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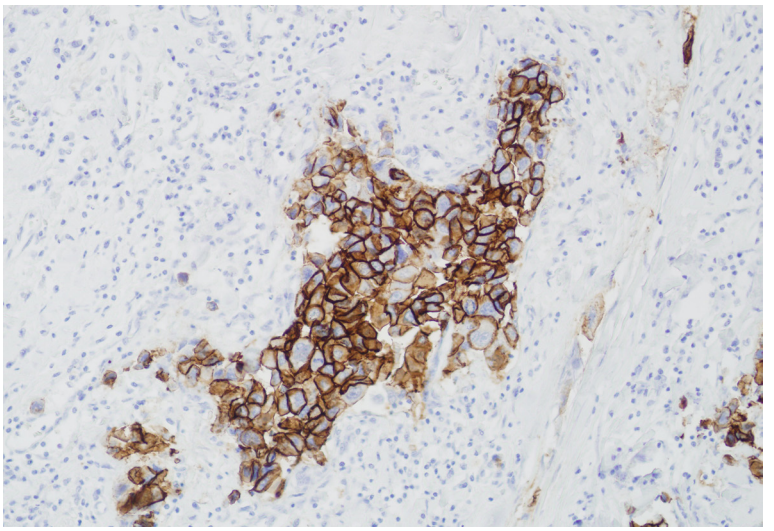

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Address for correspondence:
Krakowska Akademia im. Andrzeja Frycza-Modrzewskiego
ul. Gustawa Herlinga-Grudzińskiego 1
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Cover photo: Invasive breast carcinoma with apocrine differentiation; immunohistochemistry – strong, positive HER2 staining. Magnification 200x. Courtesy of Joanna Wysocka.

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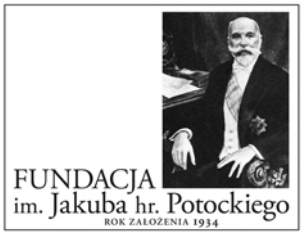

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Low platelet to lymphocyte ratio and high platelet distribution width have an inferior outcome in chronic lymphocytic leukaemia patients

Shaimaa El-Ashwah[1], May Denewer[1], Nermeen A. Niazy[2], Metwaly I. Mortada[3], Emad Azmy[1]

[1]*Clinical Hematology Unit, internal Medicine Department, Oncology Center, Mansoura University, Mansoura, Egypt*
[2]*Public Health and Community Medicine, Faculty of Medicine, Mansoura University, Mansoura, Egypt*
[3]*Hematology Unit, Clinical Pathology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt*

Introduction. Chronic lymphocytic leukaemia (CLL) is an incurable disease of the elderly, characterised by gradual accumulation of small mature B lymphocytes which escape apoptosis through inflammatory signals from the microenvironment. Elevated inflammatory markers are associated with very poor prognosis in different types of cancer. Therefore, we examined retrospectively the impact of platelet lymphocyte ratio (PLR) and platelet distribution width (PDW) on 180 CLL patients' outcome.

Materials and methods. This retrospective study included 180 patients with CLL who were diagnosed and selected among cases referred to the Oncology Center Mansoura University between January 1st, 2008 and June 30th, 2016. All the relevant information was collected from the electronic medical records of the selected patients.

Results. Our results revealed that low PLR (<2.5) was more frequently observed in patients with stage C ($p < 0.001$), with 17p deletion ($p = 0.017$), and CD38 expression ($p = 0.08$), but not with seropositive HCV patients ($p = 0.2$). High PDW (≥18.5 fl) was more frequently associated with intention to treat population ($p = 0.038$), and CD38 expression ($p = 0.068$), but not with 17p deletion ($p = 0.25$) and seropositive HCV patients ($p = 0.4$). Multivariate analysis for overall survival showed that stage A and low PDW were independent factors for overall survival ($p = 0.014$ and 0.04 respectively), while high PLR ($p = 0.05$), and seronegative HCV patients ($p = 0.1$) lost their significance.

Conclusion. Our data showed that low PLR and high PDW were associated with poor prognostic markers. Stage C-CLL and high PDW were independent predictors of survival.

Key words: chronic lymphocytic leukaemia, platelet distribution width, platelet-to-lymphocyte ratio

Introduction

Chronic lymphocytic leukaemia (CLL) is an incurable disease that is characterized by gradual accumulation of small mature B lymphocytes [1]. These lymphocytes are dormant replicational cells that accumulate in the marrow and peripheral blood, due to extrinsic survival signals from the microenvironment [2].

These leukaemic lymphocytes can resist apoptosis by inflammatory signals compared to normal B lymphocytes. Actually, CLL patients present with manifestations that typically occur in chronic inflammatory disorders which make the role of inflammation clear [3]. Thrombocytopenia in CLL patients caused by either bone marrow infiltration, immune thrombocytopenia, hypersplenism, or myelosuppression secondary to cytotoxic

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therapy or infection [4]. PLR is a novel inflammatory marker that can be applied in many diseases for predicting inflammation, and PDW represents the platelet anisocytosis and is calculated from the distribution of individual platelet volumes [5].

Further, platelet-to-lymphocyte ratio (PLR) finds its role in CLL that the lymphocyte and platelet counts are correlated to the pathogenesis of CLL directly and affect management of patients. Also, PDW does not assess heterogeneity of platelet volume only, but also platelet activity [6]. Many studies have shown that these two inflammatory biomarkers (PLR and PDW) are considered prognostic factors for some non-haematological tumours [5].

To our knowledge, PDW has not been studied in CLL. So, in our study, we aimed at investigating the role of PLR and PDW in our CLL patients.

Materials and methods

Subjects

This retrospective study included 180 patients with CLL who were diagnosed and selected among cases referred to the Oncology Center Mansoura University (OCMU) between January 1th, 2008 and June 30th, 2016. All the relevant information was obtained through the electronic medical records of the selected patients. All laboratory procedures were performed in the clinical pathology labs of OCMU. The Binet staging system was used to classify the CLL patients:

- Binet stage A: <3 areas of lymphoid tissue are enlarged, with no anaemia or thrombocytopenia.
- Binet stage B: ≥3 areas of lymphoid tissue are enlarged, with no anaemia or thrombocytopenia.
- Binet stage C: anaemia (<10 g/dL) and/or thrombocytopenia (<100 × 10^9/L) are present. Any number of lymphoid tissue areas may be enlarged.

They were treated according to our institute guidelines based on performance statue by purine based regimen or alkylators. As far as we know, patients with immune-related cytopenia or infection were excluded from our study.

Patient evaluation

Detailed history taking and clinical examination. Laboratory investigations:

1. Routine work:

- Complete blood count (haemogram): using the electronic counter (CELL-DYN 3700, Abbott, Canada), PDW and PLR were obtained, before any treatment, including PDW (fl), the lymphocyte count (k/uL) and platelet count (k/uL). We calculated the PLR by dividing the absolute count of platelets to that of lymphocytes at diagnosis with thorough examination of peripheral blood smears stained with Leishman stain.
- Liver function tests, serum creatinine, serum uric acid, and serum LDH.
- Virology screen (HCV, HBsAg, HIV): HCV Ab was detected using Murex HCV Ag/Ab Combination 4th generation ELISA kit # 4J2453 Anti-Core monoclonal antibody, recombinant antigen and peptides representing the immunodominant regions of NS3 and core. Simultaneously, the Bioelisa ELISA kit was used for detection of Hepatitis B surface antigen (HBsAg). Genscreen™ ULTRA HIV Ag-Ab. The Genscreen™ ULTRA HIV Ag-Ab is a qualitative enzyme immunoassay kit for the detection of HIV p24 antigen and antibodies to HIV-1 (groups M and O) and HIV-2 in human serum or plasma.

2. Work up for CLL diagnosis:

- Microscopic study of bone marrow and peripheral smears.
- Immunophenotyping (IPT) using American (BD FACSCAN-TOII) to diagnose the cases and exclude other types of lymphoma by incubation of washed cells from peripheral blood or bone marrow samples with fluorescein-labelled monoclonal antibody including scoring system of CLL (CD5, CD19,CD23,CD79b,sIgM,CD38), kappa and lambda. Positivity in each marker can be calculated if it is more than 20%.
- FISH for detection of 17p deletion. Interphase FISH technique was conducted on peripheral blood or bone marrow aspiration and trephine. Using the Olympus BX 61, fluorescent microscope. Interphase FISH technique was performed on samples after optimization of the protocol using commercially available probe from Cytocell UK LPH TP53 deletion FISH Probe Kit.

Statistical analysis

Data were analysed on a personal computer running SPSS© for Windows (Statistical Package for Social Scientists) Release 18. A two-tailed p value of >0.05 was considered statistically significant. For descriptive statistics of qualitative variables, the frequency distribution procedure was run with calculation of the number of cases and percentages. For descriptive statistics of quantitative variables, the median and range were used. Association between categorical variables was tested by the Chi Square Test or Fishers exact test. The independent- samples t-test was used to compare the means between two groups. Time to treat was defined as the time from diagnosis until the start of chemotherapy or death. Overall survival was calculated by the Kaplan-Meier Product-Limit Estimator. Comparison of the survival was performed by the Log-Rank Test. Exploring variables for their independent prognostic effect on survival was carried out using the multivariate stepwise Cox's proportional regression hazard model.

Results

The 180 CLL patients were (101 M; 79 F) with mean age 60.27 ± 11.49 years. The incidence of chronic HCV infection and HBV in our study were 38.3% and 3.9% respectively. At diagnosis, the median PLR was 2.5 (range 0.07–42), platelets 138.5 k/µL (range 5–459 k/µL), and the median PDW was 18.5 (range 15.6–24.9). Basic data are illustrated in table I.

Table I. Basic data of studied cases

Character	Value	Percentage
Male/female	101/79	56.1%/43.9%
HCV positive	69	38.3%
HBV positive	7	3.9%
B symptoms – present	107	59%
	Median	**Range**
WBC (k/uL)	61.85	8–960
ALC (k/uL)	52.5	6–900
HB (g/dl)	11	4.3–16.2
Platelet (k/uL)	138.5	5–459
PLR	2.5	0.07–42
PDW	18.5	15.6–24.9
Stage	**Number**	**%**
A	3	1.7%
B	94	52.2%
C	83	46.1%
Prognostic markers		
17p deletion positive (n = 35)	5	14.28%
CD38 positive (n = 93)	33	35.48%
ZAP-70 positive (n = 30)	18	60%
PLR	**Value**	**No (%)**
Low PLR	<2.5	86 (47.8%)
High PLR	≥2.5	94 (52.2%)
PDW		**No (%)**
Low PDW	<18.5 fl	82 (45.6%)
High PDW	≥18.5 fl	98 (54.4%)
Intention to treat – population	**138**	**76.7%**
Treatment protocol	**No**	**%**
Wait and watch	19	10.6%
Purine based	53	29.4%
Alkylators based	108	60%
Status (alive/dead)	115/65	63.9%/36.1%

Low PLR (<2.5) was more frequently observed in male patients (p = 0.06) with stage C (p < 0.001), with 17p deletion (p = 0.017), and CD38 expression (p = 0.08) and intention to treat (p < 0.001), but not with HCV seropositive patients (p = 0.22) and ZAP-70 positivity (p = 0.28) (table II).

High PDW (≥18.5 fl) was more frequently associated with intention to treat population (p = 0.038), and CD38 expression (p = 0.068), but not with 17p deletion (p = 0.25) and seropositive HCV patients (p = 0.43) (table III).

The median time to initiate treatment in CLL patients was 2.05 years. It was found that the majority of intention to treat population was associated with low PLR (p < 0.001), high PDW (p = 0.038), seropositive HCV (p 0.027) and seropostive HBV (p = 0.2).

The median overall survival of the studied group was 5.58 years. CLL patients with stage A, hepatitis C seronegative patients, low PDW, high PLR were associated with superior overall survival with significant value (p = 0.001, 0.017, 0.043, and 0.002 respectively figure 1a, b, c). Multivariate analysis showed that stage A and low PDW were independent factors for OS (p = 0.014 and 0.04 respectively), while high PLR (p = 0.05), and seronegative C (p = 0.1) lost their significance.

Discussion

CLL is considered a heterogeneous disorder associated with different clinical courses which were predicted by staging systems of Binet and Rai. However, these systems do not consider other CLL biological features which can affect the course of the disease [7, 8].

Hitherto, new molecular advances have resulted in the use of expensive and complicated prognostic markers like cytogenetic aberrations (17p deletions, 11q deletions and trisomy 12), β2 micro-globulin, IGHV mutational status, expression of CD38 and ZAP-70 and gene mutations like *NOTCH1*, *MYD88* and *SF3B1* [9].

Unfortunately, most of these biomarkers were not taken in all of our cases because of either the cost and or unavailability. Another limitation to this study would be immune thrombocytopenia. However, to the best of our knowledge,

Table II. Comparison between low PLR and high PLR group in CLL patients

		Low PLR (<2.5)	High PLR (≥2.5)	Test of significance	p
Male		59 (62.76%)	42 (48.84%)	3.53	0.06
Age >65		34 (36.17%)	29 (33.72%)	0.12	0.7
HCV positive		40 (42.55%)	29 (33.72%)	1.48	0.22
HBV positive		4 (4.26%)	3 (3.48%)	0.07	0.54
Stage	A	1 (1.06%)	2 (2.33%)	19.26	<0.001
	B	35 (37.23%)	59 (68.6%)		
	C	58 (58%)	25 (29.06%)		
Intention to treat population		83 (88.29%)	55 (63.95%)	14.87	<0.001
CD38 positive		21 (43.75%)	12 (26.66%)	2.96	0.08
ZAP-70 positive		10 (71.4%)	8 (50%)	1.4	0.28
del (17p)		5 (23.8%)	0 (0%)	5.65	0.017

Table III. Comparison between low PDW and high PDW group in CLL patients

		Low PDW (<18.5 fl)	High PDW (≥18.5 fl)	Test of significance	p
Male		42 (51.2%)	59 (60.2%)	1.46	0.23
Age >65		24 (29.3%)	39 (39.8%)	2.17	0.14
HCV positive		34 (41.5%)	35 (35.7%)	0.62	0.43
HBV positive		4 (4.9%)	3 (3.1%)	0.39	0.53
Stage	A	2 (2.4%)	1 (1%)		
	B	45 (54.9%)	49 (50%)	1.12	0.56
	C	35 (42.7%)	48 (49%)		
Intention to treat population		57 (69.5%)	81 (82.7%)	4.31	0.038
CD38 positive		9 (24.3%)	24 (42.9%)	3.34	0.068
ZAP-70 positive		7 (43.8%)	11 (78.6%)	3.77	0.052
del (17p)		2 (28.6%)	3 (10.7%)	1.45	0.227

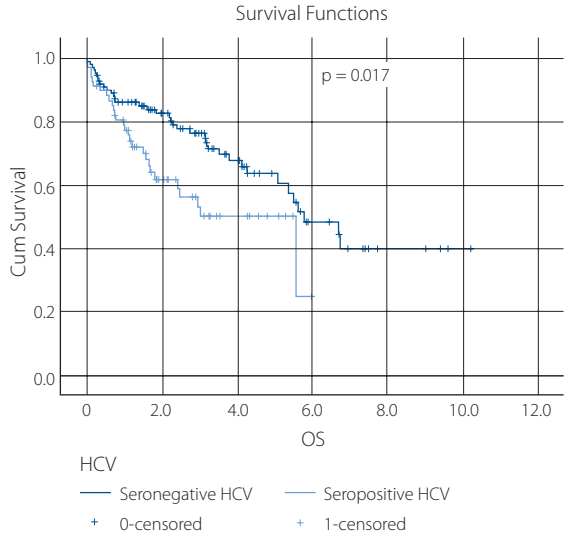

Figure 1a. Effect of HCV infection on overall survival of studied population

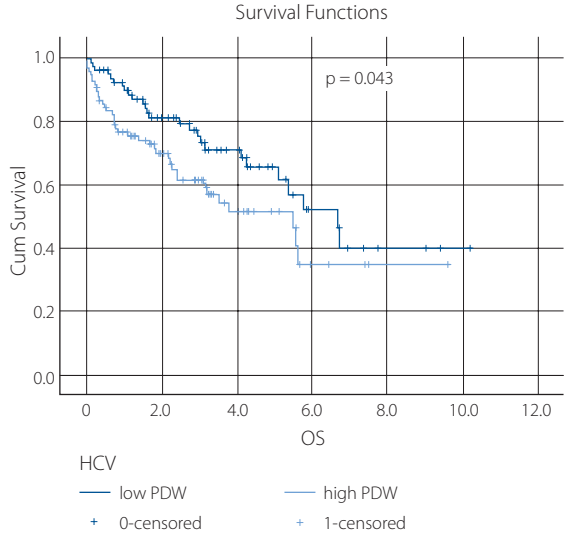

Figure 1b. Effect of PDW on overall survival of studied population

patients with auto-immune hematologic manifestations were not included in this analysis. Only two patients presented

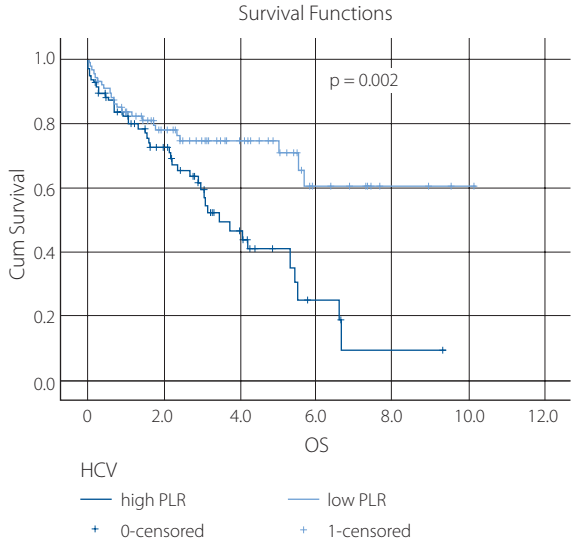

Figure 1c. Effect of PLR on overall survival of studied population

extreme thrombocytopenia and their work up did not reveal an immune phenomenon.

Recently, correlation between cancer and inflammation is an important new area of research. The antitumour activity of inflammation and the associated immune activation, induce tumour growth and progression. Inflammation is an independent predictor for response to therapy, event-free survival and overall survival (OS) in diffuse large B-cell lymphoma (DLBCL) patients [10].

Molica et al. have reported that in newly diagnosed CLL patients, the doubling time of absolute lymphocytic count was an independent predictor of outcomes in those patients [11]. Although platelet count prognostic value in CLL is not well identified, thrombocytopenia is considered a treatment indication [6]. Also, some studies have found that thrombocytopenia results in a compensatory thrombopoietin release which might correlate to some prognostic markers like ZAP-70 and CD38 [12, 13]. So, we used the PLR as it is an easily applicable clinical method that could detect the patients with a poor prognosis early.

Cytopenia in patients with CLL can have multiple causes including progressive bone marrow (BM) infiltration by abnormal lymphocytes, autoimmune disease, therapy-related, non-CLL related disorders, or a combination of these mechanisms [14]. The biological rationale in calculating PLR is that lymphocytosis and thrombocytopenia often occured in the advanced stages of CLL [6].

Our data demonstrated that Low PLR (<2.5) group was significantly associated with poor prognostic markers; stage C ($p < 0.001$), with 17p deletion ($p = 0.017$), and intention to treat ($p < 0.001$). They had significantly shorter OS compared to high PLR ($p = 0.002$) in a univariate analysis, while they lost their significance in multivariate analysis ($p = 0.05$). In solid tumours, a positive relationship between high PLR with worse prognosis for colorectal, gastroesophageal, hepatocellular, pancreatic, and ovarian cancers was identified [15].

Meanwhile, Kang et al. demonstrated that PLR had significant association with a poor prognosis in patients with non-Hodgkin's lymphoma, treated by R-CHOP [16]. Wang et al. reported that high PLR was associated with shorter OS and PFS in patients with DLBCL [10], also Seo et al. found that PLR showed independent significance in patients with advanced stage marginal zone lymphoma treated with rituximab, vincristine, cyclophosphamide, and prednisone protocol [17]. Retrospective analysis of 283 myeloma patients showed that inverse PLR had predictive value for OS and PFS [18].

Despite recent interest in the clinical implications of activated platelets in the setting of cancer, the scope of available data is still limited by the type of malignancy, sample sizes, selected population and clinical outcomes studied. PDW is a measure of platelet heterogeneity caused by heterogeneous demarcation of megakaryocytes. Several cytokines such as IL6, granulocytes colony stimulating factor (G-CSF) and macrophage colony stimulating factor (M-CSF) have dual functions including regulating megakaryopoiesis and tumour progression [19]. Another possible mechanism is that activated platelets create a procoagulant micro-environment that protect the tumour cells from the host immune system [20].

Increased PDW was found in gastric cancer and lung cancer [21, 22], and has been demonstrated to have a poor prognostic impact in melanoma, thyroid cancer, colorectal cancer, and laryngeal cancer. Also, studies, found that an increased PDW was associated with advanced TNM stages and shortened OS in patients with nasopharyngeal cancer. In contrast, other studies showed that decreased PDW was found in thyroid and breast cancer [23, 24], and is an unfavourable predictive factor for non-small cell lung cancer patient survival [25].

To the best of our knowledge, our study is the first to demonstrate the effect of high PDW in CLL patients and it revealed that High PDW (≥18.5 fl) was more frequently associated with intention to treat population ($p = 0.038$), and CD38 expression ($p = 0.068$), but not with 17p deletion ($p = 0.25$) and seropositive HCV patients ($p = 0.4$).

Conclusions

The low PLR and high PDW are associated with poor prognostic markers in CLL patients. CLL staging and PDW are independent predictors of survival. Unfortunately, the other prognostic markers as 17p deletion, CD38 and ZAP-70 were not performed for all our patients. We recommend further prospective studies to evaluate these simple applicable and cheap biomarkers in larger numbers of patients.

Conflict of interest: none declared

Shaimaa El-Ashwah
Mansoura University
Oncology Center
35516 Mansoura, Egypt
e-mail: shaimaelashwah@gmail.com

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References

1. Bannerji R, Byrd JC. Update on the biology of chronic lymphocytic leukemia. Curr Opin Oncol. 2000; 12(1): 22–29, doi: 10.1097/00001622-200001000-00004, indexed in Pubmed: 10687725.
2. Chiorazzi N, Rai KR, Ferrarini M. Chronic lymphocytic leukemia. N Engl J Med. 2005; 352(8): 804–815, doi: 10.1056/NEJMra041720, indexed in Pubmed: 15728813.
3. Burger J, Tsukada N, Burger M, et al. Blood-derived nurse-like cells protect chronic lymphocytic leukemia B cells from spontaneous apoptosis through stromal cell–derived factor-1. Blood. 2000; 96(8): 2655–2663, doi: 10.1182/blood.v96.8.2655.
4. Tsang M, Parikh SA. A Concise Review of Autoimmune Cytopenias in Chronic Lymphocytic Leukemia. Curr Hematol Malig Rep. 2017; 12(1): 29–38, doi: 10.1007/s11899-017-0366-1, indexed in Pubmed: 28197963.
5. Dührsen U, Augener W, Zwingers T, et al. Spectrum and frequency of autoimmune derangements in lymphoproliferative disorders: analysis of 637 cases and comparison with myeloproliferative diseases*. British Journal of Haematology. 2008; 67(2): 235–239, doi: 10.1111/j.1365--2141.1987.00235.x.
6. Hallek M, Cheson BD, Catovsky D, et al. International Workshop on Chronic Lymphocytic Leukemia. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008; 111(12): 5446–5456, doi: 10.1182/blood-2007-06-093906, indexed in Pubmed: 18216293.
7. Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukemia. Blood. 1975; 46(2): 219–234, doi: 10.1182/blood.v46.2.219.bloodjournal462219.
8. Binet JL, Leporrier M, Dighiero G, et al. A clinical staging system for chronic lymphocytic leukemia.Prognostic significance. Cancer. 1977; 40(2): 855–864, doi: 10.1002/1097-0142(197708)40:2<855::aid--cncr2820400239>3.0.co;2-1.
9. Amaya-Chanaga CI, Rassenti LZ. Biomarkers in chronic lymphocytic leukemia: Clinical applications and prognostic markers. Best Pract Res Clin Haematol. 2016; 29(1): 79–89, doi: 10.1016/j.beha.2016.08.005, indexed in Pubmed: 27742074.
10. Wang S, Ma Y, Sun L, et al. Prognostic Significance of Pretreatment Neutrophil/Lymphocyte Ratio and Platelet/Lymphocyte Ratio in Patients with Diffuse Large B-Cell Lymphoma. Biomed Res Int. 2018; 2018: 9651254, doi: 10.1155/2018/9651254, indexed in Pubmed: 30643825.
11. Molica S, Alberti A. Prognostic value of the lymphocyte doubling time in chronic lymphocytic leukemia. Cancer. 1987; 60(11): 2712–2716, doi: 10.1002/1097-0142(19871201)60:11<2712::aid--cncr2820601122>3.0.co;2-1.
12. Koller C, Bekele BN, Zhou X, et al. Plasma thrombopoietin compared with immunoglobulin heavy-chain mutation status as a predictor of survival in chronic lymphocytic leukemia. Blood. 2006; 108(3): 1001–1006, doi: 10.1182/blood-2005-05-2110, indexed in Pubmed: 16551975.

13. Yu H, Xu W, Shen QD. Serum levels of soluble CD (23) and thrombopoietin in chronic lymphocytic leukemia. Zhonghua nei ke za zhi. 2008; 47(10): 826–829.
14. Zent CS, Kay NE. Autoimmune complications in chronic lymphocytic leukaemia (CLL). Best Pract Res Clin Haematol. 2010; 23(1): 47–59, doi: 10.1016/j.beha.2010.01.004, indexed in Pubmed: 20620970.
15. Wang Y, Attar BM, Fuentes HE, et al. Evaluation of the prognostic value of platelet to lymphocyte ratio in patients with hepatocellular carcinoma. J Gastrointest Oncol. 2017; 8(6): 1065–1071, doi: 10.21037/jgo.2017.09.06, indexed in Pubmed: 29299368.
16. Kang HJ, Kim WS, Kim SJ, et al. Phase II trial of rituximab plus CVP combination chemotherapy for advanced stage marginal zone lymphoma as a first-line therapy: Consortium for Improving Survival of Lymphoma (CISL) study. Ann Hematol. 2012; 91(4): 543–551, doi: 10.1007/s00277-011-1337-6, indexed in Pubmed: 21922208.
17. Seo J, Kim WS, Kim JS, et al. Platelet to lymphocyte ratio (PLR) retains independent prognostic significance in advanced stage marginal zone lymphoma patients treated with rituximab, cyclophosphamide, vincristine, and prednisone combination chemotherapy (R-CVP): Consortium for Improving Survival of Lymphoma trial. Blood Res. 2017; 52(3): 200–206, doi: 10.5045/br.2017.52.3.200, indexed in Pubmed: 29043235.
18. Jung SH, Kim JS, Lee WS, et al. Prognostic value of the inverse platelet to lymphocyte ratio (iPLR) in patients with multiple myeloma who were treated up front with a novel agent-containing regimen. Ann Hematol. 2016; 95(1): 55–61, doi: 10.1007/s00277-015-2521-x, indexed in Pubmed: 26467916.
19. Zhang H, Liu Li, Fu S, et al. Higher platelet distribution width predicts poor prognosis in laryngeal cancer. Oncotarget. 2017; 8(29): 48138–48144, doi: 10.18632/oncotarget.18306, indexed in Pubmed: 28624815.
20. Santilli F, Boccatonda A, Davì G. Aspirin, platelets, and cancer: The point of view of the internist. Eur J Intern Med. 2016; 34: 11–20, doi: 10.1016/j.ejim.2016.06.004, indexed in Pubmed: 27344083.
21. Oncel M, Kiyici A, Oncel M, et al. Evaluation of Platelet Indices in Lung Cancer Patients. Asian Pac J Cancer Prev. 2015; 16(17): 7599–7602, doi: 10.7314/apjcp.2015.16.17.7599, indexed in Pubmed: 26625768.
22. Gunaldi M, Erdem D, Goksu S, et al. Platelet Distribution Width as a Predictor of Metastasis in Gastric Cancer Patients. J Gastrointest Cancer. 2017; 48(4): 341–346, doi: 10.1007/s12029-016-9886-5, indexed in Pubmed: 27826813.
23. Okuturlar Y, Gunaldi M, Tiken EE, et al. Utility of peripheral blood parameters in predicting breast cancer risk. Asian Pac J Cancer Prev. 2015; 16(6): 2409–2412, doi: 10.7314/apjcp.2015.16.6.2409, indexed in Pubmed: 25824773.
24. Yaylaci S, Tosun O, Sahin O, et al. Lack of Variation in Inflammatory Hematological Parameters between Benign Nodular Goiter and Papillary Thyroid Cancer. Asian Pac J Cancer Prev. 2016; 17(4): 2321–2323, doi: 10.7314/apjcp.2016.17.4.2321, indexed in Pubmed: 27221938.
25. Cui MM, Li Na, Liu X, et al. Platelet distribution width correlates with prognosis of non-small cell lung cancer. Sci Rep. 2017; 7(1): 3456, doi: 10.1038/s41598-017-03772-z, indexed in Pubmed: 28615714.

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Overall and GTV subvolumes tumour control probability (TCP) for head and neck cancer treated by 3D-IMRT with inhomogeneous dose distribution

Leszek Hawrylewicz[1], Bogusław Maciejewski[2], Klaus Rudiger Trott[5], Andrzej Tukiendorf[4], Leszek Miszczyk[2], Magdalena Markowska[3]

[1]*Department RT Planning, M. Skłodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland*
[2]*Department Radiotherapy, M. Skłodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland*
[3]*Division Research Programmes, M. Skłodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland*
[4]*Faculty of Health Sciences, Department of Public Health Medical University, Wroclaw, Poland*
[5]*Klinik und Poliklinik für Strahlentherapie der Technischen Universität München, Germany*

Introduction. In this study, an original model has been developed to estimate the real TCP that is a product of the TCPs calculated for GTV subvolumes of head and neck cancer based on 3D-IMRT dose planning.

Material and methods. Retrospective pilot group consist of 16 cases of oropharyngeal cancer in stage T1–2N0 previously treated with 3D-IMRT with at least 3-year follow-up. The total dose (TD) was 60–70 Gy in 2.0 Gy fractions delivered over 42–49 days. Within GTV two subvolumes were marked out: SVA with the planned 100% TD, and underdosed (90–95%) SVB. The TCP for both was calculated using the original formula developed by Withers and Maciejewski.

Results. During 3-year follow-up, 8 local recurrences (LR) occurred. In about 70% of SVB "dose cold spots" encompassed more than 50% GTV volume. This resulted in the TCP_{SVB} decrease to 60%. Thus, the real overall TCP was much lower than a priori predicted, and in these cases local recurrences occurred.

Discussion. Both cold spot SVB volumes and their dose deficit strongly correlated with a high risk of LR.

Conclusions. In conclusion the magnitude of dose deficit and the size of cold subvolume within GTV have an independent negative impact on real TCP and demand dose re-planning.

Key words: 3D-IMRT planning, cold spots within GTV, estimates of partial TCPs within GTV subvolumes

Introduction

Tumour cure using radiotherapy requires the sterilisation of all tumour stem cells. A single surviving functional tumour stem cell has a high probability of causing local tumour recurrence [1]. With increasing radiation dose to the GTV, the number of surviving tumour stem cells decreases exponentially, leading to a dose-dependent rise of tumour control probability (TCP) which follows a Poisson function of the probability that no tumour stem cell survived in the GTV. The logical consequence of this mechanism is that only two factors determine the dependence of the TCP on tumour dose (TD), but only in the case of homogeneous dose distribution in the GTV:

- the absolute number of tumour stem cells (which is related to the absolute tumour volume, the stem cell fraction among all tumour cells and the repopulation rate during the duration of the treatment);

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- the slope of the exponential decrease of the fraction of surviving tumour stem cells within the irradiated volume (which depends on the dose per fraction, the intrinsic tumour stem cell radiosensitivity, and which may also be influenced by micro-environmental factors).

The dependence of the curative dose (TCP-50) on the tumour volume has been investigated in experimental tumours (in particular by Suit [2] and by Guttenberger [3]) and in clinical studies, (e.g. Maciejewski et al. [4], Dubben et al. [5] and Magee et al. [6]). The analysis of these data suggests that a ten-fold difference in the absolute number of tumour stem cells between tumours of the same type and T-stage (which may be due to differences in gross tumour volume, tumour stem cell fraction at the start of radiotherapy or accelerated repopulation during radiotherapy) may represent a difference in TCD-50 of around 7 Gy. However, the relationship between TCP and TCD-50 is much more complicated when the dose in the GTV is heterogeneously distributed. Theoretical calculations of the impact of dose inhomogeneity within the PTV/GTV have been published, yet little clinical evidence to support these calculations has been presented so far.

When the 3D-IMRT was introduced into daily practice it became obvious that a dose gradient within the target leads to non-uniform dose distribution in the tumour volume. Tome and Fowler [7, 8] calculated an increase in the TCP for tumour subvolumes boosted to higher dose, and TCP loss within under-dosed sub-volumes ("cold spots"). It was concluded that the clinical impact of a dose deficit would depend not only on the magnitude of the deficit but also on the size of subvolume [9–11].

More than 15 years ago, Withers and Maciejewski developed a radiobiological model for changes in the TCP estimates for subvolumes and their dependence on initial tumour stem cell number represented by the size of the respective subvolumes and the total doses delivered [unpublished]. However, at that time, 2D radiotherapy with homogenous dose distribution within the target was the standard and dose differences in the GTV subvolumes were not a problem. Nowadays, 3D-IMRT with heterogeneous dose distribution within the GTV is widely used, which may impact on the TCP [12–15].

Material and methods

Dose planning data

For the present study, a pilot set of 16 consecutive 3D-IMRT treatment plans for T1–T2N0M0, sq.c.c of the oral cavity, oropharynx and supraglottic larynx, all with at least 3-year follow-up and with apparent inhomogeneous dose distribution within the GTV were selected from the treatment planning data bank in our institution. Inhomogeneous dose distribution was defined as sub-volumes larger than 5% of the GTV in which the total dose was reduced by >5%. Treatment plans with homogenous dose distribution D100 or D95 covering the whole GTV were not taken into account.

Radiotherapy

For all 16 patients, the 3D – treatment plans and DVHs were developed using the Eclipse Planning System (version 8.6 or 13, Varian). Using the Clinac 2300 accelerator with 120 MLC and 3D-IMRT technique, conventional 2.0 Gy daily fractions were delivered 5 days a week to a total dose ranging from 60 Gy in 42 days to 70 Gy in 48 days. There were no extensions of overall treatment time, and therefore the time factor is not considered in the analysis.

Tumour volume measurements

For the purpose of this study, tumour volumes were estimated from the data bank of the CT/MRI sequential scans spaced by 2–3 mm as proposed by Johnson et al. [11]. The primary tumour was outlined in each scan at the TPS workstation and the tumour volume was calculated by a computer-based analysis system. The primary tumour volume was defined as GTV, which ranged from 2.5 cm^2 to 29.2 cm^2.

For the purpose of the present analysis, the tumour volume was subdivided into two subvolumes:

- SVA – the volume of the GTV covered by 100% isodoses of the planned total dose (D100);
- SVB – the volume of the GTV covered by on average 90–95% of the planned total dose (D90–95). The total dose for this subvolume was converted into biologically normalised total dose (BNTD) if given in 2.0 Gy fractions using the L-Q model with = 10 Gy.

Initial stem cell number (K)

Following the assumptions made by McBride and Withers [9], a tumour of 1 cm in diameter (v = 0.52 cm^3) was assumed as a standard volumetric unit, containing 10^9 cells [9, 16, 17], among which 1% possesses stem cell potential (10^7 tumour stem cells). Then, the initial stem cell number in each specific primary tumour volume (V_i) would be:

$$K_i = 107 \times (V_i/0.52) \quad [1]$$

Stem cell numbers in subvolumes SVA and SVB were calculated using the same equation [1], using SVA and SVB volumetric parameters.

Tumour cure probability (TCP)

The relationship between the number of surviving tumour stem cells (K_S), tumour volume (V_i) and total dose (TD_i) approximates simple Poisson statistics [18, 19]:

$$TCP = \exp(-K) \quad [2]$$

where K_i is equal:

$$K_s = K_i \times SF_s \quad [3]$$

in which K_i is initial stem cell number and SF_S is the surviving fraction after the total dose (TD).

This equation can be rearranged as follows:

$$TCP = \exp(-K_i \times SF_S) \quad [4]$$

Surviving fractions may be estimated using various methods, such as SF2.0 (surviving fraction after a dose of 2.0 Gy), or effective D_{10} which is the dose that reduces survival to e^{-1} for a particular fraction regimen or the LQ model. These three methods are mainly used in experimental radiobiology, but are not very practical for daily clinical radiotherapy.

Mc Bride and Withers [9] suggested that the surviving fraction can more easily be determined in terms of eD_{10}, i.e. the dose which reduces stem cell survival by one decade to 10%. In our study this parameter was used. An approximate value for eD_{10} for 2.0 Gy fractions was suggested as about 7 Gy [1, 9, 16]. Therefore using $eD_{10} = 7$ Gy, for a tumour treated with the total dose TD, the absolute number of surviving functional stem cells (not surviving fractions) would be reduced to $10^{-TD/eD_{10}}$.

Combining equations the subvolume TCP_i can be calculated from equation:

$$TCP_i = \exp[-(10^7 \times (V_i/0.52) \times (10^{-TD/eD_{10}})] \quad [5]$$

where 10^7 is approximately the number of stem cells in a tumour 1 cm in diameter (0.52 cm^3), V_i – is tumour subvolume, and TD_i is the delivered total dose.

TCP_i values were calculated using the previously given parameters for the GTV and subvolumes A and B. Finally, the real TCP_{RL} was calculated as a product of the TCP_A and the TCP_B:

$$TCP_{RL} = TCP_A \times TCP_B \quad [6]$$

For all 3D-IMRT plans, TCP_{PL} and TCP_{RL} were compared and finally related with 3-year follow-up clinical results (local recurrence or disease-free survival).

Clinical data

After completing the results of TCP_{PL}, and TCP_{RL} calculations, they were compared with retrospective 3-year treatment outcomes of the selected 16 patients previously treated with 3D-IMRT. The outcome end-points, i.e. local tumour control (LTC) and local recurrence (LR) were considered. There was no incidence of distant metastases.

Results

Table I shows initially planned TCP_{PL} estimated from equation [5] for the data taken from treatment planning charts of the group of 16 cases. Dose planning and delivery had been prescribed by individual radiation oncologists generally based on the T stage criterion, even though tumour volumes differed by about 10 times (2.5 cm^3–29.2 cm^3). Although there were no extensions in overall treatment time and the standard fraction of 2.0 Gy was given regularly, 5 days a week, in hindsight, the choice of the total doses for some cases seems illogical, e.g. TD of 70 Gy was given to 4.55 cm^3 (pt. no. 2) whereas the tumour volume 2.5 larger (case no. 11) received only 60 Gy and the largest one in this series (case no. 16) received 63 Gy.

Nevertheless, except for two cases (no. 7 and no. 16), estimates of the planned TCP_{PL} are within an acceptable range and predicted a high probability of local tumour control.

The analysis of the impact of the subvolumes A and B within GTV on estimated values of the TCP (tab. II) shows that TCP_A estimated for SVA were generally very high. However they do not correlate with the incidence of local recurrence.

In contrast with SVA, the size of subvolumes SVB, and derived NTD and partial TCP_B values had a strong impact on the estimated real TCP values, which were decreased by 3–74% compared to the initial TCP_{PL} calculated from the treatment plans. Three-dimensional least square (20, 21) planes for dose-volume-TCP relationship are presented in figure 1.

The spatial distribution of these three parameters estimated prior to therapy appear to be of little use in predicting the risk of local recurrence (fig. 1 a). The correlation was even weaker when the SVA was analysed (fig. 1 b). Local recurrence was observed in patients who received the prescribed TD. In contrary, figure 1 c shows a significant impact of "cold" dose in SVB on TCP_B, which was particularly strong when, within

Table I. Planned TCP values for all 16 patients and gross tumour volume (GTV) and the calculated number of tumour stem cells and prescribed total dose (NTDp). Black dots indicate that a local tumour recurrence occurred during 3-year follow-up

Pts No	T Stage	VOL. (GTV) cm^3	Log_{10} K p	NTD p izobio Gy_2	Planned TCP p
1	T1	2.5	7.7	60	~ 88%
2	T1	4.55	7.95	70	~ 99%
3	T1	5.4	8	60	~ 77%●
4	T1	5.6	8	60	~ 77% ●
5	T2	6.2	8.1	60	~ 71% ●
6	T2	6.2	8.1	60	~ 71%
7	T2	8.1	8.2	60	~ 65%●
8	T2	9.5	8.3	66	~ 93%
9	T2	11.0	8.33	66	~ 92%
10	T2	11.5	8.34	66	~ 92%
11	T2	12.5	8.4	60	~ 51%●
12	T2	14.0	8.43	66	~ 90% ●
13	T2	15.0	8.46	70	~ 97% ●
14	T2	19.0	8.56	66	~ 87%
15	T2	22.0	8.63	70	~ 96%
16	T2	29.2	8.74	63	58% ●

Table II. Estimates of the TCP for subvolumes SVA and SVB within GTV, and realistic TCP as a product of both estimates (SVA is covered by TD100 and SVB by TD90–95). Black dots indicate that a local tumour recurrence occurred during 3-year follow-up

Pts No	SUBVOLUME A			SUBVOLUME B (V_{90-95})			TCP_{ESTIM} ($TCP_A \times TCP_B$)	TCP_P–TCP_E	3-year follow-up
	$\%VOL_{GTV}$	NTD_A izoGy$_{2.0}$	TCP_A	$\%VOL_{GTV}$	NTD_B izoGy$_{2.0}$	TCP_B			
1	V_{48}	60 Gy	94%	V_{52}	56.8 Gy	78%	73%	–15%	DFS
2	V_{73}	70 Gy	99.5%	V_{27}	61.1 Gy	95%	94%	–5%	DFS
3	V_{43}	60 Gy	88%	V_{57}	55.8 Gy	53%	47%	–41%	LR ●
4	V_{21}	60 Gy	94%	V_{79}	56.8 Gy	52%	49%	–28%	LR ●
5	V_{6}	60 Gy	98%	V_{94}	56.7 Gy	41%	40%	–31%	LR ●
6	V_{79}	60 Gy	78%	V_{21}	57.4 Gy	86%	67%	–4%	DFS
7	V_{71}	60 Gy	76%	V_{29}	55.9 Gy	62%	47%	–18%	LR●
8	V_{82}	66 Gy	95%	V_{18}	63.2 Gy	97%	92%	–3%	DFS
9	V_{5}	66 Gy	99%	V_{95}	62.4 Gy	78%	77%	–15%	DFS
10	V_{5}	66 Gy	99%	V_{95}	60 Gy	56%	55%	–37%	DFS
11	V_{80}	60 Gy	59%	V_{20}	56.3 Gy	65%	38%	–13%	LR ●
12	V_{4}	66 Gy	99.5%	V_{96}	60.1 Gy	51%	50%	–40%	LR ●
13	V_{40}	70 Gy	99%	V_{60}	56.5 Gy	23%	23%	–74%	LR ●
14	V_{13}	66 Gy	98%	V_{87}	63.1 Gy	73%	71%	–16%	DFS
15	V_{45}	70 Gy	98%	V_{55}	64.2 Gy	85%	83%	–13%	DFS
16	V_{12}	63 Gy	94%	V_{88}	60.7 Gy	35%	33%	–25%	LR ●

the GTV, the SVB was larger than the SVA. Therefore, the size of SVB and respective values of "cold" TDB, but not SVA and it parameters, substantially impacted on the decrease in the real TCP compared with the initially planned TCP. The real TCP_{RL} strongly correlated with the incidence of local recurrence.

Replanning of dose distribution in cases of large SVB

During 3D radiotherapy planning, heterogeneous dose distribution within the target volume needs detailed searching for possible "cold spots" and "cold doses", not so much in the CTV and PTV but above all in the GTV. The treatment plan and the dose distribution should be revised by a mathematically simple calculation of the realistic TCP_{RL} and compared with the conventionally determined TCP_{PL}. For this task we recommend using equation [6]. It is a simple and non-time-consuming procedure. If an unacceptable decrease in real TCP_{RL} compared with the planned TCP_{PL} is found, the dose distribution within specified volumes needs to be corrected, which should lead to as uniform a dose distribution as possible at least in the GTV.

Table III shows an option of corrections of SVA and SVB and respective TDA and TDB for 16 cases previously listed in table II to achieve uniformly high TCP_{AR} and TCP_{BR} above 90%, finally resulting in an increase in realistic TCP_{RL}. This exemplifies a way to minimise or even eliminate "cold spot" and "cold dose" in the GTV to get a real TCP_{RL} close or equal to that originally planned (TCP_{PL}).

Discussion

Many authors have emphasised that both tumour volume (TV) and tumour dose define tumour control probability (TCP) [5, 11–14, 17, 22]. Tumour stage (T), however, fails to provide reliable information of tumour volume and TCP. Therefore tumour staging cannot replace measurement of tumour volumes. Even within one tumour stage, TV can vary considerably as shown in table I: In the group of T1–T2N0M0 treatment plans for oral cavity and oropharyngeal cancer investigated, there was a 10-fold difference in the TV.

Analysing a survey of cervix, breast, head and neck and melanoma clinical data Dubben et al. [5] produced a series of steep TCP-TV-curves. Because in our model study, 16 treatment plans were randomly chosen from our clinical data bank, we cannot explain why some small TV (case no. 2) were treated with 70 Gy whereas much larger TV received 60 Gy. It was the individual choice of different radiation oncologists, who prescribed total doses according to the T-stages of tumours.

The absolute number of tumour stem cells has been shown to be proportional to the tumour volume in most rodent and human cancers (unless there are large necrotic volumes found [1, 2, 11, 12]). For the purpose of our study, we assumed that 1% of tumour cells are tumour stem cells [9].

A local control rate of 90% results if on average 0.1 tumour stem cells survive, or in other words, if one in ten irradiated tumours contains one or more tumour stem cell. In a tumour with about 10^9 tumour stem cells such as #16, the stem cell surviving fraction has to be about 10^{-10} to achieve a local control rate of 90%. Using eD_{10} of 7.0 Gy assumed in our model, it would require a total dose of approximately 70 Gy instead of the 63 Gy given to increase TCP from approximately 40% to 90%. The observed local recurrence thus had to be expected.

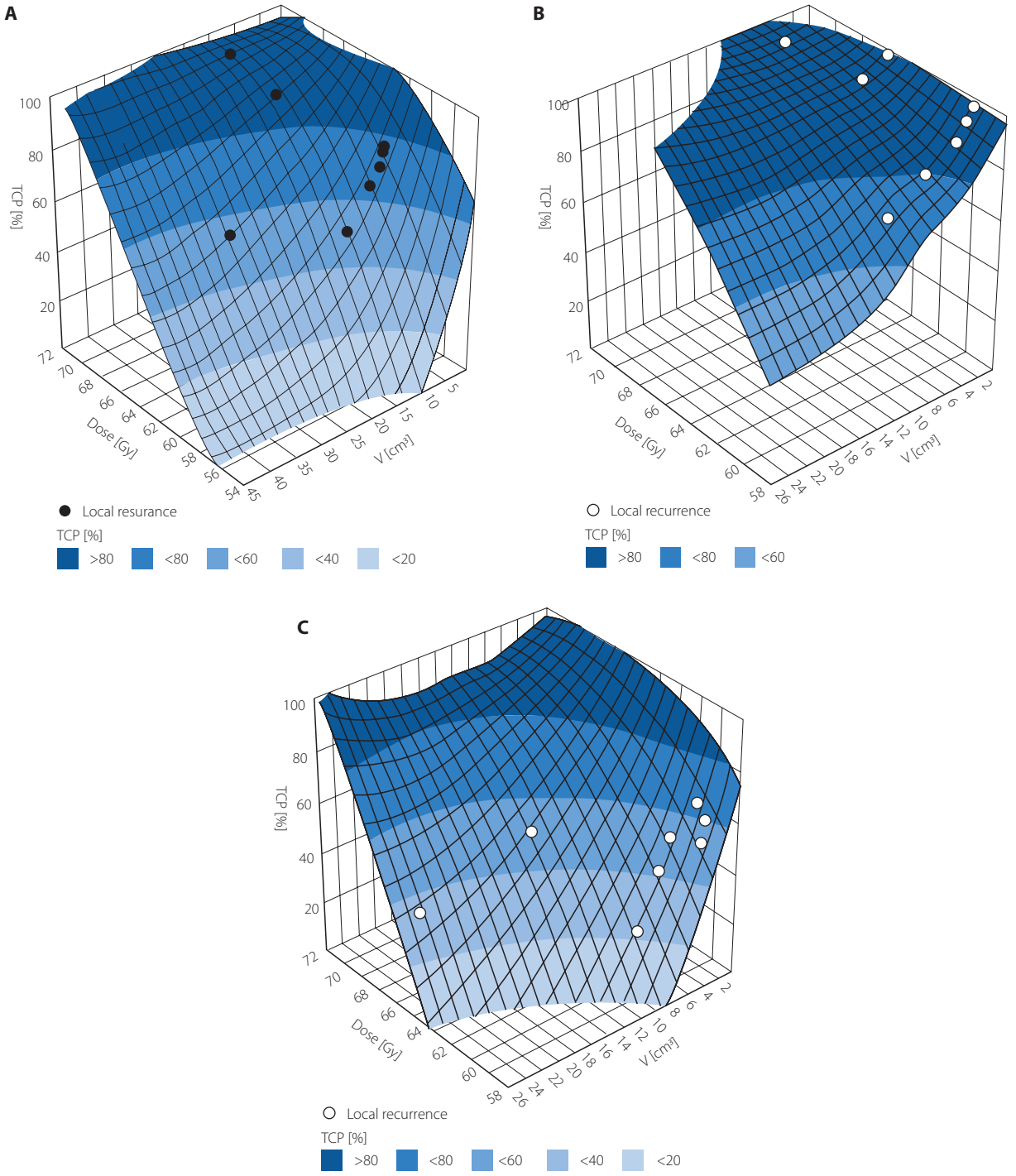

Figure 1. 3D-least square planes for dose-volume-TCP relationships: A – for planned parameters; B – for subvolume SVA; C – for subvolume SVB; black dots indicate local tumour recurrence occurred during 3-year follow-up

Table III. Examples of re-planning of dose distribution within the GTV subvolumes SVA and SVB in all patients to get similarly high TCPs in both, and also high realistic overall TCP_{RL}

Pts No	SUBVOLUME A → ACr			SUBVOLUME B → BCr			TCP_{real} (TCP_{ACr} x TCP_{BCr})
	$V_A \rightarrow V_{AR}$	$NTD_A \rightarrow NTD_{AR}$ ($izoGy_{2.0}$)	TCP_{ACr}	$V_B \rightarrow V_{BR}$	$NTD_B \rightarrow NTD_{BR}$ ($izoGy_{2.0}$)	TCP_{BCr}	
1	48% → 70%	60 Gy → 62 Gy	95%	52% → 30%	56.8 Gy → 59 Gy	95%	90%
2	change not needed			change not needed			94%
3	42% → 70%	60 Gy → 65 Gy	96%	56% → 30%	55.8 Gy → 61 Gy	95%	91%

Pts No	SUBVOLUME A → ACr			SUBVOLUME B → BCr			TCP_{real} (TCP_{ACr} x TCP_{BCr})
	$V_A \rightarrow V_{AR}$	$NTD_A \rightarrow NTD_{AR}$ ($izoGy_{2.0}$)	TCP_{ACr}	$V_B \rightarrow V_{BR}$	$NTD_B \rightarrow NTD_{BR}$ ($izoGy_{2.0}$)	TCP_{BCr}	
4	21% → 70%	60 Gy → 65 Gy	96%	79% → 30%	56.8 Gy → 61 Gy	94%	90%
5	6% → 70%	60 Gy → 65 Gy	95%	94% → 30%	56.7 Gy → 61 Gy	95%	90%
6	79%	60 Gy → 65 Gy	95%	21%	57.4 Gy → 61 Gy	95%	90%
7	63% → 70%	60 Gy → 66 Gy	95%	37% → 30%	55.9 Gy → 62 Gy	95%	90%
8	change not needed			change not needed			92%
9	5% → 70%	66 Gy	95%	95% → 30%	62.4 Gy → 63 Gy	94%	89%
10	5% → 70%	66 Gy	96%	95% → 30%	60 Gy → 63 Gy	94%	90%
11	80%	60 Gy → 67 Gy	95%	20%	56.3 Gy → 63 Gy	95%	90%
12	4% → 70%	70 Gy	97%	96% → 30%	60.1 Gy → 64 Gy	94%	90%
13	40% → 70%	70 Gy	97%	60% → 30%	56.5 Gy → 63 Gy	97%	94%
14	13% → 70%	66 Gy → 68 Gy	95%	87% → 30%	63.1 Gy → 65 Gy	94%	89%
15	45% → 80%	70 Gy	97%	55% → 20%	64.2 Gy → 66 Gy	99%	96%
16	12% → 70%	63 Gy → 70 Gy	96%	88% → 30%	60.7 Gy → 66 Gy	97%	93%

Besides the absolute number of tumour stem cells, other factors such as hypoxia, clonal radio-resistance, intercellular communication, and repopulation rate may increase inter--tumour or intra-tumour heterogeneity of stem cell density and of the resulting tumour radioresistance. Brenner [22] and Johnson et al. [11] suggested that although some deviations in cellular characteristics of the tumour might modify the volume response to radiation it would unlikely be of crucial importance. Daily fractionation with 2.0 Gy in all tumours was given which, if at all, might lead to a similar impact on repopulation, which is known to be a major factor causing local recurrences in head and neck cancer. Currently, there is no way to determine heterogeneity of repopulation rates and starting times between tumours. Thus, the contribution of this factor to the findings of our study cannot be properly evaluated. The intra-tumour heterogeneity of tumour stem cell density cannot, at present, be seriously discussed because of the lack of reliable data, however, histopathological studies on stem cell marker distribution may enable us in the future to determine stem cell density in tumours.

Particularly in 3D-IMRT there is a high risk of minor dose inhomogeneity because of the relatively steep gradient of dose within a narrow distance from the centre of the tumour. Tome and Fowler [7, 8], Withers [9, 10] and other authors discussed in detail the physical and clinical aspects of "cold spots" and "cold doses". Whereas GTV can be precisely contoured using radiological images, CTV and PTV can only be individually surmised based on the experience of the radiation oncologist because there is no chance to image small conglomerates of tumour (stem) cells outside the GTV. Therefore we focused on underdosed cold spots within the GTV. At the edge of the SVB the dose may even be a bit lower, but we used an average value to simplify our model. With constant number of fractions, the dose per fraction is also reduced. To compare biological effectiveness of the total doses in both SVA and SVB, mean total doses (NTD_s) in the SVB were normalised to the dose given in 2.0 Gy fractions using the L-Q model with = 10 Gy and listed as NTD $IzoGy_2$.

The relationship between planned and delivered NTD_S for SVA and SVB is presented in table II. The results show that the size of the SVA which received 100% of the planned total dose ranged from 5% to 82% but the mean TD in SVA was high enough to correspond with high TCP_A, except case no.11 for which the planned TD was too low to eradicate the SVA. For the SVB, the situation was worse. In 11 cases, the SVB was larger than the SVA. The real TCP values were estimated by multiplying TCP_A and TCP_B calculated for SVA and SVB. The real TCP_{RL} values significantly differ from the planned TCP_{PL} values. All local recurrences occurred in those cases in which a significantly reduced real TCP_{RL} was calculated.

Our results in the present study support the suggestions of other authors that the biological impact of heterogeneous dose distribution and dose deficit in tumour subvolumes depends not only on the dose deficit but also on the extent of the cold spot(s). Tome, Fowler, Withers [7–10] and other authors postulated that a cold spot of 20–40% of the target volume underdosed by 10% of the prescribed TD would cause the loss in TCP by about 15% or more. Our observations are in agreement with those theoretical predictions. Yet, we also agree with Tome and Fowler [7, 8] and Goitein and Niemierko [19] that a significant decrease in the TCP depends steeply on dose even for small cold volumes, and that such a deficit cannot be rectified by boosting the dose to the relatively large volume of the PTV.

It is obvious that using IMRT and other 3D-conformal techniques, some dose inhomogeneity in the GTV is unavoidable. The efficacy of these radiotherapy techniques cannot only be dealt with on the basis of physical parameters alone, disregarding radiobiological principles [10]. TCP should be

considered as a function not only of dose but also of the initial number of tumour stem cells, indirectly expressed by tumour subvolumes but not by tumour stages. The treatment outcome is strongly influenced by unaccounted differences in a spatial dose distribution. The hazard of cold spots has been clearly documented and intuitively, even a cubic millimetre of receiving a low dose may lead to recurrence. Such a risk significantly increases when the size of a cold spot enlarges from millimetres to cubic centimetres. It must be estimated a priori as an essential part of treatment planning. Our model involves the simple assumption of constant stem cell density, and uniform dose distribution in each of the two subvolumes (more than two SV can also be analysed). This model should be taken only as example of what might occur in practice.

Whereas complex TCP equations defined by Tome [7, 8] and Goitein and Niemierko [19] may be useful for mathematically sophisticated analyses, they are useless for daily planning by radiation oncologists. Our proposition of TCP estimation (i.e. our equation no. 6) is simple and can easily be used even by a mathematically inexperienced radiation oncologist, and it takes only about one minute using a simple calculator with Ln and Log functions.

The unacceptable discrepancies between the planned (tab. I) and real TCP_{RL} (tab. II) which occurred in our study, need re-planning procedures with the aim of enlarging the D100 subvolume (SVA) and minimising the size of the underdosed cold subvolume (SVB) as much as possible. Examples of such correction of the IMRT planning are shown in table III.

Conclusions

In 3D-IMRT and other conformal radiotherapy techniques, inhomogeneous dose distributions are unavoidable. Therefore the hazard of underdosed cold spot(s) within the target volume (at least GTV) should be accounted for. The efficacy of these radiotherapy techniques expressed by local tumour probability cannot be considered based on physical parameters alone, disregarding radiobiological principles. Tumour volume (but not tumour stage) is an appropriate though approximate measure of initial number of tumour stem cells which is the most relevant predictor of the TCP. The biological impact of any dose deficit in the cold spot(s) on the TCP depends not only on the magnitude of the deficit but on the size of the cold spot subvolume. Instead of the 95% isodose criterion, mapping V_{100} within the target receiving 100% of the planned dose is recommended, which should be as large as possible, minimising the biological impact of the underdosed cold subvolume(s). The real TCP_{RL} is the product of the TCP_A for the V_{100} and TCP_B for the cold subvolume. Any serious discrepancy between the real TCP_{RI} and the planned TCP_{PL} requires precise re-planning and correction of dose distribution within GTV subvolumes.

This paper is dedicated to the memory of Rod Withers who initiated the concept of the present work.

Conflict of interest: none declared

Bogusław Maciejewski
M. Skłodowska-Curie National Research Institute of Oncology, Gliwice Branch
Department Radiotherapy
Wybrzeże Armii Krajowej 15
44-102 Gliwice, Poland
e-mail: boguslaw.maciejewski@io.gliwice.pl

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References

1. Kummermehr J, Trott KR. Tumour stem cells. Stem Cells. 1997: 363–399, doi: 10.1016/b978-012563455-7/50013-1.
2. Suit HD, Shalek RJ, Wette R. Radiation Response of C3H Mouse Mammary Carcinoma Evaluated in Terms of Cellular Radiation Sensitivity. In: Cellular Radiation Biology. Williams and Wilkins , Baltimore 1965.
3. Guttenberger R, Kummermehr J, Wang J et al. 38 Ann Meeting Radiat Res Soc, abst. Cn-5 New Orleans, 1990.
4. Maciejewski BA, Skates S, Zajusz A, et al. Importance of tumor size and repopulation for radiocurability of skin cancer. Neoplasma. 1993; 40(1): 51–54, indexed in Pubmed: 8350948.
5. Dubben HH, Thames HD, Beck-Bornholdt HP. Tumor volume: a basic and specific response predictor in radiotherapy. Radiother Oncol. 1998; 47(2): 167–174, doi: 10.1016/s0167-8140(97)00215-6, indexed in Pubmed: 9683365.
6. Magee BJ, Logue JP, Swindell R, et al. Tumour size as a prognostic factor in carcinoma of the cervix: assessment by transrectal ultrasound. Br J Radiol. 1991; 64(765): 812–815, doi: 10.1259/0007-1285-64-765-812, indexed in Pubmed: 1913045.
7. Tome WA, Fowler JF. Selective boosting of Tumour subvolumes. Int J Radiat Oncol Biol Phys. 2000; 47: 1137–1143.
8. Tomé WA, Fowler JF. On cold spots in tumor subvolumes. Med Phys. 2002; 29(7): 1590–1598, doi: 10.1118/1.1485060, indexed in Pubmed: 12148742.
9. Perez C, Brady L. Principles and Practice of Radiation Oncology. Pediatr Hematol Oncol. 1999; 21(6): 560, doi: 10.1097/00043426-199911000-00025.
10. Withers HR. Biological aspects of conformal therapy. Acta Oncol. 2000; 39(5): 569–577, doi: 10.1080/028418600750013258, indexed in Pubmed: 11093365.
11. Johnson C, Thames H, Huang D, et al. The tumor voluem and clonogen number relationship: Tumor control predictions based upon tumor volume estimates derived from computed tomography. Int J Radiat Oncol Biol Phys . 1995; 33(2): 281–287, doi: 10.1016/0360-3016(95)00119-j.
12. Deasy J. Tumour control probability model for non-uniform dose distributions. In: Paliwal B, Fowler JF, Hubert D, Mehta MP. ed. Volume and Kinetics in Tumour Control and Normal Tissue Complications. The Fifth Madison International Conference on Time, Dose and Fractionation. AIP, New York 1997: 65–85.
13. Knöös T, Kristensen I, Nilsson P. Volumetric and dosimetric evaluation of radiation treatment plans: radiation conformity index. Int J Radiat Oncol Biol Phys. 1998; 42(5): 1169–1176, doi: 10.1016/s0360-3016(98)00239-9, indexed in Pubmed: 9869245.
14. Mayo CS, Ding L, Addesa A, et al. Initial experience with volumetric IMRT (RapidArc) for intracranial stereotactic radiosurgery. Int J Radiat Oncol Biol Phys. 2010; 78(5): 1457–1466, doi: 10.1016/j.ijrobp.2009.10.005, indexed in Pubmed: 20207494.
15. Guerrero Urbano MT, Clark CH, Kong C, et al. Target volume definition for head and neck intensity modulated radiotherapy: pre-clinical evaluation of PARSPORT trial guidelines. Clin Oncol (R Coll Radiol). 2007; 19(8): 604–613, doi: 10.1016/j.clon.2007.07.001, indexed in Pubmed: 17706404.
16. Bentzen SM. Quantitative clinical radiobiology. Acta Oncol. 1993; 32(3): 259–275, doi: 10.3109/02841869309093594, indexed in Pubmed: 8323764.
17. Yaes RJ. Tumor heterogeneity, tumor size, and radioresistance. Int J Radiat Oncol Biol Phys. 1989; 17(5): 993–1005, doi: 10.1016/0360-3016(89)90147-8, indexed in Pubmed: 2808062.
18. Harel D, Mills SD, Kwakkenbos L, et al. SPIN Investigators, members of the ISUP Renal Tumor Panel. Weighted kappa: nominal scale agreement

with provision for scaled disagreement or partial credit. Psychol Bull. 1968; 70(4): 213–220, doi: 10.1037/h0026256, indexed in Pubmed: 19673146.
19. Goitein M, Niemierko A. Intensity modulated therapy and inhomogeneous dose to the tumor: A note of caution. Int J Radiat Oncol Biol Phys. 1996; 36(2): 519–522, doi: 10.1016/s0360-3016(96)00348-3.
20. Muralikrishnan B, Raja J. Least-squares best fit line and plane. In: Muralikrishnan B, Raja J. ed. Computational Surface and Roundness Metrology. Springer Verlag London Ltd, London 2009: 121–130.
21. Hartigan JA, Wong MA. Algorithm AS 136: A K-Means Clustering Algorithm. Applied Statistics. 1979; 28(1): 100, doi: 10.2307/2346830.
22. Brenner DJ. Dose, volume, and tumor-control predictions in radiotherapy. Int J Radiat Oncol Biol Phys. 1993; 26(1): 171–179, doi: 10.1016/0360-3016(93)90189-3, indexed in Pubmed: 8482624.

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Survival analysis of patients with locally advanced non-small cell lung cancer treated at the Nu-Med Radiotherapy Center in Elbląg

Marcin Kurowicki[1], Karolina Osowiecka[2], Sergiusz Nawrocki[3], Łukasz Cieśliński[1], Barbara Szostakiewicz[1], Andrzej Badzio[4]

[1]*Nu-Med Radiotherapy Center, Elblag, Poland*
[2]*Department of Psychology and Sociology of Health and Public Health, School of Public Health, University of Warmia and Mazury in Olsztyn, Poland Department of Public Health, Medical University of Warsaw, Poland*
[3]*Department of Oncology, Faculty of Medical Sciences, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Poland*
[4]*Department of Oncology and Radiotherapy, Medical University of Gdansk, Poland*

Introduction. The study aimed to report the efficiency of radical radiotherapy and chemoradiotherapy in patients with non-small cell lung cancer (NSCLC) treated in the Nu-Med Radiotherapy Center in Elbląg.

Material and methods. Ninety-two patients diagnosed with NSCLC treated between 2013 and 2016 were included in the analysis. Overall survival (OS) was estimated by the Kaplan-Meier method.

Results. The 2-year OS for all patients was 36% (median 1.5 years). Two prognostic factors had a significant impact: treatment method and performance status (PS). Patients who underwent concurrent radiochemotherapy and were treated sequentially had a better 2-year OS in comparison with those treated with radiotherapy alone (respectively 46% and 37% *vs.* 25%, $p \leq 0.05$). Patients with PS 0–1 had better OS (median 1.6 years) compared with PS 2 (median 0.7 years, $p = 0.04$). Other prognostic factors analysed had no impact on OS in our study.

Conclusions. The treatment results of our patients are comparable to those in published trials and meta-analyses.

Key words: non-small cell lung cancer, chemoradiotherapy, radiotherapy, overall survival

Introduction

In 2013, of more than 12.7 million malignancies diagnosed worldwide, about 13% (1.6 million) were lung malignancies. In Poland, lung cancer is the most common type of cancer in men, and among women it ranks third. It's also the prime cause of death from malignancy for both sexes [1]. Cigarette smoking is the leading cause of lung cancer development. Smoking increases its risk 20–30 fold [2, 3]. The treatment method of patients diagnosed with lung cancer depends mainly on the clinical stage of the disease and patient comorbidities. One of the reasons for the poor prognosis is late diagnosis, and therefore most patients are disqualified from radical surgery [4]. According to EUROCARE 5 (EUROpean CAncer REgistry based study on the survival and care of cancer patients), the 5-year relative survival of lung cancer patients diagnosed between 2000 and 2007 was 14.3% for Poland, and the European average was 12.6% [5]. The most frequent histology of lung cancer is non-small cell lung cancer (NSCLC) [6]. The 5-year overall survival of patients diagnosed with NSCLC depending on clinical stage ranges 4–66% [7]. For patients with early-stage

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NSCLC surgery remains the primary treatment; for locally advanced non-small cell lung cancer chemoradiotherapy is the treatment of choice. However, the effectiveness of the latter leaves much to be desired. We have particularly high hopes for the addition of immunotherapy to chemoradiotherapy, which has significantly improved survival in inoperable patients [8].

However, there are some limitations to the data supporting treatment strategies in specific patient subsets and studies have included heterogeneous patient populations. The definition of clinical stage III has changed over time, and early reviews have often been inadequately powered to detect small differences in survival outcome, have not been randomised or have had limited time of follow-up. Development in therapy: the use of more active chemotherapy agents and refinements in radiation and surgical techniques also limit the interpretation of earlier clinical trials [9]. The aim of this study was to analyse and report the outcome of the treatment of non-small cell lung cancer patients with radical radiotherapy and chemoradiotherapy in our department.

Material and methods

A list of patients was generated from the institutional database, Mosaiq and Clininet systems. The medical records of all patients were available for this study. The research was conducted on a group of 109 patients with primary, unresectable, non-metastatic cancers, with a histopathological diagnosis of non-small cell lung cancer, who underwent curative radio- and radiochemotherapy between 2013 and 2016 in the Nu-Med Radiotherapy Center in Elbląg. Seventeen patients were excluded from the analysis. The reason for exclusion was resection in 11 patients (10%), including nine patients treated with postoperative radiation and two patients treated with preoperative radiochemotherapy. Six patients (6%) who underwent therapy because of recurrence were also excluded from the analysis. All patients were staged with computed tomography of the chest and abdominal ultrasound, 57 (62%) had PET examinations, 87 (95%) had a spirometric evaluation.

The stage was determined by the UICC TNM classification of Malignant Tumours – 7th edition. A total dose of 66 Gy with fraction dose 2 Gy was administrated in 55 patients, 66 Gy (fraction dose 2.2 Gy) in 8 patients, 60 Gy (fraction dose 2 Gy) in 27 cases and 50 Gy in 2 patients. Dose 60 Gy was prescribed for concomitant treatment, 66 Gy for the sequential scheme or for radiotherapy alone. The dose of 50 Gy was prescribed for tumours infiltrating vertebral bodies close to the spine. The CTV included lung tumour and pathological lymph nodes with 8 mm margins. In post-chemotherapy cases, the CTV consisted of residual lung tumour and lymph nodes with an 8 mm margin and initially involved mediastinal node groups. In both scenarios, the PTV was created by adding 7 mm margins radially and 10 mm in the craniocaudal direction.

Treatment plans were prepared using Prowess or Eclipse software. Radiotherapy was delivered with Artiste (Siemens) Liniacs, using photons X 6 MV, with IMRT in 79 patients (86%) and 3D technique in 13 (14%). The method was chosen by attending a radiation oncologist, after DVH comparison.

Patients treated with chemoradiotherapy received different chemotherapy regimens: carboplatin-vinorelbine (KN) (6 patients), cisplatin-vinorelbine (PN) (47 patients), carboplatin-etoposide (KE) (1 patient), cisplatin-etoposide (PE) (6 patients), cisplatin (1patient), cisplatin-pemetrexed (1 patient), KN+PN (1 patient), KN+PXL/CDDP (1 patient). The induction chemotherapy regimen was chosen and administered by medical oncologists from other hospitals.

The efficacy of radiotherapy and chemoradiotherapy was estimated by survival analysis from the date of the beginning of the treatment to the last follow-up visit/death. Variables that can impact patient survival (sex, age, BMI, place of residence, the distance between the place of residence and Nu-Med Center, baseline WHO PS, clinical stage, lymph node status, tumour localisation, type of histopathology, type of treatment) were analysed.

The proportion between subgroups: radiotherapy alone *vs.* sequential radiochemotherapy *vs.* concurrent radiochemotherapy in different factors were compared using the chi^2 test. Overall survival (OS) was estimated by the Kaplan-Meier method and differences in survival were compared by the log-rank test. Uni- and multivariable analysis was estimated through the Cox regression model. Univariate variables with $p < 0.25$ were included in the multivariable analysis. A p-value <0.05 was considered to be significant. The analysis was performed using TIBCO Software Inc. (2017) and Statistica (a data analysis software system), version 13. http://statistica.io.

Results

Ninety-two patients were included in the analysis. The majority of patients were men (72; 78%) and lived in cities ≤100 thousand (44; 48%) and villages (31; 34%). The median age was 64 years. Half of the patients (47; 51%) were of PS (performance status) grade 0 according to the WHO/ECOG scale during the first visit. Most patients were treated in clinical stage IIIA (53; 58%) and IIIB (31; 34%), with T3–4 (70%), with N2–3 (80%), with squamous cell carcinoma (68; 74%) and adenocarcinoma (19; 21%), tumour localisation on right side (59; 64%). Over half (57; 62%) had a PET examination before treatment. 28 patients (30%) underwent radiotherapy only, 38 patients (41.5%) had sequential radiochemotherapy and 26 patients (28.5%) had concurrent radiochemotherapy. Most patients (58; 63%) were referred from Szpital Specjalistyczny in Prabuty (the regional pulmonological center) for treatment to the Nu-Med Center and the 34 remaining patients (37%) where diagnosed in hospitals in Elbląg (tab. I).

More patients who received radiotherapy alone were >64 years compared with patients who underwent sequential or concurrent radiochemotherapy, respectively 89% *vs.* 32% *vs.* 23% ($p < 0.001$). There was a significant difference in perfor-

Table I. Characteristics of patients

Patient's characteristic		All		Radiotherapy alone		Sequential radio-chemotherapy		Concurrent radio-chemotherapy		Chi² test
		N	%	N	%	N	%	N	%	p
		92	100	28	30	38	41.5	26	28.5	
Age (start of radiotherapy)		**range: 46–82 years; median: 64 years**								
	≤64	49	53	3	11	26	68	20	77	<0.001
	>64	43	47	25	89	12	32	6	23	
Sex										
	women	20	22	5	18	9	24	6	23	0.84
	men	72	78	23	82	29	76	20	77	
BMI		**range: 15.8–46.1; median 26**								
	≤26	42	46	15	53.5	18	47	9	34.5	0.46
	>26	42	46	12	43	16	42	14	54	
	no data	8	9	1	3.5	4	11	3	11.5	
Place of residence										
	village	31	34	9	32	13	34	9	34.5	0.08
	cities ≤100 thous	44	48	14	50	22	58	8	31	
	cities >100 thous	17	18	5	18	3	8	9	34.5	
Distance from place of residence to Nu-Med. Center		**range: 0–616 km; median 67 km**								
	≤67	47	51	13	46	17	45	17	65	0.22
	>67	45	49	15	54	21	55	9	35	
Performance status according WHO/ECOG during first visit										
	0	47	51	10	36	17	45	20	77	0.02
	1	37	40	14	50	17	45	6	23	
	2	8	9	4	14	4	10	0	0	
Clinical stage										
	IB	3	3	3	11	0	0	0	0	0.02
	IIA	2	2	2	7	0	0	0	0	
	IIB	3	3	2	7	1	3	0	0	
	IIIA	53	58	16	57	19	50	18	69	
	IIIB	31	34	5	18	18	47	8	31	
Lymph nodes status										
	N+	79	86	20	71	35	92	24	92	0.03
	N–	13	14	8	29	3	8	2	8	
Tumor localization										
	right	59	64	17	61	26	68	16	61	0.97*
	left	29	32	9	32	12	32	8	31	
	mediastinum	3	3	2	7	0	0	1	4	
	right and left	1	1	0	0	0	0	1	4	
Type of histopathology										
	planoepitheliale	68	74	19	68	30	79	19	73	0.74^
	adenocarcinoma	19	21	7	25	7	18	5	19	
	undetermined	5	5	2	7	1	3	2	8	
PET										
	yes	57	62	21	75	14	37	22	85	<0.001
	no	35	38	7	25	24	63	4	15	

Patient's characteristic		All		Radiotherapy alone		Sequential radio-chemotherapy		Concurrent radio-chemotherapy		chi² test
		N	%	N	%	N	%	N	%	p
Time of treatment from radiochemotherapy to end of radiotherapy		**range: 15–208 days; median 47.5 days**								
	≤47.5	46	50	26	93	0	0	20	77	<0.001
	>47.5	46	50	2	7	38	100	6	23	

*p-value – comparison of the percentages between subgroups: right and left tumor localization
^p-value – comparison of the percentages between subgroups: planoepitheliale and adenocarcinoma type of histopathology

mance status (PS) according to the WHO/ECOG classification during the first visit between patients treated with concurrent radiochemotherapy (no one with PS 2) *vs.* sequential radiochemotherapy (10% of patients with PS 2) or radiotherapy alone (14% of patients with PS 2) (p = 0.02). Patients who underwent a different type of treatment significantly differed in terms of characteristics: clinical stage, lymph node status, PET examination and the time of treatment from radiochemotherapy to the end of radiotherapy (tab. I).

The 2-year overall survival for all patients was 36%. The median OS (mOS) was 1.5 years (95% confidence interval (CI): 0.7–2.8 years; (fig. 1). 31 deaths (34%) were observed during the first year, including 13 patients treated with radiotherapy alone, 9 with sequential radiochemotherapy and 9 with concurrent radiochemotherapy. Patients who underwent radiotherapy alone had a statistically significant worse 2-year OS (25%; mOS 1.1 years [95% CI: 0.5–1.9 years]) in comparison with patients treated with concurrent (46%; mOS 1.1 years [95% CI: 0.5–not reached]; p = 0.05) and sequential radiochemotherapy (37%; mOS 1.7 years [95% CI: 1.0–2.6 years]; p = 0.03). There was no significant difference observed between concurrent and sequential radiochemotherapy (p = 0.54) (fig. 2, tab. II). Patients with PS 0–1 during the first consultation had a significantly better mOS – 1.6 years (95% CI: 0.7–3.5 years) than patients with PS 2 – mOS 0.7 years (95% CI: 0.4–1.1 years; p = 0.04) (fig. 3, tab. II). Total treatment time, age, sex, BMI, place of residence, the distance from the place of residence to the Nu-Med Center, lymph node metastasis, tumour localisation, type of histopathology, clinical stage, PET examination had no impact on OS (tab. II).

Table II. Overall survival of patients

		2-year OS (%)	Median OS [years] (95% CI)		Log-Rank test p
All		36	1.5	(0.7–2.8)	
Age (at start of radiotherapy)					
	≤64 years	39	1.6	(0.7–4.2)	0.17
	>64 years	33	1.5	(0.6–2.2)	
Sex					
	women	50	1.6	(0.7–2.9)	0.42
	men	32	1.5	(0.6–2.2)	
BMI					
	≤26	36	1.5	(0.5–2.3)	0.76
	>26	36	1.6	(0.9–3.2)	
Place of residence					
	village	39	1.5	(0.7–not reached)	0.72
	cities ≤100 thous	32	1.5	(0.7–2.3)	
	cities >100 thous	41	1.6	(0.2–3.7)	
The distance from place of residence to Nu-Med Center					
	≤67 km	30	1.5	(0.5–2.2)	0.29
	>67 km	42	1.6	(0.9–3.1)	

		2-year OS (%)	Median OS [years] (95% CI)		Log-Rank test p
Performance status according to WHO/ECOG scale during first visit					
	0–1	39	1.6	(0.7–3.5)	0.04
	2	–	0.7	(0.4–1.1)	
Clinical stage					
	IB	33	1.9	(0.4–4.1)	0.63
	IIA	50	0.2	(0.2–2.3)	
	IIB	–	0.6	(0.5–1.7)	
	IIIA–B	37	1.5	(0.7–3.1)	
Lymph node status					
	N+	37	1.5	(0.7–2.6)	0.78
	N–	31	1.7	(0.5–3.1)	
Tumor localization					
	right	38	1.6	(0.7–2.6)	0.51*
	left	38	1.6	(0.7–not reached)	
Type of histopathology					
	planoepitheliale	32	1.5	(0.6–2.2)	0.29^
	adenocarcinoma	47	1.6	(1.0–4.2)	
PET					
	yes	40	1.5	(0.6–3.6)	0.52
	no	28	1.5	(0.7–2.1)	
Time of treatment from radiochemotherapy to end of radiotherapy					
	≤47.5 days	37	1.2	(0.5–2.6)	0.55
	>47.5 days	35	1.6	(1.0–2.6)	
Type of treatment					
	alone radiotherapy	25	1.1	(0.5–1.9)	0.07
	sequential radiochemotherapy	37	1.7	(1.0–2.6)	
	concurrent radiochemotherapy	46	1.1	(0.5–not reached)	

* patients with mediastinum tumor localization were excluded from the analysis
^ patients with undetermined type of histopathology were excluded from the analysis

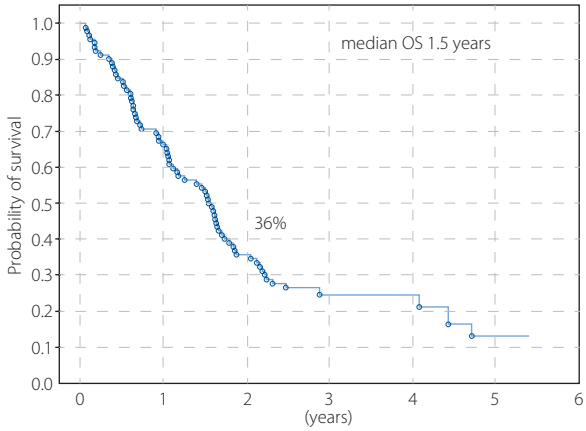

Figure 1. Overall survival for all patients

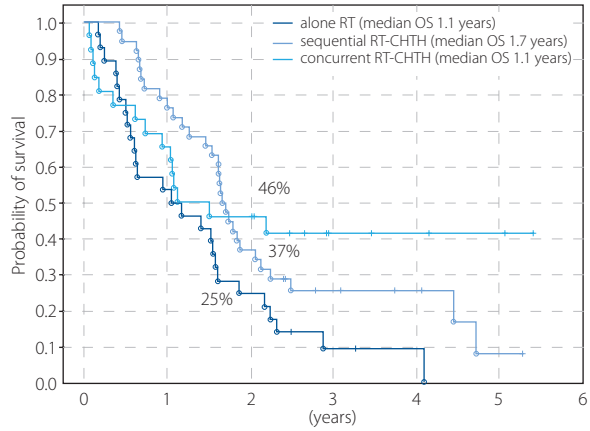

Figure 2. Overall survival by type of treatment

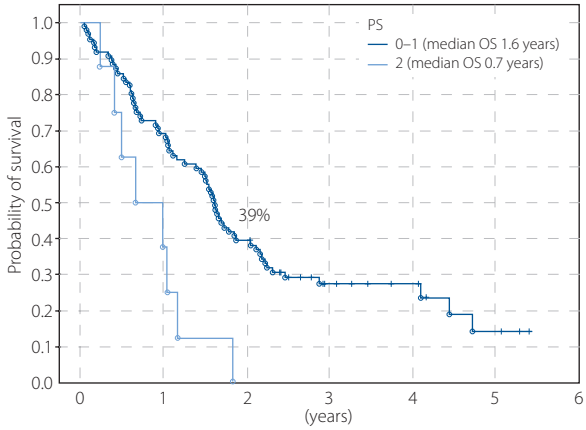

Figure 3. Overall survival by performance status during the first visit

In univariate analysis, only three factors met the inclusion criteria to a multivariate regression model ($p < 0.25$). In multivariate analysis, it was determined that performance status and type of treatment were independent factors influencing OS. The risk of death in patients with WHO/ECOG grade 2 increased by three times (PS 0–1 *vs.* 2, HR: 3.0; 95% CI: 1.4–6.6; $p = 0.006$). Increased risk of death was observed in patients treated with radiotherapy alone (HR: 2.4; 95% CI: 1.0–5.6; $p = 0.04$) compared with concurrent radiochemotherapy (tab. III).

Discussion

The optimal management of NSCLC patients depends on multiple factors, including the clinical stage of the disease, the potential to achieve a complete resection, the patient's overall condition, comorbidities and preferences. The main option for CS I–IIIA (N0–1) NSCLC remains surgery, for clinical stages: IIIA (N2), IIIB, and unresectable I–IIIA (N0–1) the standard of care is radiochemotherapy [10].

The current analysis concerned patients qualified for treatment before and after the Polish National Program of Diagnosis and Treatment of Oncological Diseases was set. Before 2015, in our centre, the decision to use the appropriate treatment was made by a team of radiation oncologists, after disqualification from surgery by thoracic surgeons. In 2015, we started to present patients at a multidisciplinary board with a radiation oncologist, a medical oncologist, a radiologist and a thoracic surgeon, where an accurate treatment plan was chosen.

Curative radiotherapy alone was chosen for elders and patients with a poorer performance status, who had con-

Table III. Uni- and multivariate survival analysis by Cox regression model

	Univariate analysis			Multivariate analysis		
Variables	**HR (95% CI)**		**p**	**HR (95% CI)**		**p**
Age (start of radiotherapy)						
≤64 years	1.0	reference		1.0	reference	
>64 years	1.4	(0.9–2.2)	0.17	0.79	(0.4–1.6)	0.50
Sex						
women	1.0	reference				
men	1.3	(0.7–2.3)	0.43			
BMI						
≤26	1.0	reference				
>26	0.9	(0.6–1.5)	0.76			
Place of residence						
village	1.0	reference				
cities ≤100 thous	1.2	(0.7–2.0)	0.59			
cities >100 thous	1.1	(0.6–2.2)	0.97			
Distance from place of residence to Nu-Med Center						
>67 km	1.0	reference				
≤67 km	1.3	(0.8–2.1)	0.30			
Performance status according to WHO/ECOG scale during first visit						
0–1	1.0	reference		1.0	reference	
2	2.9	(1.4–6.3)	0.006	3.0	(1.4–6.6)	0.006

		Univariate analysis			Multivariate analysis		
Clinical stage							
	IB	1.0	reference				
	IIA	1.3	(0.2–7.9)	0.77			
	IIB	2.1	(0.4–10.4)	0.38			
	IIIA–B	0.8	(0.3–2.7)	0.76			
Lymph nodes status							
	N–	1.0	reference				
	N+	1.1	(0.6–2.2)	0.78			
Tumor localization							
	left	1.0	reference				
	right	1.2	(0.7–2.0)	0.51*			
Type of histopathology							
	adenocarcinoma	1.0	reference				
	planoepitheliale	1.4	(0.7–2.4)	0.32^			
PET							
	yes	1.0	reference				
	no	1.2	(0.7–1.9)	0.51			
Time of treatment from radiochemotherapy to end of radiotherapy							
	>47.5 days	1.0	reference				
	≤47.5 days	1.2	(0.7–1.8)	0.55			
Type of treatment							
	concurrent radiochemotherapy				1.0	reference	
	alone radiotherapy	2.1	(1.1–4.1)	0.02	2.4	(1.0–5.6)	0.04
	sequential radiochemotherapy	1.2	(0.7–2.3)	0.53	1.1	(0.6–2.1)	0.72

* patients with mediastinum tumor localization were excluded from the analysis
^ patients with undetermined type of histopathology were excluded from the analysis

traindications to chemotherapy or in whom the application of the combined treatment would significantly increase its toxicity. The 2-year overall survival of our patients treated with radiotherapy only was 25% and this was at the upper limit of the survival time reported in the literature: 5–28% [11–15].

Patients in good general condition without significant comorbidities were qualified for combined therapies. At multidisciplinary meetings, concurrent radiochemotherapy was the preferred option. Sequential treatment was selected when the baseline tumour volume excluded radical radiotherapy and chemotherapy would provide a chance to reduce tumour mass (more advanced clinical stage, positive lymph node status).

The addition of chemotherapy to radiation has been the subject of many trials and several meta-analyses. Firstly, its beneficial influence on survival was demonstrated in the case of sequential radiochemotherapy in comparison with radical radiation alone. Adding induction chemotherapy to radiotherapy increased overall survival to 26–31% at two years [14, 16–18]. Secondly, the introduction of concurrent radiochemotherapy: although this intensification of treatment is associated with higher toxicity, most trials showed better survival with a concurrent association in comparison with sequential therapy [17, 19–24]. Combining chemotherapy and radiotherapy simultaneously increases 2-year overall survival to 35.6–55.6% [8, 17, 18, 23].

Our study showed the significant advantage of radiochemotherapy in survival outcomes when compared with radiotherapy alone. The 2-year survival of NSCLC patients treated with sequential and concomitant radiochemotherapy was 37% and 46% respectively. The results were comparable to those published in clinical trials and meta-analyses. However, this raport did not manage to show a significant difference in

efficiency between sequential and concomitant therapy. This could be limited by the small size of the subgroups compared. Unfortunately, our center, especially in the first years of operation, had no impact on the choice of combination therapy (simultaneous *vs.* sequential). The majority of patients who were suitable for concurrent treatment were referred to our department with no initial PET-CT scan and after the administration of induction chemotherapy – without the decision of a multidisciplinary board.

In the multivariate analysis, the type of treatment and performance status were independent factors influencing OS. We estimated the statistically significant increasing risk of death in patients treated with radiotherapy alone in comparison with concurrent radiochemotherapy and in patients with WHO/ECOG grade 2 at the first consultation. Polish colleagues also confirmed that performance status had a significant association with overall survival [25]. In our analyses, four PS 2 patients were treated with sequential chemoradiotherapy, and their ECOG status was probably an effect of the extent of the disease and chemotherapy toxicity.

In Poland, apart from clinical trias, institutional reports on the effectiveness of oncologic treatment of lung cancer are still lacking. A similar type of institutional report with a survival analysis of NSCLC patients was noted in the case of patients treated in the Warmia and Mazuria Oncology Center in Olsztyn, Poland. The authors showed treatment results for 130 patients treated with chemoradiotherapy in CS IIIA–IIIB and the 2-year overall survival was 37% [25]. The results are consistent with those reported by our analysis.

Nonetheless, we are aware of the limitations of this study. It is a retrospective analysis, with a small sample and a short observation time. Comparison of the groups also has limited value because of the small subgroups and potential selection bias.

Conclusions

The survival data of NSCLC patients treated in the Nu-Med Radiotherapy Center in Elblag is comparable to those published in other papers. Forty-six percent of patients treated with concurrent radiochemotherapy survived 2 years. The main risk factors which decreased OS were: the type of therapy and performance status. A significantly worse prognosis was noted in the case of radiation alone compared to radiochemotherapy. and poorer performance status during first consultation. Particular attention should be paid to the proper qualification of the lung cancer patient for the appropriate treatment – preferebly during multidisciplinary meetings.

Conflict of interest: none declared

Marcin Kurowicki
Nu-Med Radiotherapy Center
ul Królewiecka 146
82-300 Elbląg, Poland
e-mail: marcin.kurowicki@nu-med.pl

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References

1. Krajowy Rejestr Nowotworów - Nowotwory złośliwe opłucnej i płuca (C33-34). http://onkologia.org.pl/nowotwory-zlosliwe-oplucnej--pluca-c33-34/.
2. Alberg AJ, Brock MV, Ford JG, et al. Epidemiology of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013; 143(5 Suppl): e1S–e29S, doi: 10.1378/chest.12-2345, indexed in Pubmed: 23649439.
3. Moura MA, Bergmann A, Aguiar SS, et al. The magnitude of the association between smoking and the risk of developing cancer in Brazil: a multicenter study. BMJ Open. 2014; 4(2): e003736, doi: 10.1136/bmjopen-2013-003736, indexed in Pubmed: 24519874.
4. Ginsberg JR. Thoracic surgery. Churchill-Livingstone, Philadelphia 2002.
5. EUROCARE - Survival of cancer patients in Europe. https://w3.iss.it/site/EU5Results/forms/SA0007.aspx.
6. Krzakowski M, Jassem J, Dziadziuszko R. et al. Nowotwory płuca i opłucnej oraz śródpiersia. 20013: 71.
7. Yang P, Allen MS, Aubry MC, et al. Clinical features of 5,628 primary lung cancer patients: experience at Mayo Clinic from 1997 to 2003. Chest. 2005; 128(1): 452–462, doi: 10.1378/chest.128.1.452, indexed in Pubmed: 16002972.
8. Gray JE, Villegas A, Daniel D, et al. PACIFIC Investigators. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med. 2018; 379(24): 2342–2350, doi: 10.1056/NEJMoa1809697, indexed in Pubmed: 30280658.
9. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N Engl J Med. 1985; 312(25): 1604–1608, doi: 10.1056/NEJM198506203122504, indexed in Pubmed: 4000199.
10. Eberhardt WEE, De Ruysscher D, Weder W, et al. Panel Members. 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. Ann Oncol. 2015; 26(8): 1573–1588, doi: 10.1093/annonc/mdv187, indexed in Pubmed: 25897013.
11. Blanke CD, Johnson DH. Combined modality therapy in non--small cell lung cancer. Curr Opin Oncol. 1995; 7(2): 144–149, doi: 10.1097/00001622-199503000-00009, indexed in Pubmed: 7756379.
12. Cakir S, Egehan I. A randomised clinical trial of radiotherapy plus cisplatin versus radiotherapy alone in stage III non-small cell lung cancer. Lung Cancer. 2004; 43(3): 309–316, doi: 10.1016/j.lungcan.2003.09.009, indexed in Pubmed: 15165089.
13. Groen HJM, van der Leest AHW, Fokkema E, et al. Continuously infused carboplatin used as radiosensitizer in locally unresectable non-small--cell lung cancer: a multicenter phase III study. Ann Oncol. 2004; 15(3): 427–432, doi: 10.1093/annonc/mdh100, indexed in Pubmed: 14998844.
14. Dillman RO, Seagren SL, Propert KJ, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. N Engl J Med. 1990; 323(14): 940–945, doi: 10.1056/NEJM199010043231403, indexed in Pubmed: 2169587.
15. O'Rourke N, Roqué I Figuls M, Farré Bernadó N, et al. Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev. 2010(6): CD002140, doi: 10.1002/14651858.CD002140.pub3, indexed in Pubmed: 20556756.
16. Huber RM, Flentje M, Schmidt M, et al. Bronchial Carcinoma Therapy Group. Simultaneous chemoradiotherapy compared with radiotherapy alone after induction chemotherapy in inoperable stage IIIA or IIIB non--small-cell lung cancer: study CTRT99/97 by the Bronchial Carcinoma Therapy Group. J Clin Oncol. 2006; 24(27): 4397–4404, doi: 10.1200/JCO.2005.05.4163, indexed in Pubmed: 16983107.
17. Curran WJ, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst. 2011; 103(19): 1452–1460, doi: 10.1093/jnci/djr325, indexed in Pubmed: 21903745.
18. Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small--cell lung cancer. J Clin Oncol. 2010; 28(13): 2181–2190, doi: 10.1200/JCO.2009.26.2543, indexed in Pubmed: 20351327.
19. Belani CP, Wang W, Johnson DH, et al. Eastern Cooperative Oncology Group. Phase III study of the Eastern Cooperative Oncology Group (ECOG 2597): induction chemotherapy followed by either standard thoracic radiotherapy or hyperfractionated accelerated radiotherapy for patients with unresectable stage IIIA and B non-small-cell lung cancer.

J Clin Oncol. 2005; 23(16): 3760–3767, doi: 10.1200/JCO.2005.09.108, indexed in Pubmed: 15837967.
20. Provencio M, Isla D, Sánchez A, et al. Inoperable stage III non-small cell lung cancer: Current treatment and role of vinorelbine. J Thorac Dis. 2011; 3(3): 197–204, doi: 10.3978/j.issn.2072-1439.2011.01.02, indexed in Pubmed: 22263088.
21. Gouda YS, Kohail HM, Eldeeb NA, et al. Randomized study of concurrent carboplatin, paclitaxel, and radiotherapy with or without prior induction chemotherapy in patients with locally advanced non-small cell lung cancer. J Egypt Natl Canc Inst. 2006; 18(1): 73–81, indexed in Pubmed: 17237853.
22. Jalal SI, Riggs HD, Melnyk A, et al. Hoosier Oncology Group, US Oncology. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. J Clin Oncol. 2008; 26(35): 5755–5760, doi: 10.1200/JCO.2008.17.7840, indexed in Pubmed: 19001323.
23. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two--by-two factorial phase 3 study. Lancet Oncol. 2015; 16(2): 187–199, doi: 10.1016/S1470-2045(14)71207-0, indexed in Pubmed: 25601342.
24. Walraven I, Damhuis RA, Ten Berge MG, et al. Treatment Variation of Sequential versus Concurrent Chemoradiotherapy in Stage III Non-Small Cell Lung Cancer Patients in the Netherlands and Belgium. Clin Oncol (R Coll Radiol). 2017; 29(11): e177–e185, doi: 10.1016/j.clon.2017.07.012, indexed in Pubmed: 28780009.
25. Osowiecka K, Rucińska M, Każarnowicz A, et al. Przeżycia chorych na niedrobnokomórkowego raka płuca leczonych napromienianiem w latach 2003–2006 w Samodzielnym Publicznym Zakładzie Opieki Zdrowotnej Ministerstwa Spraw Wewnętrznych z Warmińsko-Mazurskim Centrum Onkologii w Olsztynie. NOWOTWORY J Oncol. 2015; 65(1): 14–22, doi: 10.5603/njo.2015.0003.

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Genetics and oncology (part 1.)
Fundamentals of genetic testing-based personalised medicine in oncology

Maria M. Sąsiadek[1], Izabela Łaczmańska[1, 2], Adam Maciejczyk[2, 3], Rafał Matkowski[2, 3], Justyna Gil[1]

[1]*Department of Genetics, Wroclaw Medical University, Wroclaw, Poland*
[2]*Wrocław Comprehensive Cancer Center, Wroclaw, Poland*
[3]*Department of Oncology, Wrocław Medical University, Wroclaw, Poland*

The dynamic development of genetics in recent decades has opened a new era in medicine. Understanding molecular mechanisms of multiple human diseases has laid the foundations for targeted medical care, based on knowledge of the basic pathogenesis of these diseases. This breakthrough is particularly evident in oncology because knowledge of the molecular basis of cancer leads to a change in the paradigm of medical care for the patients. Gradually, classification and treatment based only on organ location and histopathologic diagnosis is becoming outdated, and so is the classification considering clinical stage and malignancy of the tumour. Personalized treatment for individual patients based on the profile of genetic changes is increasingly common. Defining the genetic aetiology of neoplastic diseases was an achievement that allowed for division of neoplasms into sporadic ones and those which develop due to hereditary predisposition. It also enabled establishment of the molecular classification of neoplasms and more and more frequently – targeted treatment and precise clinical prognosis.

This article is the first one in a series of articles written by oncologists and geneticists. We hope that this series will be helpful for oncologists in understanding genetic problems and for geneticists – in understanding oncologic issues.

Key words: personalised medicine, oncology, molecular classification, predictive tests, prognostic tests

Introduction

Personalized (targeted, precise) medicine is based on knowledge of the genetic aetiology of a disease, and its objective is to introduce medical treatment adapted to specific molecular alterations that cause pathology [1–3]. The underlying concept of this approach is to optimise therapy by using precisely targeted drugs, and thus minimizing side effects and optimising patient care costs, as targeted therapy reduces the risk of administration of a therapy which is ineffective or leads to adverse effects [1–3].

Thus defined, the idea of personalized medicine is not new – it was authored by Paul Erlich (Nobel prize laureate in 1908), who developed the concept of causal treatment (magic bullet) based on identification of the pathogenic agent [4].

In oncology, introduction of personalised procedures into clinical practice has become possible with development of testing techniques that allow identification of genetic changes and molecular pathways that are key in the aetiology of cancer, and which are present or absent in individual patients with the same histopathological diagnosis of the tumour [1].

Currently, mainly genomic and genetic testing techniques are applied to identify the "molecular target of personalised medicine" (mutations of individual genes, chromosome aberrations, methylation disorders). These techniques

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include next generation sequencing (NGS), cytogenic and molecular cytogenetic tests: multiplex ligation-dependent probe amplification (MLPA), fluorescent in situ hybridization (FISH), array comparative genomic hybridization (aCGH), gene expression studies, and soon, proteomic testing techniques will be available, too [5, 6].

Genetic basis of cancer

In research aimed at understanding the genetic background of cancers, a breakthrough achievement occurred in early 1970s with development of a model of inheriting retinoblastoma based on the analysis of incidence of this neoplasm in affected families, and with development of the theory concerning mechanism of suppressor genes' effect in this model (Knudson's two hit hypothesis) [7, 8]. Publications by Knudson and al. encouraged research concerning neoplasms and nowadays, after years of epidemiologic analyses, family clinical studies and along with genetic research, 5-10% of neoplasms are known to belong to hereditary cancer syndromes, most commonly characterised by autosomal dominant, and more rarely – autosomal recessive inheritance [9, 10].

About 15% of cancer cases are familial and are determined by multifactorial inheritance mechanism (interaction of environmental, potentially carcinogenic and genetic factors that increase individual sensitivity to their effects), and the remaining approximately 75% develop as a sporadic disease [11].

Studies of the constitutional genome of cancer patients and cancer cells have led to the conclusion that they are two different genomes: the constitutional shows stability and invariability throughout lifetime, while cancer cell genome are highly heterogeneous and unstable. The instability of the latter genome is the reason for its variability both in an individual patient in the course of tumour progression, as well as in different cancer patients with the same histopathological diagnosis [12].

Genetic studies have shown that cancers classified in a single group based on histopathological studies represent actually many different types. This may be evidenced by lung cancer, traditionally classified as small-cell cancer and non-small cell cancer (adenocarcinoma and squamous cell cancer). However, genetic tests of lung cancer cells have revealed a vast complexity of its molecular forms [13].

Tumour development is a process stretched over time (most commonly it lasts 5–20 years), and its multi-stage course is determined by mutations which accumulate in the cell, leading to a change in its biological properties [14]. In 2011, Hanahan and Weinberg defined eight major biological features of cancer and two potential ones:

- proliferation independent from signals stimulating cell division,
- no reaction to proliferation inhibitors,
- no programmed cell death,
- replication immortality,
- angiogenesis,
- activation of infiltration and metastasis processes,
- genome instability,
- inflammation that promotes neoplasia,
- changes in energy metabolism,
- "escape" from the immune system's "supervision" mechanism. [15].

Currently, researchers consider two major theories of neoplastic transformation as grounded: clonal and cancer stem cells theory. Both refer to expansion of cancer cells, development of genetically variable cell clones and selection of clones of the highest potential for proliferation and adaptation to the tissue eco-system [16, 17]. The difference between these theories lies in different properties of the first cell from which the transformation process begins. According to the clonal theory, the transformation is triggered by a random cell in the body where the first mutation occurs; while according to the cancer stem cell theory – by a cancer stem cell. Cancer stem cells form a small (below 1%) subpopulation of tumour cells of particular biological properties, e.g. low proliferation potential, no capacity of final differentiation, presence of characteristic surface markers [17].

In the neoplastic transformation, the main role is played by three groups of genes: oncogenes, suppressor genes and mutator genes. Oncogenes are activated forms of protooncogenes which are present in every cell of the body. In the process of neoplastic transformation, they stimulate cell proliferation. For most cancers , it is possible to identify an oncogene which is the leading genetic force (driver mutation) responsible for uncontrolled cell division. This phenomenon is called oncogene addiction. Suppressor genes are classified as "gatekeepers" because they control cell division points, directing mutated cells to a path of repair of DNA damage or to programmed death (apoptosis). Finally, mutator genes are referred to as "caretakers" and they are responsible for removing unpaired and mispaired bases from DNA, as such bases are the cause of mutation [14].

Cancer development, clinical course and response to therapy are affected by these three groups of genes of key impact on neoplastic transformation (genes of high penetrance), but also by many genes of moderate and low penetrance (e.g. genes which are involved in the process of angiogenesis, cell array adhesion, affect the organism's immune reaction, localised tumour development, metastasis potential, reaction to therapy and many other processes) [14].

In the process of neoplastic transformation all those genes are interconnected in complex networks of mutual interdependence. Thus, they are all regulated by other genes located upstream on the signalling pathway (upstream genes), and they themselves regulate activity of downstream genes. This is the "vertical" regulation system, and at the same time mutual interrelations of genes are expressed in "horizontal" bonds - e.g. through modification of the tumour ecosystem

on the local (tissue) level and in the entire body (e.g. immune reactions) [18].

Functional alterations of oncogenes, suppressor genes and mutator genes lead to genetic instability of cancer cells. Instability may be expressed on the chromosome level (aberrations of the number and structure of chromosomes), gene level (accumulation of mutations) or in alterations of epigenetic regulation of gene expression (global hypomethylation which contributes to cells' chromosomal instability and hypermethylation of suppressor and mutator genes, thus leading to loss of their function). Accumulation of genetic alterations in cells causes changes of their biological properties and also leads to development of resistance to the therapy [14, 19].

Personalized care for cancer patients

Personalised medicine in oncology should be offered to patients with inherited cancer syndromes, as well as patients with sporadic neoplasms.

Carriers of critical mutations which determine inheritance of this syndrome receive personalised medical care including:

1. Prophylaxis: for most hereditary cancer syndromes , the increased risk concerns not only a specific, individual organ, but also other ones within the risk spectrum. This can be illustrated by the hereditary non-polyposis colorectal cancer (HNPCC), also referred to as Lynch syndrome. Its spectrum includes colonic cancer, but also cancers of the endometrium, ovary, bile ducts, urinary tract, stomach and brain [20]. Knowledge of this spectrum allows optimisation of prophylaxis by planning a test program or resection of healthy organs from the spectrum (depending on the risk of developing cancer).
2. Chemoprevention (prophylactic drug administration aimed at reduction of the risk of cancer development, e.g. administration of tamoxifen) in carriers of *BRCA1/BRCA2* gene mutation [21].
3. Personalisation of medical management, e.g. special recommendations concerning surgical management in carriers of *BRCA1* and *BRCA2* mutations and concerning targeted management (e.g. olaparib in patients with ovarian cancer and hereditary and/or somatic mutation of *BRCA1/BRCA2)* [21].
4. Genetic counselling for patients and their families, provided by clinical geneticists and based on the analysis of pedigree and clinical data and results of genetic tests. With a family and clinical analysis it is possible to diagnose or suspect the hereditary cancer syndrome and to determine the scope of genetic testing for the individual patient, but it also enables interpretation of the genetic test results in the clinical context. Moreover, it is possible to identify family members, who may carry the critical mutation, and further to select the optimal method of genetic testing for those people and genetic counselling with information on the risk of further transfer of the mutation [22]. Predictive tests, i.e. those performed in healthy people with a family risk of cancer, are legally allowed in adults and should always be performed on two independent material samples.

Rules for selection of genetic diagnosis methods in patients with cancer for the purpose of personalised medicine

Regardless of whether neoplasm development is due to inherited, family, or sporadic factors, cancer cells have their own genome of specific properties described above.

If molecular changes are identified, it is possible to determine the following markers:

- diagnostic – supporting the diagnosis process,
- predictive – enabling forecasting of response to the applied treatment,
- prognostic – allowing determination of prognosis. For this purpose, testing of DNA isolated from cancer cells is needed.

Choosing the right method of genetic testing is crucial, both for medical and economic reasons.

Genetic diagnosis in hereditary cancer syndromes

The objective of genetic testing is to identify hereditary mutations, and the tested material is isolated DNA from somatic cells (usually lymphocytes of peripheral blood, as well as skin fibroblasts or mucosal cells – smear of the internal aspect of cheek).

Most of hereditary cancer syndromes are characterized by high genetic diversity, despite the same clinical manifestations of the disease. This phenomenon is described by the concepts of genetic, allelic, and non-allelic heterogeneity. The term allelic heterogeneity means that there is more than one mutation in a critical gene (e.g., about 1,200 mutations are known in the *BRCA1* gene). Meanwhile, non-allelic heterogeneity occurs when the same disease may be conditioned by pathogenic variants in different genes. One example of non-allelic heterogeneity is the hereditary breast/ovarian cancer syndrome, which may be conditioned by mutations in multiple genes, however the most common mutations occur in *BRCA1* gene (approximately 25% of patients with this syndrome) and *BRCA2* (another 25% of patients), and in the remaining group of patients the syndrome may occur due to mutation of such genes as: *ATM, BARD1, BLM, BRIP1, CHEK2, MLH1, MRE11, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53* [23].

Out of these genes, some (e.g. *BRCA1* and *BRCA2*) belong to the "high-penetrance genes" group, which means that carriers of their pathogenic variants have a defined, high risk of developing breast/ovarian cancer. Other genes in this group are classified as "moderate-penetrance genes", which moderately increase the risk of development of a cancer and the forecast risk is based on an analysis of a genetic test result and family history of cancer [24]. In the case of some genes, researchers

have described a phenomenon of preferential occurrence of some mutations in a specific population - "founder mutations" (e.g. in the case of *BRCA1* gene, in the Polish population about 50% of patients with mutation of this gene have one of the following three mutations: c.5266dupC (former name: 5382insC), c.4035delA (former name: 4153delA), c.181T > G p.Cys61Gly (former name: C61G) [23, 25].

The situation becomes even more complicated, if one considers that not all genetic changes have the same clinical consequences. The pathogenicity of some variants is known, and clinical management standards have been developed for their carriers. On the other hand, other variants are rarely described, their pathogenicity has not yet been clearly defined, while available knowledge and bioinformatic analysis allow to classify them as potentially pathogenic changes. Some changes have not been described so far and constitute the group of lesions of unknown clinical significance (variants of unknown significance – VUS). In the ClinVar database, among the 9,073 described variants of the *BRCA1 and BRCA2* genes, approximately 2197 are variants with unknown pathogenicity [26]. As databases are constantly updated and new variants are constantly characterised, the result of NGS test analysis in a patient should indicate the date of accessing the databases and the obtained data should be stored for potential re-analysis in future.

In this complicated genetic situation, there is still no consensus concerning the scope of genetic tests to be recommended for patients with specific clinical problems.

Some authors claim that the optimal recommendation is to sequence all genes which potentially may be critical for the hereditary cancer syndrome in question (clinical panel). The benefits of this approach include reduced testing costs and reduced waiting time, as well as effective use of isolated DNA. There are also negative consequences: increased number of identified variants of unknown pathogenicity or variants in genes for which no standard clinical proceeding has been developed, as well as identification of changes in genes of moderate and low penetrance, leading to a difficult situation for the patient and doctor, when targeted clinical management cannot be introduced, even though the genetic change is known [27].

Other authors claim that the request should include testing only those genes for which there are clinical procedures developed (targetable mutations). Some countries (e.g. United Kingdom) have developed official diagnostic recommendations, e.g. Recommendations of the UK Cancer Genetics Group (2018) for diagnostics of genes whose mutations determine the risk of occurrence of hereditary breast (*BRCA1, BRCA2, PALB2, PTEN, STK11, TP53*) or ovarian (*BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, RAD51C, RAD51D*) cancer syndromes [28].

Personalized management based on genetic changes in cancer cells

Identification of genetic changes in cancer cells allowed better understanding of molecular mechanisms of neoplastic transformation, and thus, it enabled more precise, cause-based classification of cancers and development of targeted treatment. Cancer cells may be tested using DNA isolated from the primary or metastatic tumour cells, or else from cancer cells or cancer DNA circulating in the patient's blood (liquid biopsy). Consistency of the genetic tests results for the primary tumour and lymph node metastases with those for other primary tumours is uncertain, while comparison of test results for primary tumours and material circulating in the patients' serum may give variable results [29].

The genetic heterogeneity of cancer tumours and the fact that tumours of the same histopathological diagnosis differ essentially in genetic aetiology explains to a large extent the variability of patients' responses to standardised therapies and different clinical course of the disease. Currently, a molecular classification is being developed for an increasing number of cancers that allows for precise biological differentiation of tumours. This is crucial for choosing personalized clinical management. This may be evidenced by the molecular classification of brain gliomas (WHO Classification, 2016), which allows identification of different forms of low-differentiated gliomas: distinguishing primary glioblastoma multiforme (without *IDH1/IDH2* mutation, with presence of: 10q deletion, *PTEN* mutation, *EGFR* amplification, *CDKN2A/2B* deletion) from secondary glioblastoma multiforme (with *IDH1/IDH2* mutation) originating oligoastrocytomas (*IDH1/IDH2* mutation, 1p/19q co-deletion, *TP53* mutation and 9p deletion), diffuse astrocytomas (*IDH1/IDH2* and *TP53* mutations, 17p, 9p, 20q deletions) or anaplastic oligodendroglioma (1p/19q co-deletion and deletion of 9p and 10q) [30].

As genetic testing of cells of various cancers is increasingly broadly applied, it was found that there are several common pathways of signal transmission which stimulate neoplastic transformation, e.g. the pathway starting from activation of the epidermal growth factor receptor (*EGFR*) or tyrosine kinase (*RTK*), which lead to stimulation of cell proliferation [31]. Understanding that the same signalling pathways may be activated in different neoplasms leads to a modification of rules of classification of neoplastic tumours for the purpose of targeted management: the molecular classification has become important parallelly to the organ-based classification. The increasing share of medication is applied molecularly. Consequently, patients with different cancers – but with the same mutations – are treated with the same drugs [32]. For example, there is a treatment which involves blocking of factors that stimulate hyperproliferation and it is the same for cancers that differ in location and histopathology, but "depend" on the same oncogene, such as application of:

- trastuzumab in breast and stomach cancers in which the key molecular change is amplification of the *HER2* gene
- crozitinib in patients with non-small cell lung cancer with *ALK* mutations,
- gefitinib in tumours of the same histopathologic type, but with *EGFR* amplification,

- imatinib in cancer patients with the *KIT* mutation or *BCR / ABL* fusion gene,
- vemurafenib in cancer patients with *BRAF* mutations [32, 33].

Molecular testing of cancer cells allowed also for explanation of the phenomenon of non-identical response to targeted treatment in patients with the same leading molecular change, e.g. *EGFR* amplification. Different studies, e.g. concerning metastases of colonic cancer, have shown modification of functions of multiple genes involved in the signalling pathway in neoplasms, making downstream genes independent from genes located upstream the signalling path which normally regulate their expression (*EGFR – RAS – BRAF – MEK / ERK* or *EGFR – PI3K – AKT* and *PTEN*) [31, 32].

This complicated system of genetic relationships in cancer cells leads to further dilemmas in genetic diagnostics. There is a question whether assessment of prognostic markers before initiation of the targeted therapy should rely on individual genes which mutate the most commonly (e.g. *EGFR* amplification) or a panel of genes on the specific signalling pathway. There are no specific guidelines for management of most tumours yet, e.g. for metastatic colonic cancer. The US Food and Drug Administration (US FDA) has already approved a panel for testing *KRAS* and *NRAS* gene mutations to allow identification of 56 specific mutations in exons 2, 3 and 4 of these genes [34].

Treatment of cancer patients with drugs selected on the basis of molecular changes is a very promising trend in therapy. However, usually after approximately two years of treatment, patients acquire resistance to the therapy [31, 32].

The mechanisms of acquired resistance to treatment vary, but they can be classified in two main groups:

1. Internal tumour resistance (intrinsic resistance), which results from the high genetic instability of cancer cells and leads to a rapid change in their genetic characteristics, both spontaneous and in response to the treatment used (leading to the elimination of dominant cell clones, which are replaced by less numerous clones of different genetic characteristics).
2. Induced resistance (acquired resistance), which arises in response to treatment and results from:
   - activation (through mutations) of genes located on the signal pathway below the gene which is the current "target (effector)" of treatment (activation of upstream effector),
   - activation of another oncogene that stimulates cell proliferation (bypass, bypass of (onco) protein effector),
   - activation of another signalling pathway (kinase target) [35].

Prognostic and predictive tests

The clinical and genetic heterogeneity of neoplastic diseases means that frequently it is not possible to precisely predict the course of neoplastic disease for an individual patient. This is a serious medical, psychological, and social problem. Therefore, for years researchers have been striving to develop molecular tests that would allow forecasting of different aspects of the disease, e.g. overall survival rate or survival rate before metastases. Despite many years of research and multiple predictive tests offered on the market, none of them has been approved for routine application in clinical practice yet.

Currently, many predictive tests are available, meant for patients with various neoplasms, but the highest number of tests is designed for patients with breast cancer. These tests are based on analysis of expression of various genes in the tumour tissue and they differ both in the scope of predictive potential and analysed genes.

The most commonly used tests include: Mammaprint, Oncotype Dx Breast, Prosigna PAM-50 Breast Cancer Prognostic Gene Signature Assay, Breast Cancer Index (BCI) and EndoPredict. All four tests are intended for patients post breast tumour resection, with known hormonal status and condition of lymph nodes, as well as size and grade of the tumour. These tests assess the risk of distant recurrence (and Oncotype DX also assesses the response to chemotherapy) [36–38].

Prostate cancer is another type of cancer that occurs frequently and displays great clinical variability. Patients with this disease have access to two main tests available on the market, which forecast course of the disease. These are Oncotype Dx Genomic Prostate Score and Genomic Classifier, Decipher (based on assessment of 22 RNA markers).

Currently, research is underway to develop prognostic tests for patients with other cancers, too: urinary bladder cancer (Decipher Bladder), cancers with unknown primary (Response Dx, CancerTYPE ID, Rosetta Cancer Origin, ProOnc, SourceDX, PathfinderTG), colonic cancer (Oncotype DX Colon Cancer Assay, Colorectal Cancer DSA, GeneFx Colon, OncoDefender CRC), leukaemia (FoundationOne® Heme) or melanoma (Decision Dx – Melanoma, Decision Dx-UM, DermTech PLA). However, it has not been proven yet, whether these tests are clinically relevant [37].

Conclusion

Development of personalised medicine in oncology leads to a change of the paradigm of understanding neoplasms, and thus also to a change of the broadly defined medical care for oncological patients and their families. Only cooperation between oncologists and geneticists will allow introduction of truly personalised medical care based on understanding of the genetic background of cancer.

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Izabela Łaczmańska
Wroclaw Medical University
Chair and Department of Genetics
ul. Marcinkowskiego 1
50-368 Wrocław, Poland
e-mail: izabela.laczmanska@umed.wroc.pl

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References

1. Filipp FV. Precision medicine driven by cancer systems biology. Cancer Metastasis Rev. 2017; 36(1): 91–108, doi: 10.1007/s10555-017-9662-4, indexed in Pubmed: 28265786.
2. Ginsburg GS, Phillips KA. Precision Medicine: From Science To Value. Health Aff (Millwood). 2018; 37(5): 694–701, doi: 10.1377/hlthaff.2017.1624, indexed in Pubmed: 29733705.
3. Vogenberg FR, Isaacson Barash C, Pursel M. Personalized medicine: part 1: evolution and development into theranostics. P T. 2010; 35(10): 560–576, indexed in Pubmed: 21037908.
4. Strebhardt K, Ullrich A. Paul Ehrlich's magic bullet concept: 100 years of progress. Nat Rev Cancer. 2008; 8(6): 473–480, doi: 10.1038/nrc2394, indexed in Pubmed: 18469827.
5. Kowalik A, Kowalewska M, Góźdź S. Current approaches for avoiding the limitations of circulating tumor cells detection methods-implications for diagnosis and treatment of patients with solid tumors. Transl Res. 2017; 185: 58–84.e15, doi: 10.1016/j.trsl.2017.04.002, indexed in Pubmed: 28506696.
6. Ribeiro IP, Melo JB, Carreira IM. Cytogenetics and Cytogenomics Evaluation in Cancer. Int J Mol Sci. 2019; 20(19), doi: 10.3390/ijms20194711, indexed in Pubmed: 31547595.
7. Knudson AG. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci U S A. 1971; 68(4): 820–823, doi: 10.1073/pnas.68.4.820, indexed in Pubmed: 5279523.
8. Knudson AG, Hethcote HW, Brown BW. Mutation and childhood cancer: a probabilistic model for the incidence of retinoblastoma. Proc Natl Acad Sci U S A. 1975; 72(12): 5116–5120, doi: 10.1073/pnas.72.12.5116, indexed in Pubmed: 1061095.
9. Nagy R, Sweet K, Eng C. Highly penetrant hereditary cancer syndromes. Oncogene. 2004; 23(38): 6445–6470, doi: 10.1038/sj.onc.1207714, indexed in Pubmed: 15322516.
10. Garber JE, Offit K. Hereditary cancer predisposition syndromes. J Clin Oncol. 2005; 23(2): 276–292, doi: 10.1200/JCO.2005.10.042, indexed in Pubmed: 15637391.
11. McCartan D, Chatterjee S. Hereditary and familial cancer. Surgery (Oxford). 2018; 36(3): 145–150, doi: 10.1016/j.mpsur.2017.12.003.
12. Stratton MR, Campbell PJ, Futreal PA. The cancer genome. Nature. 2009; 458(7239): 719–724, doi: 10.1038/nature07943, indexed in Pubmed: 19360079.
13. Kutkowska J, Porębska I, Rapak A. Non-small cell lung cancer - mutations, targeted and combination therapy. Postepy Hig Med Dosw (Online). 2017; 71(0): 431–445, doi: 10.5604/01.3001.0010.3826, indexed in Pubmed: 28513466.
14. Bashyam MD, Animireddy S, Bala P, et al. The Yin and Yang of cancer genes. Gene. 2019; 704: 121–133, doi: 10.1016/j.gene.2019.04.025, indexed in Pubmed: 30980945.
15. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144(5): 646–674, doi: 10.1016/j.cell.2011.02.013, indexed in Pubmed: 21376230.
16. Greaves M, Maley CC. Clonal evolution in cancer. Nature. 2012; 481(7381): 306–313, doi: 10.1038/nature10762, indexed in Pubmed: 22258609.
17. Gil J, Stembalska A, Pesz KA, et al. Cancer stem cells: the theory and perspectives in cancer therapy. J Appl Genet. 2008; 49(2): 193–199, doi: 10.1007/BF03195612, indexed in Pubmed: 18436993.
18. Fronczak A. Medycyna personalizowana. Mity, fakty, rekomendacje. Plexus s.c, Łódź 2016.
19. Vargas-Rondón N, Villegas VE, Rondón-Lagos M. The Role of Chromosomal Instability in Cancer and Therapeutic Responses. Cancers (Basel). 2017; 10(1), doi: 10.3390/cancers10010004, indexed in Pubmed: 29283387.
20. Møller P. The Prospective Lynch Syndrome Database reports enable evidence-based personal precision health care. Hered Cancer Clin Pract. 2020; 18: 6, doi: 10.1186/s13053-020-0138-0, indexed in Pubmed: 32190163.
21. King MC, Wieand S, Hale K, et al. National Surgical Adjuvant Breast and Bowel Project. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA. 2001; 286(18): 2251–2256, doi: 10.1001/jama.286.18.2251, indexed in Pubmed: 11710890.
22. Lewis KM. Identifying hereditary cancer: genetic counseling and cancer risk assessment. Curr Probl Cancer. 2014; 38(6): 216–225, doi: 10.1016/j.currproblcancer.2014.10.002, indexed in Pubmed: 25432528.
23. McClellan J, King MC. Genetic heterogeneity in human disease. Cell. 2010; 141(2): 210–217, doi: 10.1016/j.cell.2010.03.032, indexed in Pubmed: 20403315.
24. Kiwerska K, Szyfter K. DNA repair in cancer initiation, progression, and therapy-a double-edged sword. J Appl Genet. 2019; 60(3-4): 329–334, doi: 10.1007/s13353-019-00516-9, indexed in Pubmed: 31468363.
25. Kowalik A, Siołek M, Kopczyński J, et al. BRCA1 founder mutations and beyond in the Polish population: A single-institution BRCA1/2 next-generation sequencing study. PLoS One. 2018; 13(7): e0201086, doi: 10.1371/journal.pone.0201086, indexed in Pubmed: 30040829.
26. Landrum MJ, Lee JM, Benson M, et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res. 2018; 46(D1): D1062–D1067, doi: 10.1093/nar/gkx1153, indexed in Pubmed: 29165669.
27. Gagan J, Van Allen EM. Next-generation sequencing to guide cancer therapy. Genome Med. 2015; 7(1): 80, doi: 10.1186/s13073-015-0203-x, indexed in Pubmed: 26221189.
28. Taylor A, Brady AF, Frayling IM, et al. UK Cancer Genetics Group (UKCGG). Consensus for genes to be included on cancer panel tests offered by UK genetics services: guidelines of the UK Cancer Genetics Group. J Med Genet. 2018; 55(6): 372–377, doi: 10.1136/jmedgenet-2017-105188, indexed in Pubmed: 29661970.
29. Qiu J, Xu J, Zhang K, et al. Refining Cancer Management Using Integrated Liquid Biopsy. Theranostics. 2020; 10(5): 2374–2384, doi: 10.7150/thno.40677, indexed in Pubmed: 32089746.
30. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016; 131(6): 803–820, doi: 10.1007/s00401-016-1545-1, indexed in Pubmed: 27157931.
31. Yamaoka T, Kusumoto S, Ando K, et al. Receptor Tyrosine Kinase-Targeted Cancer Therapy. Int J Mol Sci. 2018; 19(11), doi: 10.3390/ijms19113491, indexed in Pubmed: 30404198.
32. Krzyszczyk P, Acevedo A, Davidoff EJ, et al. The growing role of precision and personalized medicine for cancer treatment. Technology (Singap World Sci). 2018; 6(3-4): 79–100, doi: 10.1142/S2339547818300020, indexed in Pubmed: 30713991.
33. Helgadottir H, Rocha Trocoli Drakensjö I, Girnita A. Personalized Medicine in Malignant Melanoma: Towards Patient Tailored Treatment. Front Oncol. 2018; 8: 202, doi: 10.3389/fonc.2018.00202, indexed in Pubmed: 29946532.
34. Afrăsânie VA, Marinca MV, Alexa-Stratulat T, et al. KRAS, NRAS, BRAF, HER2 and microsatellite instability in metastatic colorectal cancer - practical implications for the clinician. Radiol Oncol. 2019; 53(3): 265–274, doi: 10.2478/raon-2019-0033, indexed in Pubmed: 31553708.
35. von Manstein V, Yang CM, Richter D, et al. Resistance of Cancer Cells to Targeted Therapies Through the Activation of Compensating Signaling Loops. Curr Signal Transduct Ther. 2013; 8(3): 193–202, doi: 10.2174/1574362409666140206221931, indexed in Pubmed: 25045345.
36. Smith A, Farrah K. Gene Expression Profiling Tests for Breast Cancer: A Rapid Qualitative Review. Canadian Agency for Drugs and Technologies in Health. ; 2019.
37. Vieira AF, Schmitt F. An Update on Breast Cancer Multigene Prognostic Tests-Emergent Clinical Biomarkers. Front Med (Lausanne). 2018; 5: 248, doi: 10.3389/fmed.2018.00248, indexed in Pubmed: 30234119.
38. Schildgen V, Warm M, Brockmann M, et al. Oncotype DX Breast Cancer recurrence score resists inter-assay reproducibility with RT-Profiler Multiplex RT-PCR. Sci Rep. 2019; 9(1): 20266, doi: 10.1038/s41598-019-56910-0, indexed in Pubmed: 31889145.

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Gut microbiota and neoplastic diseases of the gastrointestinal tract

Aleksandra Pilśniak[1], Urszula Dworzecka[1], Ewa Otto-Buczkowska[2]

[1]*Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland*
[2]*Medical Specialist Centre in Gliwice, Poland*

The term "microbiome" is used to describe the substantial number and diverse spectrum of microorganisms that inhabit the body. It plays an essential role in health conditions and diseases. Recent years have brought a further intensification of experimental studies on the impact of the microbiome on the human body, particularly with the aim of identifying and clarifying this impact. Many studies indicate that diet, lifestyle and drugs can affect the composition of the intestinal microflora, which, in turn, can modulate the development and progression of gastrointestinal tract tumors. It is suspected that the gut microbiome plays a significant role in the formation of gastrointestinal tumors. On the other hand, the role of the intestinal microflora in inhibiting the processes of oncogenesis suggests that this mechanism may be used to prevent and treat gastrointestinal cancer. Using probiotics to modify the microbiome may be beneficial in cancer therapy and may be used as a supportive treatment for classic cancer therapies such as chemotherapy, radiotherapy and surgical treatment. Intestinal microbiome analysis can be potentially used to develop non-invasive diagnostic tests. These tests could be useful as new protective markers for colorectal cancer, or as prognostic markers and predictive markers of response to treatment, especially immunotherapy.

Key words: microbiome, gastrointestinal cancer, probiotics

Introduction

The term "microbiome" is used to describe the substantial number and diverse spectrum of microorganisms that inhabit the body. It was suggested by Joshua Lederberg in 2001 to cover the entire population of commensal, symbiotic and pathogenic microorganisms. It has been established that with a mass of about 2 kg, the number of cells in the microbiome exceeds the number of cells that make up the healthy human body by 10 times. It plays an essential role in health conditions and diseases. Recent years have brought a further intensification of experimental studies on the impact of the microbiome on the human body, particularly with the aim to identify and clarify this impact.

Each part of the body is inhabited by a specific microbial population. The biggest and most heterogenous is that of the gut microbiota. This plays an important role in many diseases of the digestive and other systems, and exhibits a broad spectrum of actions, including effects on the immune system. Toll-like receptors (TLR) are sensors of infections caused by microorganisms and the microbiome, which play a major role in identifying the threat and initiating the inflammation and immune response. The intestinal microbiome stimulates both specific and non-specific immune mechanisms of the body. It is also involved in regulating immune responses. It affects the lymphoid tissue associated with the mucosal associated lymphoid tissue (MALT) and stimulates the synthesis of antibodies. Saprophytic bacteria of the gastrointestinal tract inhibit inflammation and affect the tightening of the intestinal epithelial barrier [1, 2].

It has been found that gastrointestinal cancers account for up to one third of all cancer diseases. A number of factors are

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involved in oncogenesis – both extracellular, and intracellular, such as cellular membrane proteins and transmembrane proteins localized in the cytosol or nucleus. Many studies indicate that diet, lifestyle and drugs can affect the composition of the intestinal microflora, which, in turn, can modulate the development and progression of gastrointestinal tract tumors. Therefore, it is suspected that the gut microbiome plays a significant role in the formation of gastrointestinal tumors [3–5].

Intestinal bacteria stimulate the production of the tumor necrosis factor (TNF), which affects the activity of lymphocytes, cell metabolism, as well as the apoptosis of cancer cells. They can enhance the development and progression of gastrointestinal tumors by damaging DNA, activating oncogenic signaling pathways, producing tumor-stimulating metabolites such as secondary bile acids, and suppressing anti-tumor immunity [6].

It has been found that metabolites, such as the secondary fatty acids produced by some bacterial species, may promote the development of gastrointestinal tumors [7]. Experimental studies have identified microorganisms that can promote oncogenesis by increasing cell proliferation and the production of metabolites such as butyrate [8]. In contrast, the short-chain fatty acids (SCFA) produced by other species play a suppressing role in cell proliferation and cell apoptosis induction processes and are responsible for maintaining balance in anti-inflammatory and pro-inflammatory reactions. They are characterized by the induction of T-regulatory cells (Treg) through free fatty acid receptors (GPR). To summarize, SCFA can suppress inflammatory processes and oncogenesis. In particular, a high concentration of butyric acid may inhibit oncogenesis. Cancer cells are characterized by a high rate of proliferation and the anti-tumor activity of butyric acid is based on inhibiting this proliferation.

Recently presented research results show that some bacterial species produce metabolites such as secondary bile acids, and an increased concentration of these intensifies the development of gastrointestinal tumors due to their cytotoxicity [7].

The role of the intestinal microflora in inhibiting the processes of oncogenesis suggests that this mechanism may be used in preventing and treating gastrointestinal cancer.

The use of probiotics in preventing and treating cancerous diseases of the gastrointestinal tract

There is a connection between the intestinal microflora, its metabolic activity and the mode of nutrition. Combined with genetic predisposition, unfavorable environmental factors and bad eating habits may disturb the composition of the gastrointestinal microflora. Therefore, research is being carried out on the use of probiotics to modify the disbalance of gut microbiota [7]. Negative metabolic changes induced by intestinal microorganisms can cause toxic oncogenic substances to form; these, in turn, may contribute to the development of cancer [9].

Administering probiotics increases the pool of beneficial intestinal microflora, and thus seems to create conditions for limiting changes in the intestines [10–12]. Researchers from Italy have presented a discussion of the results of studies which had been conducted on this problem [13]. Their review suggests that probiotics may reduce the risk of cancer through a number of mechanisms, including the degradation of potential carcinogenic factors and the production of anti-cancer compounds.

Another literature review presents the results of research conducted on the impact of probiotics on the suppression of gastrointestinal and other cancers, and also on their mechanisms of action [14]. Other authors have also presented a review of literature on the mechanisms of probiotics in neoplastic diseases of the gastrointestinal tract [15]. Though numerous studies conducted on animal models can serve as evidence to the beneficial effects of probiotics in the prevention of neoplastic processes, it is necessary to conduct extensive clinical trials on humans to determine potential bacterial strains, dosages and schedules of administration depending on the types and stages of cancer development [16, 17].

The fecal microbiota transplant (FMT), which is a method used to cure specific diseases by reconstructing normal functioning and the immune system, is also worth mentioning in this context. Its influence on the recipient's immune system is complicated and unpredictable, so further investigation is necessary to answer numerous questions which still remain [18].

Among the modern drugs used in cancer therapy, much attention has been given to immunological drugs, i.e. to anti-CTLA4, anti-PD-1 and anti-PD-L1 inhibitors, whose action is designed to stimulate the immune system [19]. The problem is that only those patients who are positive for the CTLA4 protein, the so-called programmed death receptor 1 (PD-1) and its ligand (PD-L1) are eligible for such treatment. However, the effectiveness of microflora participation in controlling these activities requires further research [20].

Many studies indicate that the intestinal microflora not only plays a role in the formation of cancer, but also modifies the effectiveness of therapy [19]. Recently, research has been presented on the regulation of the composition and methods of using probiotics in patients undergoing chemotherapy and radiotherapy [18]. Suggestions to use the microflora as supportive treatment for other cancer therapies, such as chemotherapy and immunotherapy, are also being considered [16, 17].

There are also studies that show the benefits of regulating the intestinal microflora through the use of probiotics in patients treated oncologically with 5-fluorouracil (5-FU), which is one of the chemotherapeutic agents used in the treatment of cancer. This drug significantly damages the microflora, and, therefore, its correction with the use of probiotics is highly desirable [21]. In addition to the unquestionable benefits of supra-cancer therapy, the use of probiotics may also cause adverse effects in immunocompromised patients. Attempts are being made to

develop the possibility of individually selecting bacterial species, taking into account the specific needs of each patient. That kind of program would allow for obtaining the beneficial effects of using probiotics while avoiding side effects [22, 23].

Wieczorska et al. emphasize that intestinal microbiome analysis can be potentially used to develop non-invasive diagnostic tests. These tests could be useful as new protective markers for colorectal cancer, or as prognostic markers and predictive markers of the response to treatment, especially immunotherapy [24, 25].

Conclusions

At present, it is generally accepted that intestinal bacteria have an important influence on the cancer process. Depending on the composition of the microbiome, this influence may intensify cancer processes; however, it may also consist in protective functions, as well as preventing or slowing oncogenesis when the composition of the microbiome changes. The research conducted shows that modifying the microbiome using probiotics may be beneficial in cancer therapy and may be used as a supportive treatment for classic cancer therapies such as chemotherapy, radiotherapy and surgical treatment. Extensive clinical trials are nonetheless required to identify the dosages and administration regimes as a supportive or alternative cancer treatment. Further work is also needed on re-selecting systems for the selection of optimal microbiome compositions for the individual needs of each patient, i.e. on so-called microbiological biological engineering [26].

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Aleksandra Pilśniak
Maria Sklodowska-Curie National Research Institute of Oncology
Gliwice Branch
Wybrzeże Armii Krajowej 15
44-102 Gliwice, Poland
e-mail: dudek.ola@op.pl

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References

1. Majewska M, Szczepanik M. [The role of Toll-like receptors (TLR) in innate and adaptive immune responses and their function in immune response regulation]. Postepy Hig Med Dosw (Online). 2006; 60: 52–63, indexed in Pubmed: 16474276.
2. Majewska M, Szczepanik M. [Contact sensitivity reaction, its mechanism and regulation]. Postepy Hig Med Dosw (Online). 2009; 63: 47–57, indexed in Pubmed: 19252464.
3. Sonnenburg ED, Smits SA, Tikhonov M, et al. Diet-induced extinctions in the gut microbiota compound over generations. Nature. 2016; 529(7585): 212–215, doi: 10.1038/nature16504, indexed in Pubmed: 26762459.
4. Zhernakova A, Kurilshikov A, Bonder MJ, et al. LifeLines cohort study. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. Science. 2016; 352(6285): 565–569, doi: 10.1126/science.aad3369, indexed in Pubmed: 27126040.
5. Alhinai EA, Walton GE, Commane DM. The Role of the Gut Microbiota in Colorectal Cancer Causation. Int J Mol Sci. 2019; 20(21), doi: 10.3390/ijms20215295, indexed in Pubmed: 31653078.
6. Mima K, Ogino S, Nakagawa S, et al. The role of intestinal bacteria in the development and progression of gastrointestinal tract neoplasms. Surg Oncol. 2017; 26(4): 368–376, doi: 10.1016/j.suronc.2017.07.011, indexed in Pubmed: 29113654.
7. O'Keefe SJD. Diet, microorganisms and their metabolites, and colon cancer. Nat Rev Gastroenterol Hepatol. 2016; 13(12): 691–706, doi: 10.1038/nrgastro.2016.165, indexed in Pubmed: 27848961.
8. Abreu MT, Peek RM. Gastrointestinal malignancy and the microbiome. Gastroenterology. 2014; 146(6): 1534–1546.e3, doi: 10.1053/j.gastro.2014.01.001, indexed in Pubmed: 24406471.
9. Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. Nat Rev Microbiol. 2014; 12(10): 661–672, doi: 10.1038/nrmicro3344, indexed in Pubmed: 25198138.
10. Dos Reis SA, da Conceição LL, Siqueira NP, et al. Review of the mechanisms of probiotic actions in the prevention of colorectal cancer. Nutr Res. 2017; 37: 1–19, doi: 10.1016/j.nutres.2016.11.009, indexed in Pubmed: 28215310.
11. Wasilewska E, Złotkowska D, Pijagin ME. [The role of intestinal microflora and probiotic bacteria in prophylactic and development of colorectal cancer]. Postepy Hig Med Dosw (Online). 2013; 67: 837–847, doi: 10.5604/17322693.1061847, indexed in Pubmed: 24018449.
12. Yu AQ, Li L. The Potential Role of Probiotics in Cancer Prevention and Treatment. Nutr Cancer. 2016; 68(4): 535–544, doi: 10.1080/01635581.2016.1158300, indexed in Pubmed: 27144297.
13. Orlando A, Russo F. RETRACTED ARTICLE: Intestinal Microbiota, Probiotics and Human Gastrointestinal Cancers. J Gastrointest Cancer. 2012; 44(2): 121–131, doi: 10.1007/s12029-012-9459-1.
14. So SSY, Wan MLY, El-Nezami H. Probiotics-mediated suppression of cancer. Curr Opin Oncol. 2017; 29(1): 62–72, doi: 10.1097/CCO.0000000000000342, indexed in Pubmed: 27792053.
15. Javanmard A, Ashtari S, Sabet B, et al. Probiotics and their role in gastrointestinal cancers prevention and treatment; an overview. Gastroenterol Hepatol Bed Bench. 2018; 11(4): 284–295, indexed in Pubmed: 30425806.
16. Gopalakrishnan V, Helmink BA, Spencer CN, et al. The Influence of the Gut Microbiome on Cancer, Immunity, and Cancer Immunotherapy. Cancer Cell. 2018; 33(4): 570–580, doi: 10.1016/j.ccell.2018.03.015, indexed in Pubmed: 29634945.
17. McQuade JL, Daniel CR, Helmink BA, et al. Modulating the microbiome to improve therapeutic response in cancer. Lancet Oncol. 2019; 20(2): e77–e91, doi: 10.1016/S1470-2045(18)30952-5, indexed in Pubmed: 30712808.
18. Ding C, Tang W, Fan X, et al. Intestinal microbiota: a novel perspective in colorectal cancer biotherapeutics. Onco Targets Ther. 2018; 11: 4797–4810, doi: 10.2147/OTT.S170626, indexed in Pubmed: 30147331.
19. Andrews MC, Wargo JA. Cancer Evolution during Immunotherapy. Cell. 2017; 171(4): 740–742, doi: 10.1016/j.cell.2017.10.027, indexed in Pubmed: 29100071.
20. Pouncey AL, Scott AJ, Alexander JL, et al. Gut microbiota, chemotherapy and the host: the influence of the gut microbiota on cancer treatment. Ecancermedicalscience. 2018; 12: 868, doi: 10.3332/ecancer.2018.868, indexed in Pubmed: 30263059.
21. Singh S, Kotla NG, Tomar S, et al. A nanomedicine-promising approach to provide an appropriate colon-targeted drug delivery system for 5-fluorouracil. Int J Nanomedicine. 2015; 10: 7175–7182, doi: 10.2147/IJN.S89030, indexed in Pubmed: 26648721.
22. Vivarelli S, Salemi R, Candido S, et al. Gut Microbiota and Cancer: From Pathogenesis to Therapy. Cancers (Basel). 2019; 11(1), doi: 10.3390/cancers11010038, indexed in Pubmed: 30609850.
23. Nagano T, Otoshi T, Hazama D, et al. Novel cancer therapy targeting microbiome. Onco Targets Ther. 2019; 12: 3619–3624, doi: 10.2147/OTT.S207546, indexed in Pubmed: 31190864.
24. Wieczorska K, Stolarek M, Stec R. The Role of the Gut Microbiome in Colorectal Cancer: Where Are We? Where Are We Going? Clin Colorectal Cancer. 2020; 19(1): 5–12, doi: 10.1016/j.clcc.2019.07.006, indexed in Pubmed: 31678050.
25. Wong SH, Yu J. Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. Nat Rev Gastroenterol Hepatol. 2019; 16(11): 690–704, doi: 10.1038/s41575-019-0209-8, indexed in Pubmed: 31554963.
26. Meng C, Bai C, Brown T, et al. Human Gut Microbiota and Gastrointestinal Cancer. Genomics, Proteomics & Bioinformatics. 2018; 16(1): 33–49, doi: 10.1016/j.gpb.2017.06.002.

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Oncogeriatrics (part 7.)
Geriatric assessment for older patients with cancer

Jakub Kenig, Kinga Szabat

Department of General, Oncological and Geriatric Surgery, Jagiellonian University Medical College, Krakow, Poland

The geriatric assessment (GA) is defined as a multidimensional, interdisciplinary diagnostic process focusing on determining an older person's medical, psychosocial, and functional capabilities that are not identified by routine evaluation. There is more and more data on the benefits of the GA in the evaluation and management process of older patients with cancer. It allows for the development of an individual cancer treatment plan resulting in less postoperative complications, reduced treatment toxicity, improved quality of life and very often without compromising survival. However, the relationship between specific domains of the GA and post-treatment medical outcomes, functional status and quality of life remains unknown. Moreover, there is still no consensus over what the "golden standard" GA should look like, which tools should be included and what cut-off should be used. This is still an active area of research. However, there is no doubt that understanding the health status of an older patient with cancer should be as important as cancer staging and tumour biology.

Key words: older patients, elderly, comprehensive geriatric assessment, frailty

As has been mentioned in the previous articles, older adults are a heterogeneous group having varying degrees of comorbidities, functional reserves, cognitive impairments and social support [1]. Therefore, chronological age alone and the routine format of medical history, physical examination, biochemistry and imaging tests often do not provide adequate information needed for optimal and tailored treatment. Many older adults have unidentified, uncommunicated, and therefore unaddressed aging-related conditions that are associated with morbidity and early mortality [2]. To help guide treatment decisions the geriatric assessment (GA) was introduced, a milestone in the field of geriatrics. Moreover, at present, cancer treatment for older patients is very often planned based on extrapolations of evidence derived from clinical trials in which younger patients or fit older patients enrolled [3].

The GA is defined as a multidimensional, interdisciplinary diagnostic process focusing on determining an older person's medical, psychosocial, and functional capabilities. In turn, the term comprehensive geriatric assessment (CGA) refers to a GA which also includes a plan for the further management of identified problems. Therefore, the main goal of the CGA in older cancer patients is to provide a comprehensive health appraisal to guide targeted interventions and appropriate cancer treatment selection [4].

The GA was initially developed and validated in the general older population for detecting vulnerability and aging-related issues that were associated with mortality [5]. However, numerous studies, though not all, have proved its usefulness equally in cancer patients:

- The GA allows the determination of a baseline health status, monitoring of changes and a diagnostic of the frailty status, which is an exponent of biological old age;
- The GA can identify age-related areas of vulnerability that can be missed in routine clinical evaluation in up to 50% of patients [6]. These impairments concern physical functioning and nutritional status, but also very often geriatric

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syndromes such as: dementia, delirium, depression, incontinence, sarcopenia, osteoporosis/spontaneous fractures which are independent risk factors of worse outcome [6]. Routinely used oncological tools like the Eastern Cooperative Oncology Group (ECOG) or the Karnofsky performance status have been shown to poorly reflect functional impairment in older patients with cancer. In patients with an ECOG score <2 almost 40% of patients were dependent on some form of instrumental activities for daily living [7];

- Performing the GA can change treatment decisions for up to 50% of older patients [8, 9]. In these studies, in the case of up to 28% of patients, the treatment was intensified and in case of up to 37%, the treatment intensity was reduced [10, 11];
- The GA can identify areas for further rehabilitative actions such as: review of diet and nutrition, physical performance, psychological support, medication review and social support. In some studies, applying the GA reduced the number of treatment related complications. Other studies have not confirmed this, but in case of high-risk patients its use allowed the completion of the cancer treatment with fewer treatment modifications [12];
- The GA can predict survival of and adverse events during cancer treatment. Thus, it may assist clinical decision-making.
- The GA can improve patient physician communication about aging-related concerns and their influence on the treatment outcome [13]. A practical and convenient GA summary with recommendations for aging-sensitive interventions improves patient-cantered outcomes and patient satisfaction.

Biological age does not correspond with the chronological age. Therefore, it is difficult to arbitrarily set the level of age at which the GA should be implemented. Most of the guidelines recommend it at the age of 70 years. However, in our opinion, the age should be set at the level of 65 years in Polish society. It also should be performed in younger patients identified in screening tests [14].

The GA consists of several domains evaluating: functional status, mobility/falls, cognitive level, mood, comorbidity, polypharmacy, fatigue and social support. At present, there are several well-validated tools available. Table I presents an overview of the different tests with literature-based cut-offs that may be used in the GA process. There has been no consensus about which tools should be included in the GA and until now there have been no studies showing the superiority of one specific tool over another. Therefore, the choice of score might rely on local preferences, the aim of the tool and present resources.

The number of incorporated GA domains has a great influence on the diagnosis of frailty and on adequate risk assessment as we showed in one previous study. The summary deficit score based on the GA consisting of functional, mobility, cognitive, depression, nutritional, co-morbidity, polypharmacy, and social support questionnaires was the most accurate predictor of post-operative complications in comparison to models with less incorporated domains [33].

In turn, two large prospective studies – Cancer and Aging Research Group (CARG) and Chemiotherapy Risk Assessment Scale for High-Age Patients (CRASH) – identified which parameters of the GA were capable of predicting severe chemotherapy-related complications in a heterogeneous cancer population (tab. II) [33, 34]. Both scores revealed their superiority over the Karnofsky performance status or other classic oncological evaluation tools. They can also help determine the risks and benefits of treatment, promoting shared decision-making. High-risk patients can be monitored closely. A randomized study of GA-directed therapy for older patients with advanced lung cancer demonstrated reduced toxic effects of treatment and less treatment discontinuation in the GA group [35].

In case of radiotherapy the literature is still scarce. Spyropoulou et al. observed higher risk of not completing radiation in the case of impaired score on a VES-13 (screening frailty tool) [36].

There are various models of the GA. It can be performed within a geriatric ward with a specialized geriatric team. Six meta-analyses showed that this model is the most effective method with lower mortality, less institutionalization, and less functional decline compared with a standard ward [37–39]. In the case of the model with a specialized geriatric team that ap-

Table I. Glossary of the most common tools used in the geriatric assessment process

Test		Number of items	Range	Cut-off score
ADL (Katz Activities of Daily Living) [15]	Functional status	6	0–6	<5
IADL (Lawton Instrumental Activities of Daily Living) [16]		8	0–8	≤7
The Duke OARS Assessment of IADL [17]		6	12	<9
Barthel scale [18]		10	0–100	≤60
Self reported number of falls within different time frames		1	0–∞	>2 within last 6 months
TUG (Timed Up and Go) [19]	Physical activity	1	0–∞	≥15
Gait speed [20]		1	0–∞	

Test		Number of items	Range	Cut-off score
Charlson Comorbidity Scale [21]	Comorbidity	19	0–37	≥3
Cumulative Illness Rating Scale (CIRS-G) [22]		13	0–52	>4
Geriatric Depression Scale [23]	Depression	15	0–15	>5
Mini-Mental State Examination [24]	Cognitive function	8	0–30	<24
Montreal Cognitive Assessment [25]		7	0–30	<26
Abbreviated mental test score AMTS (Hodgkinson) [26]		10	0–10	≤6
The Blessed Orientation-Memory-Concentration (BOMC) Test [27]		6	0–28	>10
Clock Drawing Test (CDT-test) [28]		7	0–7	≤4
Mini Nutritional Assessment [29]	Nutritional assessment	6	0–14	<12
MNA full [29]		18	0–30	<24
Number of medications	Toxicity risk	1	0–∞	>4
Brief Fatigue Inventory [30]	Self-perceived fatigue	9	0–90	0–3 no/mild fatigue 4–7 moderate >7 severe
RAND MOS Social Support Scale [31]	Social Support	19	0–5	<4

plies the GA in non-geriatric wards, one meta-analysis could not show significant improvement in the outcome of the patients. However, the main reason for this was the low adherence rate to the geriatric team's recommendations [40]. In turn, joint geriatric and specialized care on the ward is gaining in popularity and showing promising results in more and more studies [41].

In conclusion, all physicians treating older patients with cancer should include some form of geriatric assessment in their clinical practise. Multiple organizations including the International Society of Geriatric Oncology, the National Comprehensive Cancer Network and the European Organization for the Research and Treatment of Cancer recommend the use of the GA prior to the initiation of cancer treatment. However, it is still not routinely performed due to a false belief in its complexity and time consumption. Various forms of the GA allow its incorporation in busy clinical settings. The use of a given tool and cut-off is, in light of current research results, not as important as the incorporation of the following domains: functional status, mobility/falls, cognition function, depression/anxiety, comorbidities, polypharmacy, nutritional status and social support. The more domains included, the more adequate the risk assessment that will be achieved.

Table II. CARG and CRASH score

CARG score (Cancer and Aging Research Group)		CRASH (Chemiotherapy Risk Assessment Scale for High-Age Patients)			
Variable	Score	Variable	Points		
			0	1	2
– Age ≥72 years old	2	**Hematologic score**			
– Cancer type (gastrointestinal or genitourinary)	2	Diastolic BP	≤72	>72	>459
– Chemiotherapy dosing (standard dosing)	2				
– Number of chemiotherapy drugs (polychemitherapy)	2	IADL	26–29	10–25	>0.57
– Hemoglobin (<11 g/dL in males, 10 g/dL in females)					
– Creatinine clearance (<34 mL/min)	3	LDH	0–459		
– Hearing (fair or worse)	3				
– Number of falls in the past 6 months (one or more)	2	Chemotox	0–0.044	0.45–0.57	
– Take medications with some help/ unable	3				
– Walking one block, somewhat limited/ limited a lot	1	**Nonhematologic score**			
– Decreased social activity because of physical/ emotional health problem (limited at least sometimes)	2 1	ECOG PS	0	1–2	3–4
		MMS	30		<30
		MNA	28–30		<28
		Chemotox	0.0.44	0.45–0.57	>0.57

BP – blood pressure, Chemotox – toxicity of the chemotherapy regimen, ECOG PS – Eastern Cooperative Oncology Group performance status, IADL – Instrumental Activities of Daily Living, LDH – lactate dehydrogenase, MMS – Mini Mental Health Status, MNA – Mini Nutritional Assessment

Frailty screening tools (the topic of one of the next articles) are useful. These are simple and quick tools to identify fit older patients who do not require additional assessments or interventions. However, in the case of older patients with cancer, qualified for abdominal surgery, recognised as high-risk surgery, their predictive value, as the only assessment tool, is currently insufficient.

The arguments raised about the time-consuming nature of the GA/CGA are absurd, particularly when one considers the time and resources required to treat complications. Therefore, understanding the health status of an older patient with cancer should be as important as cancer staging and tumour biology.

Conflict of interest: none declared

Jakub Kenig
Jagiellonian University Medical College
Department of General, Oncologic and Geriatric Surgery
ul. Prądnicka 35-37
31-202 Kraków, Poland
e-mail: jkenig@cm-uj.krakow.pl

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References

1. Loh KP, Soto-Perez-de-Celis E, Hsu T, et al. What Every Oncologist Should Know About Geriatric Assessment for Older Patients With Cancer: Young International Society of Geriatric Oncology Position Paper. J Oncol Pract. 2018; 14(2): 85–94, doi: 10.1200/JOP.2017.026435, indexed in Pubmed: 29436306.
2. Klabunde CN, Ambs A, Keating NL, et al. The role of primary care physicians in cancer care. J Gen Intern Med. 2009; 24(9): 1029–1036, doi: 10.1007/s11606-009-1058-x, indexed in Pubmed: 19597893.
3. Hurria A, Mohile S, Gajra A, et al. Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer. J Clin Oncol. 2016; 34(20): 2366–2371, doi: 10.1200/JCO.2015.65.4327, indexed in Pubmed: 27185838.
4. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol. 2014; 32(24): 2595–2603, doi: 10.1200/JCO.2013.54.8347, indexed in Pubmed: 25071125.
5. Balducci L, Beghe C. The application of the principles of geriatrics to the management of the older person with cancer. Crit Rev Oncol Hematol. 2000; 35(3): 147–154, doi: 10.1016/s1040-8428(00)00089-5, indexed in Pubmed: 10960797.
6. Kenis C, Bron D, Libert Y, et al. Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study. Ann Oncol. 2013; 24(5): 1306–1312, doi: 10.1093/annonc/mds619, indexed in Pubmed: 23293115.
7. Repetto L. Comprehensive Geriatric Assessment Adds Information to Eastern Cooperative Oncology Group Performance Status in Elderly Cancer Patients: An Italian Group for Geriatric Oncology Study. Journal of Clinical Oncology. 2002; 20(2): 494–502, doi: 10.1200/jco.20.2.494.
8. Hamaker ME, Schiphorst AH, ten Bokkel Huinink D, et al. The effect of a geriatric evaluation on treatment decisions for older cancer patients--a systematic review. Acta Oncol. 2014; 53(3): 289–296, doi: 10.3109/0284186X.2013.840741, indexed in Pubmed: 24134505.
9. Decoster L, Kenis C, Van Puyvelde K, et al. The influence of clinical assessment (including age) and geriatric assessment on treatment decisions in older patients with cancer. J Geriatr Oncol. 2013; 4(3): 235–241, doi: 10.1016/j.jgo.2013.04.010, indexed in Pubmed: 24070461.
10. Girre V, Falcou MC, Gisselbrecht M, et al. Does a geriatric oncology consultation modify the cancer treatment plan for elderly patients? J Gerontol A Biol Sci Med Sci. 2008; 63(7): 724–730, doi: 10.1093/gerona/63.7.724, indexed in Pubmed: 18693227.
11. Chaïbi P, Magné N, Breton S, et al. Influence of geriatric consultation with comprehensive geriatric assessment on final therapeutic decision in elderly cancer patients. Crit Rev Oncol Hematol. 2011; 79(3): 302–307, doi: 10.1016/j.critrevonc.2010.08.004, indexed in Pubmed: 20888781.
12. Kalsi T, Babic-Illman G, Ross PJ, et al. The impact of comprehensive geriatric assessment interventions on tolerance to chemotherapy in older people. Br J Cancer. 2015; 112(9): 1435–1444, doi: 10.1038/bjc.2015.120, indexed in Pubmed: 25871332.
13. Mohile SG, Epstein RM, Hurria A, et al. Communication With Older Patients With Cancer Using Geriatric Assessment: A Cluster-Randomized Clinical Trial From the National Cancer Institute Community Oncology Research Program. JAMA Oncol. 2019 [Epub ahead of print]: 1–9, doi: 10.1001/jamaoncol.2019.4728, indexed in Pubmed: 31697365.
14. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol. 2014; 32(24): 2595–2603, doi: 10.1200/JCO.2013.54.8347, indexed in Pubmed: 25071125.
15. Katz S, Akpom C. A Measure of Primary Sociobiological Functions. Int J Health Serv. 1995; 6(3): 493–508, doi: 10.2190/uurl-2ryu-wryd-ey3k.
16. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969; 9(3): 179–186, indexed in Pubmed: 5349366.
17. Pfeiffer E. Multidimensional functional assessment: The OARS methodology. , Durham 1975.
18. MAHONEY FI, BARTHEL DW. FUNCTIONAL EVALUATION: THE BARTHEL INDEX. Md State Med J. 1965; 14: 61–65, indexed in Pubmed: 14258950.
19. Podsiadlo D, Richardson S. The timed„Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991; 39(2): 142–148, doi: 10.1111/j.1532-5415.1991.tb01616.x, indexed in Pubmed: 1991946.
20. Bohannon RW. Reference values for the timed up and go test: a descriptive meta-analysis. J Geriatr Phys Ther. 2006; 29(2): 64–68, doi: 10.1519/00139143-200608000-00004, indexed in Pubmed: 16914068.
21. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5): 373–383, doi: 10.1016/0021-9681(87)90171-8, indexed in Pubmed: 3558716.
22. Miller MD, Towers A. A. A manual of guidelines for scoring: The cumulative Illness Rating Score for Geriatrics. 1991.
23. Brink TL, Yesavage J, Lum O, et al. Screening Tests for Geriatric Depression. Clin Gerontol. 2008; 1(1): 37–43, doi: 10.1300/j018v01n01_06.
24. Folstein M, Folstein S, McHugh P. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12(3): 189–198, doi: 10.1016/0022-3956(75)90026-6.
25. Loh KP, Pandya C, Zittel J, et al. Associations of sleep disturbance with physical function and cognition in older adults with cancer. Support Care Cancer. 2017; 25(10): 3161–3169, doi: 10.1007/s00520-017-3724-6, indexed in Pubmed: 28455547.
26. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry. 1968; 114(512): 797–811, doi: 10.1192/bjp.114.512.797, indexed in Pubmed: 5662937.
27. Ball LJ, Bisher GB, Birge SJ. A simple test of central processing speed: an extension of the Short Blessed Test. J Am Geriatr Soc. 1999; 47(11): 1359–1363, doi: 10.1111/j.1532-5415.1999.tb07440.x, indexed in Pubmed: 10573448.
28. Watson YI, Arfken CL, Birge SJ. Clock completion: an objective screening test for dementia. J Am Geriatr Soc. 1993; 41(11): 1235–1240, doi: 10.1111/j.1532-5415.1993.tb07308.x, indexed in Pubmed: 8227899.
29. Guigoz Y, et al. Mini Nutritional Assessment: a practical assessment tool or grading the nutritional state of elderly patients. Facts and Research in Gerontology. 1994; 2: 15–59.
30. Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. Cancer. 1999; 85(5): 1186–1196, doi: 10.1002/(sici)1097-0142(19990301)85:5<1186::aid-cncr24>3.0.co;2-n, indexed in Pubmed: 10091805.
31. Sherbourne CD, Stewart AL. The MOS social support survey. Soc Sci Med. 1991; 32(6): 705–714, doi: 10.1016/0277-9536(91)90150-b, indexed in Pubmed: 2035047.
32. Kenig J, Olszewska U, Zychiewicz B, et al. Cumulative deficit model of geriatric assessment to predict the postoperative outcomes of older patients with solid abdominal cancer. J Geriatr Oncol. 2015; 6(5): 370–379, doi: 10.1016/j.jgo.2015.03.004, indexed in Pubmed: 26144556.
33. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol. 2011; 29(25): 3457–3465, doi: 10.1200/JCO.2011.34.7625, indexed in Pubmed: 21810685.

34. Extermann M, Boler I, Reich RR, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer. 2012; 118(13): 3377–3386, doi: 10.1002/cncr.26646, indexed in Pubmed: 22072065.
35. Corre R, Greillier L, Le Caër H, et al. Use of a Comprehensive Geriatric Assessment for the Management of Elderly Patients With Advanced Non-Small-Cell Lung Cancer: The Phase III Randomized ESOGIA-GFPC--GECP 08-02 Study. J Clin Oncol. 2016; 34(13): 1476–1483, doi: 10.1200/JCO.2015.63.5839, indexed in Pubmed: 26884557.
36. Spyropoulou D, Pallis AG, Leotsinidis M, et al. Completion of radiotherapy is associated with the Vulnerable Elders Survey-13 score in elderly patients with cancer. J Geriatr Oncol. 2014; 5(1): 20–25, doi: 10.1016/j.jgo.2013.08.002, indexed in Pubmed: 24484714.
37. Ellis G, Langhorne P. Comprehensive geriatric assessment for older hospital patients. Br Med Bull. 2004; 71: 45–59, doi: 10.1093/bmb/ldh033, indexed in Pubmed: 15684245.
38. Baztán JJ, Suárez-García FM, López-Arrieta J, et al. Effectiveness of acute geriatric units on functional decline, living at home, and case fatality among older patients admitted to hospital for acute medical disorders: meta-analysis. BMJ. 2009; 338: b50, doi: 10.1136/bmj.b50, indexed in Pubmed: 19164393.
39. Ellis G, Whitehead MA, Robinson D, et al. Comprehensive geriatric assessment for older adults admitted to hospital: meta-analysis of randomised controlled trials. BMJ. 2011; 343: d6553, doi: 10.1136/bmj.d6553, indexed in Pubmed: 22034146.
40. Deschodt M, Flamaing J, Haentjens P, et al. Impact of geriatric consultation teams on clinical outcome in acute hospitals: a systematic review and meta-analysis. BMC Med. 2013; 11: 48, doi: 10.1186/1741-7015-11-48, indexed in Pubmed: 23433471.
41. González-Montalvo JI, Alarcón T, Mauleón JL, et al. The orthogeriatric unit for acute patients: a new model of care that improves efficiency in the management of patients with hip fracture. Hip Int. 2010; 20(2): 229–235, doi: 10.1177/112070001002000214, indexed in Pubmed: 20544649.

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Letters to Editor

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Does the type of a centre in which the resection of extensive tumours of the limbs and truck is performed, affect the patients' survival?

Dear Editor,

Modern reconstructive surgery is based on the appropriate application of the available reconstruction methods, including microvascular ones. Their combination with radio- and chemotherapy leads to optimal treatment results. Nevertheless, the issue of immediate resections and reconstructions in the treatment of extensive tumours still arises many unnecessary controversies.

Although the origin of the concept of immediate reconstruction after resection goes back to the 18th century [1], the theses contained in Halsted's works from the end of the 19th century [2] with fundamental significance for oncological surgery, led to a situation in which the closure of postresection bed and let alone the use of more advanced techniques of the defect completion, materialised as late as in the 1990s [3]. The results of the studies from this period proved that immediate reconstruction – even in the case of extensive resections – is literally safe. Moreover, planning of appropriate reconstructive surgical procedure allows for a maximally extensive resection, which additionally increases the radicality of the surgery [4, 5].

Oncological and Reconstructive Surgery Clinic of the Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch has a rich clinical material concerning immediate reconstructions in the case of extensive tumour resections of almost any region of the body. Each year, more than 200 microsurgical procedures are performed in the clinic.

The treatment results of the above group of patients with extensive tumours of the trunk and the limbs were analysed (fig. 1). The obtained results support the thesis of the effectiveness of the microsurgery techniques in the restoration of the limbs function and also make a valuable point in the debate concerning the extensive resections outside the centres which have appropriate experience and the equipment base for such procedures.

Recently some tendency to perform extensive tumour resections in the centres which do not have large experience in such procedures has been observed. There is a concern that – with regards to the lack of possibility of performing an immediate reconstruction – the scope of the resection may not be adequate in terms of obtaining complete radicality of the procedure.

Oncological and Reconstructive Surgery Clinic of the Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch analysed the treatment results of 71 patients operated in 2006–2017 for extensive tumours of the trunk and limbs. The basic clinical data of the study group are presented in tables I and II.

The obtained results show, among others, that the patients with primary treatment (resection surgery) outside the National Research Institute of Oncology had a significantly shorter recurrence free survival. The patients whose resection surgeries were performed in the National Research Institute of Oncology had a longer recurrence-free survival periods than the patients treated in other centres ($p < 0.05$). The comparison showed that the statistically significant difference in a five-year recurrence-free survival period is present when the primary surgery is performed in the National Research Institute of Oncology (fig. 2).

The above results may be regarded as an important voice justifying performing extensive resective and reconstructi-

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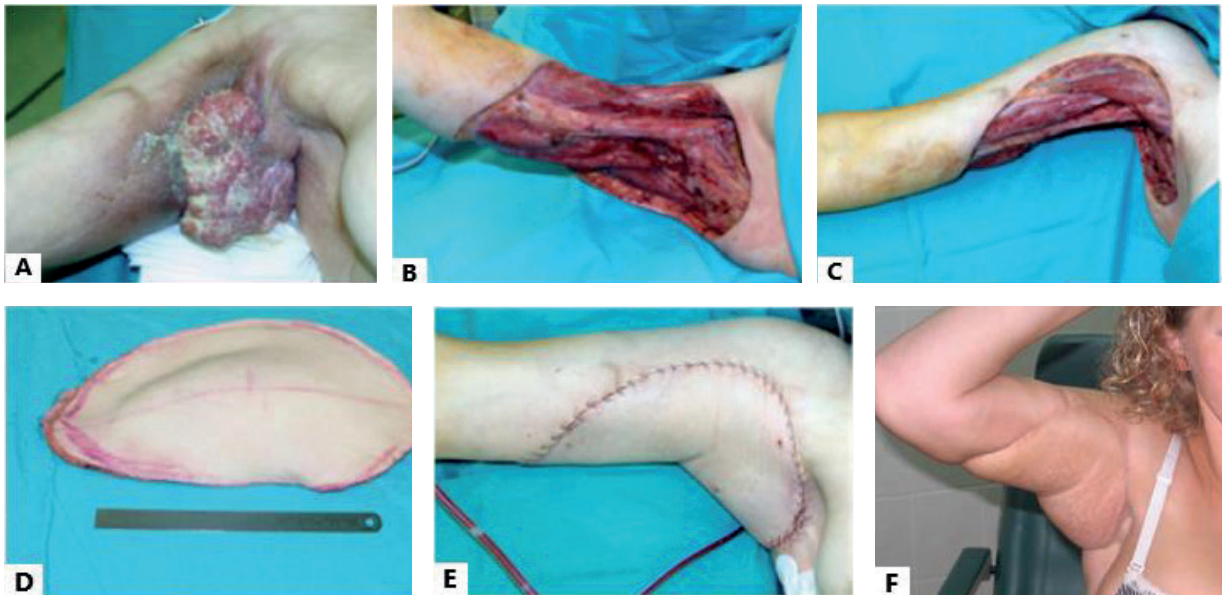

Figure 1. A – an extensive tumour of the right shoulder and axilla; B, C – post-resection bed sparing axillary vessels and the nerves of the brachial plexus; D – dissected antero-lateral flap of the thigh; E – the flap on the donor site anastomosed to the subscapular vessels; F – remote post-operative results

Table I. Age characteristics of selected patients

Variable	Total	Female subjects	Male subjects	F vs. M
	n = 71	n = 27	n = 32	p
Age (year of life):				
M ± SD	56.1 ± 15.5	59.7 ± 15.0	53.8 ± 15.5	0.121
Me [Q_1; Q_3]	58 [46, 65]	62 [48, 72]	55 [46, 63]	
Min–Max	19– 86	29–82	19–86	

Table II. Clinical characteristics of the primary tumour and its treatment in the patient study group

Variable	Total		Female subjects		Male subjects		F vs. M
	n = 71		n = 27		n = 44		p
	n	%	n	%	n	%	0.045
Location of the primary tumour:							
Hand and arm	9	12.7%	4	14.8%	5	11.4%	0.045
Shoulder and shoulder girdle	10	14.1%	2	7.4%	8	18.2%	
Foot, lower thigh	17	23.9%	3	11.1%	14	31.8%	
Thighs, groins, buttocks	22	31.0%	14	51.9%	8	18.2%	
Front chest	11	15.5%	3	11.1%	8	18.2%	
Back chest	2	2.8%	1	3.7%	1	2.3%	
Histopathological assessment of the primary tumour:							
Ca plano	24	33.8%	9	33.3%	15	34.1%	0.316
Sarcomas	26	36.6%	10	37.0%	16	36.4%	
Melanomas	6	8.5%	2	7.4%	4	9.1%	
BCC	5	7.0%	1	3.7%	4	9.1%	
Other	7	9.9%	5	18.5%	2	4.5%	
Non oncological	3	4.2%	0	0.0%	3	6.8%	
TNM assessment of the primary tumour							0.022
1 – T1 and T2	50	70.4%	25	92.6%	25	56.8%	

2 – T3 and T4	7	9.9%	0	0.0%	7	15.9%	
3 – N+ with T1 and T2	8	11.3%	1	3.7%	7	15.9%	
4 – N+ with T3 and T4	3	4.2%	1	3.7%	2	4.5%	
5 – does not apply	3	4.2%	0	0.0%	3	6.8%	
Centre where the surgery was performed:							
At the OI	49	69.0%	21	77.8%	28	63.6%	0.457
Outside OI	11	15.5%	3	11.1%	8	18.2%	
Resection outside OI, reconstruction at the OI	11	15.5%	3	11.1%	8	18.2%	

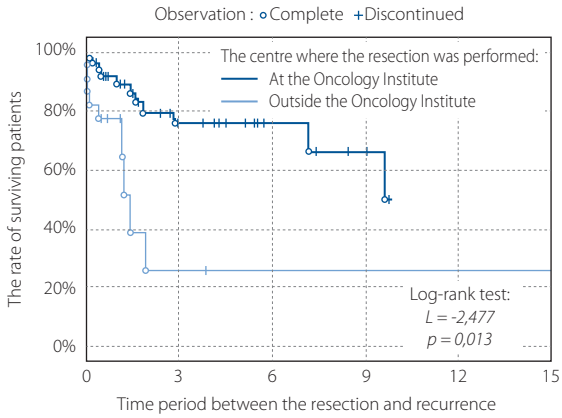

Figure 2. Kaplan-Meier curves of the recurrence free survival after the resection in patients with regards to the difference in the centre in which the procedure was performed

ve surgeries on advanced tumours in the centres with large experience in this respect. This is important especially in the times when some resection procedures, for economic reasons are transferred to the centres which do not have appropriate base for a compre- hensive treatment and thus are unable to guarantee the best possible treatment results to their patients.

Piotr H. Drozdowski, Łukasz J. Krakowczyk, Adam J. Maciejewski
Oncological and Reconstructive Surgery Clinic, The Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland
e-mail: piotr_drozdowski@wp.pl

References

1. Tagliacozzi G. De Curtorum Chirurgia per insitionem. Bindoni, Venecja 1597.
2. Halsted WS. I. The Results of Radical Operations for the Cure of Carcinoma of the Breast. Ann Surg. 1907; 46(1): 1–19, doi: 10.1097/00000658-190707000-00001, indexed in Pubmed: 17861990.
3. Ho AL, Lyonel Carre A, Patel KM. Oncologic reconstruction: General principles and techniques. J Surg Oncol. 2016; 113(8): 852–864, doi: 10.1002/jso.24206, indexed in Pubmed: 26939879.
4. Parrett BM, Kashani-Sabet M, Leong SPL, et al. The safety of and indications for immediate reconstruction of head and neck melanoma defects: our early experience. Ann Plast Surg. 2014; 72 Suppl 1: S35–S37, doi: 10.1097/SAP.0000000000000166, indexed in Pubmed: 24691340.
5. Gieni M, Avram R, Dickson L, et al. Local breast cancer recurrence after mastectomy and immediate breast reconstruction for invasive cancer: a meta-analysis. Breast. 2012; 21(3): 230–236, doi: 10.1016/j.breast.2011.12.013, indexed in Pubmed: 22225710.

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The end of menthol cigarettes – missed opportunity or a great step toward decrease of lung cancer burden among women in Poland?

To the Editor,

on May 20th 2020, due to enforcement of the Directive 2014/40/EU, in Poland and other European Union (EU) countries, ban on selling menthol cigarettes came into force. This long-waited law raises health hopes – in particular for Polish female smokers. In accordance to the latest data sourced from the National Cancer Registry in Poland [1], in 2017 lung cancer was main cause of cancer deaths, both – in men and women populations and has contributed respectively to 15 499 (ASW = 45,3) and 7 825 (ASW = 17,8) deaths. Despite the beneficial changes in smoking patterns among Polish men in the last period of time (about 9 percentage points (pp) less smokers in 2019 in comparison with 2012 [2]) epidemiological trends of lung cancer suggest that there is no parallel and favorable change in women population as well. 2017 was another year (since 2007) where number of deaths among women caused by lung cancer was higher in comparison with breast cancer which is the most frequent one in terms of incidence. Adopted law on menthol cigarettes ban can be considered as one of the greatest chances since years to change this phenomenon and to reverse this adverse trend. Although the data on menthol cigarettes consumption in Poland is scarce, there are some evidence that women smoke menthols more eager than men (8.4% *vs.* 2.5%). In the same study authors indicate that menthol smokers feel greater reward and satisfaction during smoking in comparison with regular smokers [3]. Moreover, some of the observations suggest also that menthol cigarettes are perceived by women as more socially acceptable than non-menthol ones [4]. Other studies stress higher addictive potential of the flavored cigarettes as well [5]. At the same time there are also certain evidence of high effectiveness of menthol cigarettes ban in reducing or even quitting smoking in menthol smokers group [4].

Despite the right direction of changes in anti-tobacco law, there is an emerging question on pace and complexity of implemented solutions. Discussed ban does not include e-cigarettes and heated tobacco products. Additionally, period between adoption and enforcement of the law (about 6 years) seems to be much too long. This gap gave tobacco industry the opportunity to prepare for changes and the chance for development of the new tobacco products for women and young people – main menthol cigarettes users. From this perspective, the chance for favorable changes in women's health behaviors seems to be not fully taken or even lost. However, in the coming years ban on slim cigarettes selling will force into life as well. This particular type of cigarettes has been designed also especially for women, therefore there is a hope that jointly with excise tax increase, these regulations will contribute to decrease in the lung cancer burden among Polish women.

Paweł Koczkodaj, Magdalena Cedzyńska, Joanna Didkowska
Cancer Epidemiology and Primary Prevention Department, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw
e-mail: pawel.koczkodaj@pib-nio.pl

References

1. Didkowska J, Wojciechowska U, Czaderny K, Olasek P, Ciuba A. Nowotwory złośliwe w Polsce w 2017 roku. , Warszawa 2019.
2. Centrum Badań Opinii Społecznej, Komunikat z Badań nr 104/2019 Palenie papierosów, ISSN 2353-5822, Centrum Badań Opinii Społecznej, Komunikat z Badań nr 104/2019 Palenie papierosów, ISSN 2353-5822 2019.

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3. Pinkas J, Kaleta D, Zgliczyński WS, et al. The Prevalence of Tobacco and E--Cigarette Use in Poland: A 2019 Nationwide Cross-Sectional Survey. Int J Environ Res Public Health. 2019; 16(23), doi: 10.3390/ijerph16234820, indexed in Pubmed: 31801221.
4. Kaleta D, Usidame B, Szosland-Fałtyn A, et al. Use of flavoured cigarettes in Poland: data from the global adult tobacco survey (2009-2010). BMC Public Health. 2014; 14: 127, doi: 10.1186/1471-2458-14-127, indexed in Pubmed: 24502292.
5. Wickham RJ. How Menthol Alters Tobacco-Smoking Behavior: A Biological Perspective. Yale J Biol Med. 2015; 88(3): 279–287, indexed in Pubmed: 26339211.

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Protection and ownership of research results

Justyna Ożegalska-Trybalska

Department of Intellectual Property Law, Jagiellonian University, Cracow, Poland

Introduction. This article aims to present the rules concerning the protection and ownership of the results of scientific research and development works and related know-how, including those jointly generated in multicentre research projects.
Material and methods. The analysis focuses on the identification of types of medical research results and the possibility of protecting them under intellectual property law, including copyright, patent and unfair competition law. It also considers regulations providing provisions on the ownership and commercialisation of R&D results acquired under research programmes, projects and sponsored research, including clinical trials.
Results. The lack of protection of research results as such by intellectual property rights, the different nature of those results, as well as potential conflicts of interests that arise from the exploitation of data which has both scientific and market value, may in practice cause problems in regard to who is entitled to them and what are the rules for their use and publication. Situations of conflict may arise at the interface between the interests of the different actors involved in conducting and financing research (researchers, research centres, sponsors).
Conclusion. Effective management of research and development results requires identification of the appropriate regime (statutory, project or contractual) under which they were obtained and are going to be exploited. Although the rules in force for the acquisition of rights can only be modified contractually to a certain extent, it is strongly recommended to supplement them with detailed contractual provisions specifying the rules for the co-ownership of results, the rights and obligations of the entities involved in the research, as well as ensuring confidentiality and restrictions on their disclosure with and/or without the consent of co-authors and sponsors financing research.

Key words: protection of research results, ownership of research results, joint research, clinical trials, confidentiality of research results.

Introduction

Research results lack uniform rules on their protection, ownership, and exploitation. There are additional aspects to this problem with regard to medical research results, which include the need to transfer them into practice, financing costly research, meeting administrative requirements for the authorization of medical products, ensuring ethical standards and protecting the privacy of individuals in clinical trials. Thus, medical research results have an important characteristic: they are not purely scientific, but most often utilitarian and commercial, and in terms of their ownership and accessibility, the interests of individual scientists, research sponsors and members of society should be considered, who claim the right of freedom of research and the right to access to the latest treatments for the protection of their health.

Material and methods

The starting point for establishing rules for the protection and acquisition of rights to research results is to clarify this term, which in the field of medicine may relate to scientific discoveries, concepts and hypotheses (in particular those related to the use of new substances and therapies), the results of clinical

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research and assessments, tests, medical experiments, biomedical, epidemiological, behavioral research, results obtained through screening programmes, diagnostic tests, treatment trials, as well as the results of medical technology research and factors influencing health. A separate category is made up of results used in specific products and technologies applied in medicine. Such a heterogeneous group determines the problems in regard to the legal grounds for determining the ownership of results [1]. This applies especially to the results of studies conducted jointly by many research centres (domestic and foreign), and results obtained in sponsored clinical trials that are subject to specific statutory regulations.

Although the intuitive regime protecting the results of research and development activity is intellectual property law – contrary to common belief – this does not provide tools for the protection of research results as such, even though they have undeniable scientific, commercial and application value. The results of research and scientific activities, including the results of clinical trials as numerical data, parameters and statistics, are not subject to copyright or patent protection, and thus the regulations do not provide for the acquisition of exclusive intellectual property rights to them [2]. A legal monopoly on the results of medical research is not available in order to not limit the access of society to such results and to allow the execution of a constitutionally guaranteed principle of freedom of research. Even though entities conducting research do not acquire property rights to the results, they retain a kind of "authorship" of the results under the protection of personal rights which ensures affiliation with research results.

The absence of exclusive rights to the results of research does not preclude their actual or contractual monopolization as data possessing certain scientific or market value. Exclusive intellectual property rights may be acquired to works in which research results have been described, discussed and verified (scientific articles, conference posters presenting results, reports, studies, databases containing results). Inventions which use these results can be also patented. According to the general ownership regimes of IP rights, an author's economic rights to a work or the right to obtain a patent for an invention are vested in the author or co-authors on the principle of the commonality of rights (Article 8 and 9 of the Copyright Act and Article 11 paragraph 1 and 2 of the Industrial Property Act). If such creations have been created by an employee in the performance of his/her duties, the rights are acquired by the employer which employs the scientist (researcher), unless the employment contract provides for other rules in this respect (Article 12 of the Copyright Act and Article 11 paragraph 3 of the Industrial Property Act). Depending on the contractual arrangements for the involvement of an individual participant in the research, in the case of multicentre research, rights may be acquired by the centres employing them or those individuals (if they are researching on a basis other than a contract of employment or outside of their employment obligations). The exception to this rule concerns employee copyrighted scientific works created in universities and research centres, to which the author's economic rights are vested in the employees and not in the research unit. The latter has only a legally guaranteed right to the first publication of the scientific work (Article 14 of the Copyright Act). Due to the competition of scientific centres regarding the affiliation of publications containing the most current or pioneering research results, collisions in the exercise of priority rights concerning co-publications involving authors from different centres are possible.

Results

Despite the exclusion of research results from intellectual property law protection, it is possible to acquire actual exclusivity of results which have market applicability and value by safeguarding their confidentiality. The legal basis for the protection of confidential research results is the Act on Combating Unfair Competition of 16 April 1993 [3]. According to Article 11 of this regulation that has recently been harmonized with EU standards, it is possible to protect such results as a so-called company secret (confidential know-how) from disclosure, use or unauthorized acquisition, provided that they are not generally known to persons normally dealing with such results or are not easily accessible to such persons and the entity entitled to the results has taken steps, with due diligence, to keep them confidential. The requirement to take steps to keep results confidential should be implemented in practice, in particular by signing clauses or confidentiality agreements with employees, members of research teams, researchers involved in sponsored trials, clinical trial or health technology assessments. The right to use or dispose of results whose market value is due to their confidentiality may belong to the research team or centres where the research is conducted or the research sponsor. Disclosure or obtaining such results shall constitute an act of unfair competition, if it occurs without the consent of the rightsholder and results from unauthorized access, misappropriation, or the copying of documents, objects, materials, substances or electronic files containing the results. Obtaining results identical to somebody else's confidential know-how is permissible when it has occurred as a result of independent discovery, production, observation, research, or testing, or to protect a legitimate public interest (e.g. to avoid the use of falsified or unreliable results of medical research, for the functioning of the health care system, obtaining permission to market a medicine, etc.).

In addition to the general statutory regulations, the provisions providing for who is entitled to research results, what the rules are for their use, publication and commercialisation may result from separate statutory or contractual regulations, including agreements with clinical trial sponsors or research funding schemes for national and international research projects.

In the coming years, the most important research funding mechanism for Polish researchers in the EU will be Horizon

Europe 2021–2027, which also provides, under priority research areas, funding for research in the area of health. Although the EU regulation on participation in research projects implemented under the program is not yet approved, it will set out detailed rules, binding for participants, on the management of research results obtained from projects financed from this source in regard to the ownership of research results, obligations related to their protection and dissemination and the granting of so-called access rights to them [4].

At the national level, specific provisions on the management of and know-how related to research and development results are laid down in the Act on Higher Education and Science of 20 July 2018 and the Act on Research Institutes of 30 April 2010 [5]. Issues concerning the ownership of the results of research projects financed from the resources of the National Centre for Science (NCN) and the National Centre for Research and Development (NCBiR) are regulated by the respective acts [6] and may be subject to specific rules for the implementation of strategic programs (such as, for example, NCBiR's program "Prevention and treatment of civilization diseases" – STRATEGME). As far as intellectual property rights are concerned, they respect the general principles of acquiring rights indicated earlier, by mentioning that, in the case of results obtained in NCN and NCBiR projects, they belong to the entity to which the funds have been allocated unless an agreement between the Centre and the entity receiving the funds or the decision to allocate funds provides otherwise [6].

Independent standards apply to the results of clinical trials, both commercial and non-commercial, which, at the national level, are provided for in the Pharmaceutical Law of 6 September 2001 [7] and the implementing Act on Good Clinical Practice [8]. It follows from these regulations that the ownership of clinical trial results is vested in the sponsor, who may transfer the ownership of all or part of the data or the right to dispose of all or part of the data related to the clinical trial to another entity by means of a written agreement. The limitations in use and transfer apply to results generated in non-commercial clinical trials, i.e. where the owner of the results generated in the course of the clinical trial is a university or other scientific institution, investigator or organization of researchers. The results of non-commercial clinical trials are intended to serve cognitive, scientific, non-commercial purposes and may be disseminated, for example, through scientific publications. However, they may not be used for marketing purposes or to make changes to an existing marketing authorization required for a medicinal product to be put on the market.

Conclusion

On the one hand, research results as such do not constitute an independent object of protection, on the other hand, they are an essential element required for the development and marketing of medical products and services. This may cause a conflict of interest between the free use of research results and making them available to the public (in particular by publishing them as soon as possible in scientific journals or as part of conference speeches) and maintaining their confidentiality (novelty), necessary for market monopolization based on know-how or patent protection. Potential areas of conflict are situations where research results are obtained through joint research activities, where the problem of priority of their publication, joint commercialisation or use in further, independent research may arise. This requires the taking adoption of legal measures and contractual tools [9].

To avoid disputes concerning the ownership of results and their use in scientific and commercial activities, it is recommended to conclude agreements on joint research work or to adapt model agreements relevant for a given research activity (such as, e.g. NCN projects, multicentre research, projects founded from EU programs). These should specify: the rules for the allocation of intellectual property rights generated by the research project or access rights to the results generated by joint research, as well as the rights and obligations of research stakeholders in the use of the results, including their publication and commercialization. The contracts should require, in particular, that participants keep research logs documenting the contributions of individuals in their research team.

Provisions concerning the confidentiality of research results, the prohibition of their disclosure, the rules of notification of planned publication of results and the transfer of intellectual property rights should be specified in particular in contracts for sponsored studies, including contracts for conducting clinical trials [10]. It should be borne in mind that the disclosure of the results of studies which have scientific value and validity, e.g. in an individual scientific publication or a research centre, may deprive such results of their application and market value, including preventing the funding entity or sponsor from obtaining exclusivity under the intellectual property rights system for products and technologies which use such results.

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Justyna Ożegalska-Trybalska
Jagiellonian University
Intellectual Property Law Chair
ul. Józefa 19
31-056 Kraków, Poland
e-mail: j.ozegalska-trybalska@uj.edu.pl

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References

1. Kasprzycki D. Ochrona wyników badań naukowych. In: Adamczak A. ed. Ochrona, wyczerpanie i korzystanie z praw własności intelektualnej, z uwzględnieniem prawa i orzecznictwa unijnego oraz praktyki EPO, Wynalazczość i ochrona własności intelektualnej. Nr 37. 2013: 19.
2. Wyraźne wyłączenie idei, odkryć, metod, danych statystycznych zawierają zarówno regulacje międzynarodowe, jak i krajowe przepisy ustawy o prawie autorskim i prawach pokrewnych z 4 lutego 1994 r., t.j. Dz. U. z 2019 r. poz. 1231, z 2020 r. poz. 288., a w zakresie twórczości

wynalazczej – ustawy Prawo własności przemysłowej z 30 czerwca 2000 r. t.j. Dz. U. z 2019 r., poz. 1010, 1649.
3. Dz. U. z 2019 r. poz. 1010, 1649.
4. Wniosek-Rozporządzenie Rady ustanawiające program badawczo-szkoleniowy Europejskiej Wspólnoty Energii Atomowej na lata 2021–2025 uzupełniający program ramowy w zakresie badań naukowych i innowacji „Horyzont Europa", COM/2018/437 final - 2018/0226 (NLE).
5. Art. 153-158 ustawy z dnia 20 lipca 2018 r. Prawo o szkolnictwie wyższym i nauce, t.j. Dz. U. z 2020 r. poz. 85, 374, 695, 875 oraz ustawa z dnia 30 kwietnia 2010 r. o instytutach badawczych, t.j.Dz. U. z 2019 r. poz. 1350, 2227, z 2020 r. poz. 284.
6. Ustawa z dnia 30 kwietnia 2010 r. o Narodowym Centrum Nauki, t.j. Dz. U. z 2019 r. poz. 1384 oraz ustawa z dnia 30 kwietnia 2010 r. o Narodowym Centrum Badań i Rozwoju, t.j. Dz. U. z 2019 r. poz. 1770, 2020, z 2020 r. poz. 284, 695.
7. Dz. U. z 2008 r. Nr 45, poz. 271, z późn. zm.
8. Rozporządzeniu Ministra Zdrowia z dnia 2 maja 2012 r., Dz. U. z 2012 r. poz. 489.
9. Bakalarz T. Ochrona wyników badań naukowych. Przegląd Prawa Gospodarczego. 2011(6): 35.
10. Swatyniec Ł. Umowy w badaniach klinicznych, komentarz praktyczny. LEX.