tumor depth, in the HDR BRT the planned dose is estimated for the bottom-baseline of the tumor which increases towards its surface. Treatment planning and dose delivery is realized using the intracavitary mould applicator and a microselection remote after-loading device (Nucletron) using to real-time implementation of the 192Ir (Iridium-192) sources.

The first part of the HYPO-BRT starts 3–4 weeks after completing the delivery of 45–50 Gy of the CONV external irradiation, and consists of the radio-opaque clips inserted to the tumor during endoscopy to marks and visualize tumor position (Fig. 5). After 2–3 days, mould applicator with two balloons are inserted to the rectum under-mild intravenous anesthesia. When the device is in the desired position, the balloons are inflated with water to immobilize the applicator. The ipsilateral balloon flattens the tumor to receive the planned dose distribution within the defined GTV, whereas the contralateral one displaces normal rectal mucosa opposite to the tumor [20]. According to the old Manchester-McComb and Quimby law, the ipsilateral balloon also improves homogenous dose distribution within the tumor GTV.

Once the applicator is immobilized, serial computed tomography (CT)-based HDR BRT treatment planning is carried out using 3D dose calculation (PLATO system) for the tumor GTV based on serial CT images. For treatment planning, only dwell positions in catheters proximal to the tumor are selected. The PLATO *"real time"* planning system also provides an option to plan optimal dose distribution, highly conformal to the target volume, with a proper sparing of the surrounding critical normal structures. When a satisfactory plan is confirmed (Fig. 6 and 7), the central tungsten shield is placed before the start of the treatment. This original technique designed by Te Vuong [20] is adapted by Kraszkiewicz and Wojcieszek to realize

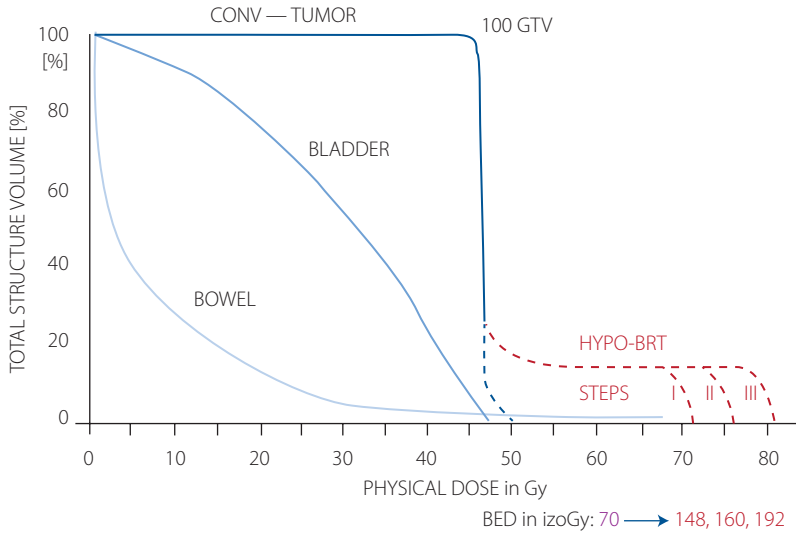


**Figure 7.** Cumulative dose volume histogram for combined CONVentional with HYPOfractionated regimen (CONV-HYPO) planning example shown on Figure 5; BED — biologically effective dose; BRT — brachytherapy

in Gliwice the three-step- treatment-protocol for $T_2$–$T_3$ $N_0$ rectal cancer. To optimize the size of high dose fraction, in the first step 3 fractions of 8 Gy are planned. If such schedule will be well tolerated, then the patients will be recruited to the second step using 3 × 10 Gy, and finally if it will also be well tolerated then the third step with 3 × 12 Gy is planned. The respective BED doses are shown in Table I. Since the tumor regression progressed slowly, diagnostic biopsy can be performed not sooner than six months after completing treatment.

The CONV-HYPO therapy used to treat rectal cancer is just an example of an wide spectrum of the use this approach including other tumor types and localization as lung, esophageal, head and neck cancers and soft tissue sarcomas, with or without concurrent chemotherapy, as a sole or postoperative therapy to improve long term local control and disease free survival. Therefore, there is no longer radiobiological and clinical arguments to continue and escalate conventionally fractionated radiotherapy, since for years it has not resulted in a pronounced improvement of the long-term efficacy so far. It seems reliable that this traditional fractionation should no longer be continued, even for palliative radiotherapy.

## Article information and declarations

### *Authors contributions*

Bogusław Maciejewski — conceptualization, methodology, writing – original draft preparation, writing — review & editing.
Małgorzata Kraszkiewicz — conceptualization, writing — original draft preparation.
Piotr Wojcierszek — data correction, methodology, writing — original draft preparation.
Jean-Pierre Gerard — conceptualization, validation, writing — review & editing.


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**Bogusław Maciejewski**
*Department of Radiotherapy*
*Maria Skłodowska-Curie National Research Institute of Oncology*
*Wybrzeże Armii Krajowej 15*
*44–102 Gliwice, Poland*
*e-mail: boguslaw.maciejewski@gliwice.nio.gov.pl*



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## References


1. Maciejewski B, Withers HR, Taylor JM, et al. Dose fractionation and regeneration in radiotherapy for cancer of the oral cavity and oropharynx: tumor dose-response and repopulation. Int J Radiat Oncol Biol Phys. 1989; 16(3): 831–843, doi:10.1016/0360-3016(89)90503-8, indexed in Pubmed: 2921175.
2. Bourhis J, Audry H, Overgaard J, et al. Meta-analysis of conventional versus altered fractionated radiotherapy in head and neck squamous cell carcinoma (HNSCC): Final analysis. Int J Radiat Oncol Biol Phys. 2004; 60: S190–S191, doi: 10.1016/s0360-3016(04)01183-6.
3. Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. Chest. 2003; 124(5): 1946–1955, doi: 10.1378/chest.124.5.1946, indexed in Pubmed: 14605072.

4. Flickinger JC, Nirjah A. Stereotactic radiosurgery and radiotherapy. In: Nirjah A. ed. Perez and Brady's Principle and Practice of Radiation Oncology. Lippincott Williams and Williams, Philadelphia : 351–361.
5. Ang KK, Trotti A, Brown BW, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2001; 51(3): 571–578, doi: 10.1016/s0360-3016(01)01690-x, indexed in Pubmed: 11597795.
6. Dale RG. The radiobiology of Papillon-type treatments. Clin Oncol (R Coll Radiol). 2007; 19(9): 649–654, doi: 10.1016/j.clon.2007.07.010, indexed in Pubmed: 17709233.
7. Fowler J. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol. 2014; 62(740): 679–694, doi: 10.1259/0007-1285-62-740-679, indexed in Pubmed: 2670032.
8. Joiner MC, Bentzen SM. Fractionation: the linear-quadratic approach. In: Bentzen SM. ed. Joiner and van der Kogel Basic Clinical Radiobiology. IV ed. Hodder-Arnold 2009: 102–119.
9. Papillon J. Intracavitary irradiation of early rectal cancer for cureA series of 186 cases. Cancer. 1975; 36(S2): 696–701, doi: 10.1002/1097-0142(197508)36:2+<696::aid-cncr2820360813>3.0.co;2-x, indexed in Pubmed: 1157030.
10. Gérard JP, Myint AS, Croce O, et al. Renaissance of contact x-ray therapy for treating rectal cancer. Expert Rev Med Devices. 2011; 8(4): 483–492, doi: 10.1586/erd.11.28, indexed in Pubmed: 21728733.
11. Gerard JP, Chapet O, Ramaioli A, et al. Long-term control of T2-T3 rectal adenocarcinoma with radiotherapy alone. Int J Radiat Oncol Biol Phys. 2002; 54(1): 142–149, doi: 10.1016/s0360-3016(02)02879-1, indexed in Pubmed: 12182984.
12. Gerard JP, Chapet O, Nemoz C, et al. Improved sphincter preservation in low rectal cancer with high-dose preoperative radiotherapy: the lyon R96-02 randomized trial. J Clin Oncol. 2004; 22(12): 2404–2409, doi: 10.1200/JCO.2004.08.170, indexed in Pubmed: 15197202.
13. Gérard JP, Barbet N, Gal J, et al. Planned organ preservation for early T2-3 rectal adenocarcinoma: A French, multicentre study. Eur J Cancer. 2019; 108: 1–16, doi: 10.1016/j.ejca.2018.11.022, indexed in Pubmed: 30560125.
14. Gérard JP, Barbet N, Dejean C, et al. Contact X-ray brachytherapy for rectal cancer: Past, present, and future. Cancer Radiother. 2021; 25(8): 795–800, doi: 10.1016/j.canrad.2021.04.006, indexed in Pubmed: 34052134.
15. Gerard JP, Frin AC, Doyen J, et al. Organ preservation in rectal adenocarcinoma (T1) T2-T3 Nx M0. Historical overview of the Lyon Sud - nice experience using contact x-ray brachytherapy and external beam radiotherapy for 120 patients. Acta Oncol. 2015; 54(4): 545–551, doi: 10.3109/0284186X.2014.975840, indexed in Pubmed: 25389568.
16. Gerard JP, Myint AS, Barbet N, et al. Targeted Radiotherapy Using Contact X-ray Brachytherapy 50 kV. Cancers (Basel). 2022; 14(5), doi: 10.3390/cancers14051313, indexed in Pubmed: 35267621.
17. Sun Myint A, Stewart A, Mills J, et al. UK Papillon team. Treatment: the role of contact X-ray brachytherapy (Papillon) in the management of early rectal cancer. Colorectal Dis. 2019; 21 Suppl 1: 45–52, doi: 10.1111/codi.14507, indexed in Pubmed: 30809905.
18. Stewart AJ, Van Limbergen EJ, Gerard JP, et al. GEC ESTRO ACROP consensus recommendations for contact brachytherapy for rectal cancer. Clin Transl Radiat Oncol. 2022; 33: 15–22, doi: 10.1016/j.ctro.2021.12.004, indexed in Pubmed: 35243017.
19. Appelt AL, Pløen J, Vogelius IR, et al. Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. Int J Radiat Oncol Biol Phys. 2013; 85(1): 74–80, doi: 10.1016/j.ijrobp.2012.05.017, indexed in Pubmed: 22763027.
20. Vuong Te, Garant A, Vendrely V, et al. Image-Guided Brachytherapy for Rectal Cancer: Reviewing the Past Two Decades of Clinical Investigation. Cancers (Basel). 2022; 14(19), doi: 10.3390/cancers14194846, indexed in Pubmed: 36230770.
21. Cheng T, Peng R, Qu A, et al. High-dose rate endorectal brachytherapy for rectal cancer: A state-of-the-art review. Cancer Sci. 2023; 114(11): 4145–4156, doi: 10.1111/cas.15959, indexed in Pubmed: 37702196.

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Review article

Liver tumors

# New targeted therapies used in the treatment of patients with advanced cholangiocarcinoma

Aleksandra Śnios[1], Natalia Ziaja[1], Maksymilian Kruczała[2, 3]

[1]*Student, Medical College of Rzeszow University, Poland*
[2]*Department of Oncology, Radiotherapy and Translational Medicine, Institute of Medical Sciences, Medical College of Rzeszow University, Poland*
[3]*Mrukmed Medical Center in Rzeszow, Poland*

Cholangiocarcinoma (CC) is a rare yet exceptionally aggressive malignancy originating from the epithelium of the bile ducts. At the time of diagnosis, most patients are already in an advanced stage of the disease and qualify only for palliative treatment. Despite advances in oncological treatment, the prognosis for patients with advanced CC remains poor. Recently, several new molecularly targeted drugs have been developed, and their use may improve the prognosis for these patients. This article presents information about new molecules used in the treatment of patients with advanced CC: pemigatinib, futibatinib, and ivosidenib.

**Keywords:** cholangiocarcinoma, molecularly targeted therapy

## Introduction

Cholangiocarcinoma (CC), also known as bile duct cancer, is a rare but exceptionally aggressive malignancy originating from the epithelium of the bile ducts. The incidence of CC in developed countries appears to be increasing [1]. The only method that offers a chance of curing the patient is surgical intervention; however, at the time of diagnosis, most patients are already ineligible for surgery. The standard first line chemotherapy for palliative treatment of bile duct cancer is gemcitabine combined with cisplatin [2]. Second-line treatment options are limited, with the FOLFOX regimen usually applied, which only slightly improves the prognosis when compared to symptomatic treatment alone. In patients with bile duct cancer, genomic profiling has led to the discovery of several potentially oncogenic alterations, including those in genes coding the fibroblast growth factor receptor (FGFR).

Fibroblast growth factor receptor alterations can lead to erratic FGFR signalling, driving oncogenesis through increased cell proliferation, migration, survival and invasion [3]. Fibroblast growth factor receptor 2 mutations are found almost only in intrahepatic bile duct cancer, occurring in less than 20% of patients [4–6]. Therefore, FGFR inhibitors appear promising for the treatment of bile duct cancer patients. Another potential therapeutic target in bile duct cancer is the mutated isocitrate dehydrogenase 1 (mIDH1). This article presents the results of studies on new molecularly targeted drugs used in the treatment of patients with advanced bile duct cancer.

## Pemigatynib

Pemigatinib is a selective oral inhibitor of FGFR1-3. In a phase 2 study (FIGHT-202) [7], adult patients with advanced CC, who had disease progression after one or more lines of therapy and had FGFR2 mutations, or no FGF/FGFR alterations, received pemigatinib until progression of the disease or unacceptable treatment toxicity [7]. The primary study endpoint was the objective response rate (ORR) [7].

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Among 107 patients with FGFR2 mutations, 38 achieved an objective response. Three patients had a complete response (CR) and 35 had a partial response (PR) [7]. Disease control was achieved in 88 out of 107 patients. The median duration of response among responders was 7.5 months. The median progression-free survival (PFS) was 6.9 months [7]. Objective responses in patients with FGFR2 fusions or rearrangements were observed across all assessed subgroups, and the median PFS was generally similar.

The most common adverse event of any grade, regardless of causality, was hyperphosphatemia (reported in 88 out of 146 patients). Grade 3 or 4 adverse events occurred in 93 (64%) patients and included hyperphosphatemia, arthralgia, stomatitis, hyponatremia, abdominal pain and fatigue. Overall, there were 71 deaths, most commonly due to progression of the disease. No deaths related to pemigatynib were considered [7].

The introduction of FGFR inhibitors represents a significant advancement in treatment options. However, despite the presence of FGFR2 fusions or rearrangements, the duration of response and PFS were short for some patients. New research suggests that the short duration of response in these patients may be due to clonal evolution leading to acquired resistance mutations during FGFR inhibitor treatment [8]. Currently, pemigatinib is approved for previously treated patients with advanced CC with FGFR2 fusions/rearrangements in the USA (FDA) [9] and the European Union (EMEA).

## Futibatinib

Futibatinib is a next-generation inhibitor of FGFR1–4. In a phase 2 study, the efficacy of the drug was evaluated in individuals with advanced CC with disease progression after previous systemic therapy and with FGFR2 alterations (fusions or rearrangements) [10]. Futibatinib was administered continuously to 103 patients at a dose of 20 mg orally. The primary endpoint of the study was the response to treatment (partial or complete), with secondary endpoints including duration of response, PFS and overall survival (OS).

Treatment response was observed in 43 patients [42%; 95% confidence interval (CI) 32–52) with an almost 10 month median duration response. After a median follow-up period of 17 months, the median PFS was 9 months, and the median OS was 21.7 months [10]. The most common grade 3 adverse events were hyperphosphatemia, elevated liver enzymes, stomatitis and fatigue. Treatment was discontinued due to adverse events in 2% of patients, and no treatment-related deaths were reported. Futibatinib has been approved by the FDA and EMEA for previously treated patients with advanced intrahepatic bile duct cancer with FGFR2 fusions or rearrangements.

## Ivosidenib

In the ClarIDHy study [11], the efficacy and safety of ivosidenib, the first-in-class mIDH1 inhibitor, were evaluated. A total of 187 patients with previously treated advanced CC with an *IDH1* mutation were randomly assigned (2:1) to receive either ivosidenib or a placebo. The primary endpoint of the study was PFS, with secondary endpoints including OS, ORR, safety, quality of life. Upon disease progression, 70% of patients in the placebo group crossed over to the ivosidenib arm. The study demonstrated a significant benefit in PFS [hazard ratio (HR) = 0.37; $p < 0.0001$] and an ORR of 2.4% (3 PR) and 50.8% (63 stable disease) in the ivosidenib group compared to 0% and 27.9% (17 stable disease) in the placebo group. The drug was well-tolerated, with the most common adverse events being nausea, diarrhoea, fatigue, anaemia, and constipation. No treatment-related deaths were reported. Ivosidenib has been approved by the FDA and EMEA for previously treated patients with advanced CC harbouring the *IDH1* R132 mutation.

## Summary

Cholangiocarcinoma remains a disease with a poor prognosis, and until recently, there were virtually no further treatment options after progression on cisplatin and gemcitabine chemotherapy. In recent years, three new targeted therapies have been registered for this indication: pemigatinib, futibatinib and ivosidenib. Compared to purely symptomatic treatment, these represent a significant advance; however, they have several limitations. It is important to remember that the use of these drugs is limited to patients with specific genetic alterations. Additionally, even when a response to treatment is achieved, the median time to disease progression is measured in months. The very significant cost of these therapies should also be noted. An undeniable advantage of these drugs is their relatively good tolerance and lack of negative impact on quality of life, which, considering their proven efficacy, makes them meet the fundamental goals of palliative treatment. Currently, none of the discussed drugs are reimbursed in Poland. In cases of disease progression after standard treatment and identification of a mutation justifying targeted therapy, individual applications must be submitted to the National Health Fund.

## Article information and declarations

### Authors contributions

Aleksandra Śnios — writing, conceptualization.
Natalia Ziaja — writing, conceptualization.
Maksymilian Kruczała — writing, conceptualization.


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The authors declare no conflict of interest.

## Supplementary material

None.

**Aleksandra Śnios**
*Faculty of Medicine*
*Medical College of Rzeszow University*
*Warzywna 1a*
*35–310 Rzeszów, Poland*
*e-mail: aleksandra.snios@gmail.com*

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## References

1. Bergquist A, von Seth E. Epidemiology of cholangiocarcinoma. Best Pract Res Clin Gastroenterol. 2015; 29(2): 221–232, doi: 10.1016/j.bpg.2015.02.003, indexed in Pubmed: 25966423.
2. Valle J, Wasan H, Palmer DH, et al. ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010; 362(14): 1273–1281, doi: 10.1056/NEJMoa0908721, indexed in Pubmed: 20375404.
3. Babina IS, Turner NC. Advances and challenges in targeting FGFR signalling in cancer. Nat Rev Cancer. 2017; 17(5): 318–332, doi: 10.1038/nrc.2017.8, indexed in Pubmed: 28303906.
4. Farshidfar F, Zheng S, Gingras MC, et al. Cancer Genome Atlas Network, Cancer Genome Atlas Network. Integrative Genomic Analysis of Cholangiocarcinoma Identifies Distinct IDH-Mutant Molecular Profiles. Cell Rep. 2017; 18(11): 2780–2794, doi: 10.1016/j.celrep.2017.02.033, indexed in Pubmed: 28297679.
5. Ross JS, Wang K, Gay L, et al. New routes to targeted therapy of intrahepatic cholangiocarcinomas revealed by next-generation sequencing. Oncologist. 2014; 19(3): 235–242, doi: 10.1634/theoncologist.2013-0352, indexed in Pubmed: 24563076.
6. Graham RP, Barr Fritcher EG, Pestova E, et al. Fibroblast growth factor receptor 2 translocations in intrahepatic cholangiocarcinoma. Hum Pathol. 2014; 45(8): 1630–1638, doi: 10.1016/j.humpath.2014.03.014, indexed in Pubmed: 24837095.
7. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol. 2020; 21(5): 671–684, doi: 10.1016/S1470-2045(20)30109-1, indexed in Pubmed: 32203698.
8. Goyal L, Saha SK, Liu LY, et al. Polyclonal Secondary Mutations Drive Acquired Resistance to FGFR Inhibition in Patients with FGFR2 Fusion-Positive Cholangiocarcinoma. Cancer Discov. 2017; 7(3): 252–263, doi: 10.1158/2159-8290.CD-16-1000, indexed in Pubmed: 28034880.
9. Patel TH, Marcus L, Horiba MN, et al. FDA Approval Summary: Pemigatinib for Previously Treated, Unresectable Locally Advanced or Metastatic Cholangiocarcinoma with FGFR2 Fusion or Other Rearrangement. Clin Cancer Res. 2023; 29(5): 838–842, doi: 10.1158/1078-0432.CCR-22-2036, indexed in Pubmed: 36206041.
10. Goyal L, Meric-Bernstam F, Hollebecque A, et al. FOENIX-CCA2 Study Investigators. Futibatinib for -Rearranged Intrahepatic Cholangiocarcinoma. N Engl J Med. 2023; 388(3): 228–239, doi: 10.1056/NEJMoa2206834, indexed in Pubmed: 36652354.
11. Zhu A, Macarulla T, Javle M, et al. Final results from ClarIDHy, a global, phase III, randomized, double-blind study of ivosidenib (IVO) versus placebo (PBO) in patients (pts) with previously treated cholangiocarcinoma (CCA) and an isocitrate dehydrogenase 1 (*IDH1*) mutation. J Clin Oncol. 2021; 39(3_suppl): 266–266, doi: 10.1200/jco.2021.39.3_suppl.266.

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# The positive significance of skin complications after immunotherapy

Aneta Podczerwińska[1, 2], Clara Kuzminski[2, 3], Marek Ziobro[2], Aleksandra Grela-Wojewoda[2]

[1]*Specialist Hospital named after Stefan Żeromski, Kraków, Poland*
[2]*National Cancer Institute, Maria Skłodowska-Curie Memorial Institute, Kraków, Poland*
[3]*Independent Public Healthcare Team in Brzesko, Poland*

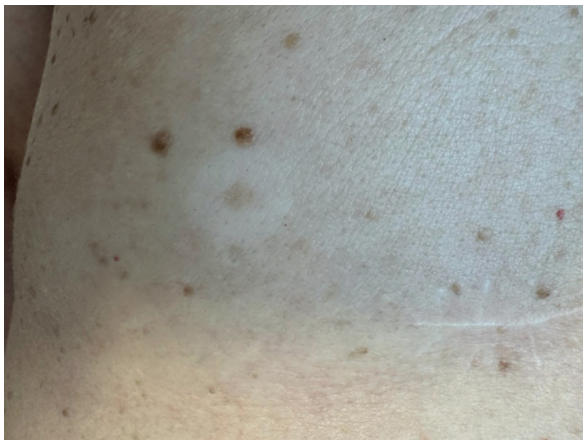

**Figure 1.** Vitiligo-like lesions caused by immunotherapy in a patient with advanced melanoma

Immunotherapy with PD-1 inhibitors, such as checkpoint inhibitors targeting the programmed cell death 1 receptor (PD-1), is one of the main systemic treatments for metastatic melanoma. The axis of PD-1 and its ligand, PD-L1, acts as a negative regulator of the immune response, preventing autoimmune reactions by inhibiting T-cell proliferation, activation, and functional efficacy [1]. The immune-related side effects of PD-1 inhibitors include, among others, skin reactions [2]. We present the case of a 62-year-old woman with malignant melanoma of the torso (with a current BRAF gene mutation in codon V600). In 2017, she underwent primary lesion removal with wide margins and sentinel lymph node excision. Three years later, she underwent lymphadenectomy of the right axillary lymph node metastasis. She also received the BRAF/MEK inhibitors due to mediastinal lymph node metastasis, which resulted in disease progression. Immunotherapy with a PD-1 inhibitor, nivolumab, led to improvement. Based on the improvement and at the patient's request, a decision was made to discontinue treatment in October 2021. The patient has been regularly monitored without tumor progression. In 2023, 2 years after treatment discontinuation, she developed vitiligo patches on the skin (Fig. 1). The appearance of secondary vitiligo patches two years after discontinuing immunotherapy indicates that heightened immune activation has been maintained. From the perspective of treating the underlying disease, this is a favorable sign, indicating the continued efficacy of the therapy [2].

## References

1. Eddy K, Chen S. Overcoming Immune Evasion in Melanoma. Int J Mol Sci. 2020; 21(23), doi: 10.3390/ijms21238984, indexed in Pubmed: 33256089.
2. Simeone E, Grimaldi AM, Festino L, et al. Immunotherapy in metastatic melanoma: a novel scenario of new toxicities and their management. Melanoma Manag. 2019; 6(4): MMT30, doi: 10.2217/mmt-2019-0005, indexed in Pubmed: 31871619.

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# Breast cancer 3 years after a contralateral risk reduction mastectomy

Wojciech Figurny, Maciej Łukaszek, Mateusz Wichtowski

*Univeristy Hospital in Poznan, Poland*

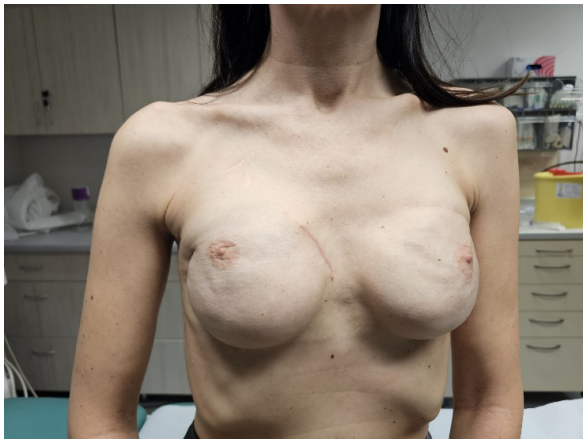

**Figure 1.** Operation

A 37-year old BRCA1-positive woman was diagnosed during follow-up with a subsequent contra-lateral breast cancer 3 years after undergoing treatment for left-sided breast cancer T2N0M0 [no special type (NST) with 30% estrogen receptor (ER); 0% progesterone receptor (PgR); human epidermal growth factor receptor 2 (HER-2) negative; Ki-67 of 70%]. The previous treatment was neoadjuvant chemotherapy followed by a 2-stage bilateral nipple-sparing mastectomy with subpectoral reconstruction with additional lower pole coverage with the use of a mesh, left sentinel node biopsy, with adjuvant endocrine therapy.

The secondary lesion was diagnosed during follow-up. The tumor location was the upper-inner quadrant of the right breast in the residual-glandular tissue, with no involvement of the pectoralis muscle in the magnetic resonance imaging (MRI). A core needle biopsy was performed resulting in a cancer diagnosis — NST, grade 3, now with a profile of 85% ER; PgR < 1%; HER-2 negative; Ki-67 of 80%.

The surgical approach was to perform a wide local excision of the tumor with a sentinel lymph node biopsy. Due to the tumor location above the pectoralis muscle, enough margin of healthy tissue was present to not damage the breast implant or its capsule. Final staging for the right-side breast cancer was pT1cpN0M0, with an acceptable cosmetic outcome (Fig. 1). Subsequent treatment was radiotherapy and further endocrine therapy.

Residual glandular tissue is identified in 6–76.2% of breasts after mastectomy [1]. Based on the literature, the risk of developing breast cancer after risk-reduction mastectomy is low — in the cohort cited below [2] there was no breast cancer case in the risk-reduction mastectomy arm of the study, yet the authors point out a median follow-up of 3 years.

This case shows the need for a careful follow-up after mastectomy with annual MRI screening in high-risk patients with a thorough examination of the residual glandular tissue.

## References

1. Dietzel F, Kolberg L, Vesper AS, et al. Factors Influencing Residual Glandular Breast Tissue after Risk-Reducing Mastectomy in Genetically Predisposed Individuals Detected by MRI Mammography. Cancers (Basel). 2023; 15(3), doi: 10.3390/cancers15030829, indexed in Pubmed: 36765786.
2. Jakub JW, Peled AW, Gray RJ, et al. Oncologic Safety of Prophylactic Nipple-Sparing Mastectomy in a Population With BRCA Mutations: A Multi-institutional Study. JAMA Surg. 2018; 153(2): 123–129, doi: 10.1001/jamasurg.2017.3422, indexed in Pubmed: 28903167.

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