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Analysis of the effects of immunotherapy depending on cancer subtypes on survival - a single center experience

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Abstract
Background: The type of tumor is a huge determinant of survival and treatment outcomes, particularly with immunotherapy, which uses the immune system to target cancer cells. The response to immunotherapy varies depending on tumor types and is influenced by factors such as genetic mutations and the tumor microenvironment.
Materials and methods: The present retrospective study analyzed records for 151 patients who underwent immunotherapy at a single center between 2019 and 2023. The cohort included adults diagnosed with solid tumors, primarily NSCLC (non-small cell lung cancer). Immunotherapy agents included pembrolizumab, nivolumab, and others. Data on age, cancer stage, treatment response, adverse events, overall survival (OS), and progression-free survival (PFS) were collected. Statistical analyses, including the Cox proportional hazards model, assessed the impact of tumor types and subtypes on survival outcomes.
Results: The median age of the cohort was 69 (SD, 10.3) years, and the majority of the patients were men (64.9%). NSCLC was the predominant tumor type (78.1% of cases). In comparison to adenocarcinoma NSCLC, squamous NSCLC showed a significantly higher hazard ratio (HR) for OS (HR 1.49) and PFS (HR 1.47). Renal cell carcinoma and bladder cancer had lower HRs, suggesting a better prognosis.
Conclusions: This study highlights how responses to immunotherapy can differ widely based on tumor type, emphasizing the importance of personalized therapy approaches. These insights underscore the need for further research to tailor immunotherapy more effectively to different cancer types.

Keywords: Immunotherapy; Oncology; NSCLC; Cancer Subtypes; Renal Cell Carcinoma; Bladder Cancer; Immune Checkpoint Inhibitors

Introduction

The impact of tumor type on patient survival and treatment outcomes has gained significant attention, particularly in the context of immunotherapy. Immunotherapy, which leverages the body's immune system to attack tumor cells, has shown varying degrees of efficacy across different tumor types, highlighting the importance of tumor-specific approaches in cancer treatment [1]. Tumor microenvironment, genetic mutations, and the presence of specific biomarkers significantly influence how different cancers respond to immunotherapy, making it essential to understand these aspects for optimizing treatment strategies [2].
In recent years, studies have demonstrated that certain tumor types respond more favorably to immunotherapy. For instance, non-small-cell lung cancer (NSCLC) patients have shown

improved overall survival (OS) rates with the use of immune checkpoint inhibitors, such as pembrolizumab and nivolumab [3, 4].

Renal cell carcinoma (RCC) and melanoma are among the tumor types that have shown significant benefits from immunotherapy. The introduction of immune checkpoint inhibitors has revolutionized the treatment landscape for these cancers, leading to substantial improvements in patient outcomes [5].

Bladder cancer is another example where immunotherapy has made significant strides. The use of PD-1 and PD-L1 inhibitors has resulted in meaningful clinical benefits for patients with advanced or metastatic bladder cancer, showcasing the differential impact of tumor type on immunotherapy outcomes [6]. Avelumab and atezolizumab are inhibitors that have received approval for bladder cancer treatment, reflecting significant improvements in response rates and survival metrics [7]. These advancements highlight the necessity of understanding tumor-specific responses to tailor treatment plans effectively [8].

This study aims to investigate the impact of different tumor types and subtypes on patient survival and treatment outcomes in the context of immunotherapy. By analyzing the responses of various cancer types to immunotherapy, our research seeks to provide a comprehensive understanding of how specific tumor characteristics influence the efficacy of these treatments.

2. Materials and methods

This single-center, observational study was conducted using medical records of the 151 patients with any solid tumor treated with at least one dose of immunotherapy with or without chemotherapy in the Department of Clinical Oncology and Chemotherapy in the Independent Public Hospital No. 4 in Lublin between 2019 and 2023. Data cut-off date was 26 April 2023. All examined patients were adults (>18 years old), with varying cancer subtypes-predominantly NSCLC. Immunotherapy administered included pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab and ipilimumab in addition to PD-1 inhibitor. Chemotherapy regimens consisted of platinum in combination with other drugs, such as pemetrexed, docetaxel, gemcitabine, or paclitaxel/nab-paclitaxel. We collected patient baseline clinical data through electronic medical records, including age, sex, cancer stage, histology, differentiation, smoking history including smoking status and pack years, TNM classification, line of therapy, treatment type, clinical response, time of onset of the irAEs, type of the irAEs (organ-specific), grade of the irAEs, overall survival (OS) and progression-free survival (PFS).

Patients' irAEs were defined based on pathological proof, laboratory results and clinician decision after excluding other causes. Toxicities were graded by physicians based on Common Terminology for Adverse Events criteria, v4.0 (CTCAE v4.0). In patients receiving immunotherapy with chemotherapy or who received chemotherapy as a previous treatment line, we distinguished between immunotherapy-related and chemotherapy-related adverse events based on the differences in the toxicity spectrum (incidence rate and treatment specific adverse effects) and the time of toxicity onset. Hematological disorders and neuropathy were the most excluded adverse effects.

Tumor response was evaluated by the tomography scan results using the RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria. PFS was defined from the first

administration of the immunotherapy until the disease progression, unacceptable toxicity resulting in the change of treatment line, death, or follow-up cut-off date.
OS was defined as from the first day of ICI treatment administration of the immunotherapy until death, or follow-up cut-off date. This study was approved by the Medical University of Lublin institutional review board (No KE-0254/198/10/2022).
The data distribution was tested for normality with the Shapiro-Wilk test. The irregularity of the distribution allowed for the utilization of non-parametric statistical methods for the analyzed variables. To compare the survival time between groups, the log-rank test has been used. In the context of analyzing the impact of multiple factors on the survival time, the multivariable Cox proportional hazard model was used. The significance of the model and individual variables were investigated by tests: likelihood ratio test, Walda and score. Before using the Cox model, the proportional hazard test was evaluated.
The effect size for individual variables was expressed using the hazard ratio (HR). The multivariable Cox proportional hazard model fitting was rated by using the R^2 Nagelkerke factor, that provides information about the proportion of variances in survival times explained by the models.
For assessing the association between two continuous variables, the Spearman's rank correlation coefficient was used. The statistical significance of the correlation coefficient was computed using an asymptotic approximation of the distribution *t*.
The significance of differences between two or more groups with non-normal distribution was estimated with the ANOVA Kruskal-Wallis test. In terms of effect size, the measure of epsilon squared was calculated. Every statistical analysis results were presented with an adequate significance level, which enabled the assessment of the credibility of the observed relationships and conclusions drawn from the study.
The analysis was performed using the statistic language R (version 4.3.1; R Core Team, 2023), in the Windows 10 pro 64 bit system (compilation 19045), using the *car* packages (version 3.1.2; Fox J, Weisberg S, 2019), *sjPlot* (version 2.8.15; Lüdecke D, 2023), *parameters* (version 0.21.3; Lüdecke D et al., 2020), performance (version 0.10.8; Lüdecke D et al., 2021), report (version 0.5.7; Makowski D et al., 2023), *ggsurvfit* (version 1.0.0; Sjoberg D et al., 2023), *gtsummary* (version 1.7.2; Sjoberg D et al., 2021), *survival* (version 3.5.5; Therneau T, 2023), *ggplot2* (version 3.4.4; Wickham H, 2016), *readxl* (version 1.4.3; Wickham H, Bryan J, 2023) and *dplyr* (version 1.1.3; Wickham H et al., 2023).

3. Results

In the study group among patients with cancer, the median age was 69.0. Women represented 35.1% (n=53) and men 64.9% (n=98) of the cohort. Ex-smokers constituted nearly 41% and active smokers 26.5% of the group. Non-smokers represented almost 1/3 of the cohort (32.5%). Median of pack-years amounted to 20. In most patients immunotherapy constituted for the first (n=69, 45,7%) or second (n=77, 51%) line of the systemic treatment. Among 151 patients, most of them (65.6%, $n = 99$) were treated with the anti-PD-1 antibodies, while the other 34.4% *(*$n = 52$*)* with anti-PD-L1 antibodies.
Among 151 patients, the most common cancer type was the non-small cell lung cancer (NSCLC) which constituted 78.1% of the cases ($n = 118$). Bladder cancer was the second

most prevalent cancer type, representing 9.3% of the population (*n* = 14). The analysis of 115 NSCLC patients disclosed that the most common diagnosed subtype was squamous cell carcinoma (48.7%, *n* = 56) and adenocarcinoma (43.5%, *n* = 50).
Survival status demonstrated that 49.0% patients (*n* = 74) died, and 51.0% (n = *77*) were censored during the analysis meaning that they were still alive or their tracking data were lost. Progression status revealed that 53.0% of patients (n = 80) experienced progression of the disease, and 47.0% (n = 71) had no proof of the disease progression.
Most of the patients (63.6%) had no toxicity symptoms, mild symptoms occurred in 12.6% of the patients. Moderate (17.0%) and severe (6.0%) toxicity were found in 26 and 9 patients. Very severe toxicity was found in one patient (0.7%). Most common site specific toxicity was thyroid toxicity (11,8% n=18).
Characteristics of the study cohort are presented in *Table 1.*

Table 1. Demographic characteristics of the patients cohort

Characteristics	*N*	*Distribution*[1]
Age (years)	151	69.0 (64.5, 73.0)[2]
Sex	151	
Female		53 (35.1%)
Male		98 (64.9%)
Smoking status:	151	
Active smoker		40 (26.5%)
Non-smoker		49 (32.5%)
Previously smoker		62 (41.0%)
Packyears	151	20.0 (0, 40.0)
Type of cancer:	151	
NSCLC		118 (78.1%)
Urinary bladder cancer		14 (9.3%)
SCLC		9 (6.0%)
Kidney cancer		7 (4.6%)
Other		3 (2.0%)

Characteristics	*N*	*Distribution*[1]
NSCLC subtype	115	
Squamous cell carcinoma		56 (48.7%)
Adenocarcinoma		50 (43.5%)
NOS		3 (2.6%)
Pleomorphic cell carcinoma		1 (0.9%)
Large cell carcinoma		5 (4.3%)
Cancer stage		
I		14 (9,3%)
II		22 (14,6%)
III		28 (18,5%)
IV		87 (57,6%)
Metastases status		
Yes		67 (44,4%)
No		45 (29,8%)
Unknown		39 (25,8%)
Treatment:	151	
anti-PD1		99 (65.6%)
anti-PD-L1		52 (34.4%)
Immunotherapy therapeutic		
Atezolizumab		38 (25,2%)
Avelumab		10 (6,6%)
Durvalumab		4 (2,6%)

Characteristics	*N*	*Distribution*[1]
Nivolumab		28 (18,5%)
Pembrolizumab		71 (47%)
Immunotherapy monotherapy		106 (70,2%)
Immunotherapy plus chemotherapy		42 (27,8%)
Immunotherapy PD-1 plus CTLA-4		3 (2%)
Number of the previous systemic treatment lines:		
0		69 (45,7%)
1		77 (51%)
2 and more		5 (3,3%)
Overall survival (OS), weeks	151	35.6 (21.9, 55.1)
Progression free survival (PFS), weeks	151	26.6 (13.4, 44.4)
Survival status:	151	
Dead		74 (49.0%)
Censored		77 (51.0%)
Progression status:	151	
Progression		80 (53.0%)
No progression		71 (47.0%)
Initial response		
Partial response		33 (21,9%)

Characteristics	*N*	*Distribution*[1]
Disease stabilization		69 (45,7%)
Progression		24 (15,9%)
Death		20 (13,2%)
Not reached		5 (3,3%)
Toxicity	151	
None		96 (63.6%)
Mild		19 (12.6%)
Moderate		26 (17.2%)
Severe		9 (6.0%)
Extremely severe		1 (0.7%)
[1] *n* (%) [2] *Mdn* (*Q1*, *Q3*);		

Annotatioa: N – sample size, *n* – group size, *Mdn* – median, *Q1* – first quartile (25%), *Q3* – third quartile (75%).

3.2. Analysis of the effects of cancer types and subtypes on overall survival (OS)

As a further analysis, the multivariate model previously discussed in Section 2.5 was expanded with additional variables representing the diversity of cancer types and subtypes. A dedicated statistical model was designed and adapted for each identified cancer type. The goal of this approach is to gain a deeper understanding of how the unique characteristics of specific cancers may impact cancer patient survival predictions.

Table 2. presents the results of adjusted effects of each of the studied cancer types and subtypes in relation to their absence. These values were precisely estimated by using separate models for each cancer category, which allowed for a more accurate adaptation of the base model.

Table 2. Cox model fitting results. N_{obs} = 151.

Exposition	$R^2_{Nagelkerke}$	*Overall survival (OS)*

		HR	*CI 95%*	*p*
SCLC [yes]	0.13	1.53	0.58 – 4.06	0.390
NSCLC [yes]	0.14	1.75	0.79 – 3.88	0.167
NSCLC squamous [yes]	0.14	1.49	0.89 – 2.49	0.131
NSCLC adenocarcinoma [yes]	0.12	1.08	0.65 – 1.80	0.775
NSCLC large cell carcinoma [yes]	0.13	0.68	0.19 – 2.44	0.550
NSCLC NOS. pleomorphic. SCC [yes]	0.14	0.22	0.03 – 1.63	0.138
Kidney cancer [yes]	0.13	0.33	0.04 – 2.47	0.279
Bladder cancer [yes]	0.14	0.32	0.07 – 1.43	0.137
Kidney cancer + Bladder cancer [yes]	0.15	0.29	0.09 – 1.00	0.050
Other cancers [yes]	0.13	0.49	0.06 – 4.18	0.516

Annotation: Nobs – number of observations. $R^2_{Nagelkerke}$ - Nagelkerke pseudo coefficient of determination. *HR* – hazard ratio; *CI 95%* – confidence interval 95%. *p* – statistical test *p*-value

SCLC

The HR of 1.53, although without statistical significance (p = 0.390), suggested a trend towards an increased risk of death compared with the baseline population.

NSCLC

Differences in HR between NSCLS subtypes indicated the complexity of this cancer. For example, squamous NSCLS has an HR of 1.49 (p = 0.131), which may indicate a higher risk of death compared to adenocarcinoma NSCLS, where the HR was 1.08 (p = 0.775).

Kidney and bladder cancer

HR values of 0.29 (p = 0.05) close to statistical significance may suggest a better prognosis compared to other tested types of cancer. However, wide confidence intervals require careful interpretation.

Other cancers

The "Other cancers" category gathers individual cancers not belonging into the above types. Due to its heterogeneity it did not show significant differences in prognosis between individual cancers, which indicated a potential need for further subclassification and analyses.

3.3. Analysis of the effects of cancer types/subtypes on progression-free survival (PFS)

The current study examined the effects of cancer types and subtypes on PFS. The results are presented in Table 3.

Table 3. Cox model fitting results. N_{obs} = 151.

Exposition	$R^2_{Nagelkerke}$	*progression-free survival (PFS)*		
		HR	*CI 95%*	*p*
SCLC [yes]	0.18	1.58	0.62 – 4.01	0.336
NSCLC [yes]	0.18	1.86	0.85 – 4.08	0.123
NSCLC squamous [yes]	0.18	1.47	0.90 – 2.41	0.123

NSCLC adenocarcinoma [yes]	0.17	0.88	0.54 – 1.43	0.595
NSCLC large cell carcinoma [yes]	0.17	1.55	0.51 – 4.70	0.439
NSCLC NOS. pleomorphic. SCC [yes]	0.17	0.75	0.18 – 3.15	0.698
Kidney cancer [yes]	0.18	0.51	0.12 – 2.20	0.369
Bladder cancer [yes]	0.19	0.31	0.07 – 1.38	0.125
Kidney cancer + bladder cancer [yes]	0.19	0.36	0.12 – 1.05	0.062
Other cancers [yes]	0.18	0.28	0.03 – 2.51	0.253

Annotation: Nobs – number of observations. $R^2_{Nagelkerke}$ - Nagelkerke pseudo coefficient of determination. *HR* – hazard ratio; *CI 95%* – confidence interval 95%. *p* – statistical test *p*-value

SCLC

HR 1.58 indicated an increased risk of progression; however, wide confidence intervals (CI 95%: 0.62 - 4.01) and a p value of 0.336 mean a statistically insignificant result.

NSCLC

NSCLS subtypes showed different HRs, which may indicate the heterogeneity of this cancer. E.g., the HR for squamous NSCLS was 1.47 (p = 0.123), suggesting a trend towards an increased risk of progression compared with adenocarcinoma NSCLS, where the HR is 0.88 (p = 0.595).

Kidney and bladder cancer

These tumors exhibited lower HR values (0.51 and 0.31, respectively), which may suggest better PFS, but these results were not statistically significant and thus require further study.

When examining kidney and bladder cancer together, the observed HR was 0.36 with a 95% confidence interval of 0.12 to 1.05, suggesting a potentially significant reduction in the risk of disease progression compared with other cancer types in the study population. The p-value of 0.062 was close to the threshold for statistical significance, which may indicate a trend towards significance.

Other cancers

The very low HR (0.28) in this group indicated a potentially better PFS; however, the wide confidence interval and p-value of 0.253 meant no statistical significance.

Discussion

Immunotherapy has revolutionized cancer treatment by harnessing the body's immune system to target and destroy cancer cells. Its efficacy varies among different cancer types, showing remarkable success particularly in melanoma, lung cancer, and renal cell carcinoma [4, 5, 9]. The rise in immunotherapy's popularity is attributed to its potential to induce durable responses [10].

The benefits of ICIs in NSCLC are well-documented, with substantial improvements in ORR, PFS, and OS. For instance, in 2016 study, it was concluded that pembrolizumab was associated with significantly longer PFS and OS [3]. The effectiveness of immunotherapy in lung cancer is further supported by comprehensive analyses that compare these treatments with conventional options. Another study included patients with squamous-cell lung cancer who received 4 immunochemotherapy cycles followed by maintenance treatment with pembrolizumab. Median overall survival of 17.2 months versus 11.6 months for chemotherapy was obtained [11]. However, the variability within NSCLC subtypes necessitates personalised treatment approaches. Our study highlights that squamous NSCLC has a higher hazard ratio for both OS (HR 1.49) and PFS (HR 1.47) compared to adenocarcinoma NSCLC (HR 1.08 for OS and HR 0.88 for PFS). This suggests that squamous NSCLC may require more aggressive or combined therapeutic regimens, while adenocarcinoma NSCLC patients might benefit from more tailored strategies.

Similarly, renal cell carcinoma, patients treated with ICIs like nivolumab show improved survival outcomes, particularly in those with high-risk features or those unresponsive to traditional therapies [9]. Our data indicates favourable prognosis trends, with HRs of 0.51 for PFS, suggesting that early intervention with ICIs can significantly enhance disease control and survival outcomes. Similarly, urothelial carcinoma patients treated with ICIs such as atezolizumab have demonstrated enhanced survival rates [6].

The lack of statistical significance in the analysis of the cancer types/subtypes effects on PFS did not allow for unequivocal clinical recommendations. However, the observed trends indicate potential differences in the dynamics of the disease, which may be important in individual treatment planning. These results may suggest that patients with squamous NSCLS might require more aggressive treatment or closer monitoring compared with adenocarcinoma NSCLS patients, given the observed trend of increased risk of progression. Lower HRs for kidney and bladder cancer may indicate the potential for early detection and intervention, which may lead to prolonged PFS in these populations.

The effectiveness of ICIs varies widely across different cancer types and subtypes, necessitating individualized therapeutic strategies. The observed HRs for survival and progression in different cancers highlight the heterogeneity in treatment responses. For instance, the higher HR for squamous NSCLC highlights the need for more aggressive or combined treatment regimens, whereas the lower HRs for kidney and bladder cancers suggest potential benefits from early intervention.
The presented data and interpretation suggested that the type and subtype of cancer influence the prognosis and survival of patients. HR values for various cancers may be used to better understand the risks associated with specific types of cancer, which is crucial in the clinical decision-making process.
However, these results should be seen as a starting point for further, more detailed studies that take into consideration larger samples and complementary prognostic factors.

Conclusions

Despite these promising results, some patients still exhibit limited responses to ICIs, highlighting the necessity for ongoing research into new combination strategies and treatment modalities. Thus, while ICIs represent a significant advancement in cancer treatment, optimizing their effectiveness requires tailored approaches and further exploration into their role across various cancer types and patient populations.

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