# Real-World Evidence from the TriNetX Network: Assessing Immunotherapy's Impact on Second Primary Cancer Risk in Metastatic Lung Cancer

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## *Abstract*

**Background:** Lung cancer survivors are at high risk of developing a second primary cancer (SPC). This study investigated the impact of immune checkpoint inhibitors (ICIs) on the risk to develop a SPC in a large cohort of metastatic lung cancer patients.

**Objective:** This study investigated the impact of immune checkpoint inhibitors (ICIs) on the risk to develop a SPC in a large cohort of metastatic lung cancer patients.

**Methods:** Using a retrospective cohort from the TriNetX Global Collaborative research network, the study analyzed the incidence of SPC in metastatic lung cancer (MLC) patients treated with ICIs against those who were not. Propensity score matching and Kaplan-Meier to assess the effect of ICIs on the development of SPCs.

**Results:** The study analyzed 2,844 MLC patients, with 685 receiving ICIs and 2,157 not receiving ICIs. Post-propensity score matching, each cohort included 685 patients. The 5-year analysis revealed a lower incidence of SPCs in the ICI group (1.5%) compared to the non-ICI group (4.2%), with a Hazard Ratio (HR) of 0.49 (95%CI [0.24-1.01]) indicating a reduced risk. Treatment with ICIs was associated with a significant risk reduction of SPC or death (HR=0.78; 95%CI [0.62-0.89]).

**Conclusions:** ICIs reduce the risk of SPCs in metastatic lung cancer patients. Despite limitations, the study confirms the preventive role of ICIs and the importance of real-world data to identify novel paradigm changing strategies. Clinical Trial: Not applicable

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# Real-World Evidence from the TriNetX Network: Assessing Immunotherapy's Impact on Second Primary Cancer Risk in Metastatic Lung Cancer

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**Words count : 2150**

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**Key words:** second primary cancer; lung cancer; immunotherapy; immune checkpoints inhibitors; second malignant neoplasia, real world data.



## ABSTRACT

Background: Lung cancer survivors are at high risk of developing a second primary cancer (SPC). This study investigated the impact of immune checkpoint inhibitors (ICIs) on the risk to develop a SPC in a large cohort of metastatic lung cancer patients.

Methods: Using a retrospective cohort from the TriNetX Global Collaborative research network, the study analyzed the incidence of SPC in metastatic lung cancer (MLC) patients treated with ICIs against those who were not. Propensity score matching and Kaplan-Meier to assess the effect of ICIs

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Conclusion: ICIs reduce the risk of SPCs in metastatic lung cancer patients. Despite limitations, the study confirms the preventive role of ICIs and the importance of real-world data to identify novel paradigm changing strategies.



## Introduction

The trajectory of cancer treatment has undergone transformative evolution, heralding the integration of immune checkpoint inhibitors (ICIs) as a seminal component in the therapeutic armamentarium [1].

This shift has been characterized by innovative strategies encompassing neoadjuvant, adjuvant, and, more recently, peri-operative applications of ICIs changing treatment paradigms and integrating immunotherapies improve therapeutic outcomes and patient survival [2]. These strategies, aspire to enhance the efficacy of primary tumor management, reducing disease relapse, enabling less invasive surgical interventions, and targeting minimal residual diseases in a spectrum of cancer types.

A recently identify positive facet of significant interest is the potential role of ICIs in mitigating the risks associated with the occurrence of second primary cancers (SPCs)— observed in over 7% of cancer survivors [3]. Amidst a confluence of risk factors such as genetics, environmental exposures, and therapeutic side effects, SPCs emerge as a significant risk impacting long term survival of cured patients, warranting innovative preventive strategies. A retrospection into clinical data suggest a

spectrum of impacts associated with ICIs utilization, ranging from associations with reduced SPC occurrences [4-7] to a lack of conclusively protective effects [8, 9]. This nuanced clinical tableau underscores the inherent complexities and variables, including histologic considerations and therapeutic contexts, that influence the potential effectiveness of ICIs as a preventive arsenal against SPCs. Although a phase II randomized trial is currently enrolling to answer this important question (NCT05855811) [10], it seems fundamental to continue evaluating the potential impact of immunotherapy on the risk of SPC, utilizing new extensive retrospective cohorts of cancer patients. That is why, we analyzed data from TriNetX global health research platform that includes data on 30 million patients from Europe to US. to contribute to improve scientific knowledge [11, 12].

The primary objective of this study is to utilize real-world data from the TriNetX federated data network to investigate the impact of ICIs on the risk of SPC in patients treated for metastatic or locally advanced lung cancer. This exploration aims to provide insights into the potential of ICIs to serve as a preventive strategy against SPCs, thereby informing clinical practice and guiding future research in this critical area.

## MATERIALS AND METHODS

### Data source and patient selection

This non-interventional, retrospective cohort study used data from the international TriNetX Global Collaborative research data network. We studied patients from TriNetX with metastatic lung cancer (MLC) aged 18 or over. TriNetX is a global collaborative research network that provides real-time access to electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information) from over 135 million patients from 114 healthcare organizations, primarily from North America and Western Europe. All data collection, processing, and transmission is done in compliance with all Data Protection laws applicable to the contributing HCOs, including the EU Data Protection Law Regulation 2016/679, the General Data Protection Regulation on the protection of natural persons with regard to the processing of personal data and the Health Insurance Portability and Accountability Act, the US federal law which protects the privacy and security of healthcare data. The Global Collaborative Network is a distributed network, and analytics are performed at the HCO with only aggregate results being returned to the platform. Individual personal data does not leave the HCO. TriNetX is ISO 27001:2013 certified and maintains a robust IT security program that protects both personal data and health care data. Data collection and quality control methods have been described [11]. As a federated network, research studies using TriNetX are compliant with requests from Ethics committees of all contributing countries. To comply with legal frameworks and ethical guidelines guarding against data re-identification, the identity of participating HCOs and their

individual contribution to each dataset are not disclosed. The TriNetX platform only uses aggregated counts and statistical summaries of de-identified information. No Protected Health Information or Personal Data is made available to the users of the platform. Research studies done with TriNetX platform do not require ethical approval. Any data is displayed on the TriNetX Platform in the form of aggregated and statistical summaries of de-identified information. No Protected Health Information or Personal Data is made available to the users of the platform. The process by which the data is de-identified is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule. This formal determination by a qualified expert, refreshed in December 2020, supersedes the need for TriNetX's previous waiver from the Western Institutional Review Board.

Selected patients were men or women, aged 18 or over, with a diagnosis of metastatic lung cancer between February 1, 2004 and February 1, 2024. Patients were excluded when : a) patient died or had a non lung cancer diagnosis within the first 6 months after the metastasis diagnosis; b) patients never had a visit to the HCO before the metastasis diagnosis; c) patients never had a follow-up visit after 6 months of the metastasis diagnosis; d) patients had lung cancer as the second primary cancer given the difficulty in clinical practice in differentiating a second primary lung cancer from a new metastatic localization of the treated lung cancer ; and e) patients did not have any data of treatment after the metastasis. The initial group of participants was then divided into two cohorts. The group "ICI" included patients treated with ICI after the metastasis diagnosis and "no-ICI" included the patients never treated with ICI. For the present study, data were collected until February 25, 2024 (i.e. database extraction date). The details on the codes and criteria used to define the cohorts can be found in the Supplementary Table 1 and 2.

Objectives

The primary goal of this research is to evaluate the effect of ICI treatment for metastatic lung cancer on the likelihood of developing a second primary cancer outside the lungs in a real-world scenario.

Statistical analysis

All the statistical analysis was done using TriNetX platform built-in analysis features. ICI and no-ICI cohorts were propensity score matched (PSM) before the comparison on age at the moment of the metastasis diagnosis, gender, race (when available), de novo MLC, smoking, patient dependency status. The index event of both cohorts was the metastasis diagnosis and the follow-up time window was 10 years.

Baseline characteristics before and after PSM are presented with the number and percentage for categorical variables and mean and SD when variables are numeric. Categorical variables are compared between cohorts with the Fisher's exact test p value and the standardized mean differences. Numeric variables are compared with the t-test p value and standard difference.

Kaplan-Meier analysis was performed on the matched cohorts to calculate the time between the MLC diagnosis and the SPC. Cox proportional hazard ratios (HR) and 95% CI are presented.

## RESULTS

### Study population

The current analysis considered the 2,844 metastatic primary lung cancer patients selected in the TriNetX network. The study population included 685 patients in the ICI group and 2,157 in the no-ICI group. Patient characteristics are summarized in Table 1. After PSM both cohorts included 685 patients. A total of 292 (42.5 %) in ICI and 290 (42.3%) no-ICI patients were women, with mean age of 66.8±9.7 years and 67.0±10.0 years, respectively. Among them, 216 (31.5 %) patients had de novo metastatic disease and 171 (25.0 %) were smokers or former smokers in the ICI cohort. In addition to ICI, 684 (99.9%) of the exposure cohort received at least one chemotherapy regimen and 75 (10.9%) at least one more targeted treatment. Concerning loco-regional treatment, 231 patients (33.7%) were treated by radiotherapy and 41 (6.0%) had surgery in metastatic setting. The median follow-up was 20.2 months for ICI and 68.37 months for no-ICI.

Overall, 39 (2.8%) patients had a diagnosis of SPC. 10 (1.5%) SPC patients were reported in the cohort of receiving ICI for their lung cancer in a median interval of 13.9 months vs 23 (3.6%) in a median interval of 17.8 months in patients who did not receive immunotherapy (HR = 0.49, 95%CI 0.24-1.01) (Figure 1). Among the patients who received ICI, the median time between the diagnosis of advanced or metastatic LC and ICI is 34 days. The median time between ICI initiation and the diagnosis of SPC was 9.0 months (min-max: [1.4 – 15.1]).

Age, gender, race, de novo MLC, smoking, patient dependency status were identified as potential confounding variables and were included into the propensity score analyses. Standardized mean differences after weighting were within ±0.1 for all observed confounding variable (Supplementary Table 1).

Figure 2 presents the time from the diagnosis of MLC to the date of SPC diagnosis or the date of death in patients having received ICI or not for lung cancer. Treatment with immunotherapy for lung cancer was associated with a significant risk reduction of SPC or death (HR=0.74, 95%CI [0.62-0.89]). The median months to MLC or death was 9.6 and 11.2 for patients treated with ICI and not

treated with ICI, respectively.

## DISCUSSION

Our study, encompassing 2,844 metastatic primary lung cancer patients from the TriNetX network, indicates a significant impact of immune checkpoint inhibitors (ICIs) on the incidence of secondary primary cancers (SPCs) and overall survival showcasing the power of large-scale data in generating valuable insights. This study highlights the critical role of big data and digital health in advancing cancer treatment and research. The TriNetX network, encompassing numerous international centers, exemplifies how big data can be leveraged to conduct extensive and robust studies. The analysis, balanced post-propensity score matching with 685 patients in each cohort, revealed that ICI treatment was associated with a reduced risk of developing SPCs. Specifically, the incidence of SPCs excluding lung cancer was 1.5% in the ICI group compared to 3.6% in the non-ICI group, translating into a risk difference of -0.028 and a favorable Hazard Ratio (HR) of 0.49. Additionally, our findings demonstrated a reduction in the risk of SPC or death in patients treated with ICIs, with a significant HR of 0.78. This suggests not only the efficacy of ICIs in treating primary tumors but also their potential role in preventing secondary malignancies. The median time to MLC or death was notably higher in the ICI-treated group, further emphasizing the survival benefits of ICIs. Of course, our study of many limitations began with its retrospective nature. Even if the TriNetX network is extremely important, with numerous international centers, it clearly appears that the scope of the available data remains limited since we do not have, for example, the histological subtypes, nor the smoking status and even less the molecular characteristics of cancers. These missing data constitute a major limitation to the conclusions of our study and to the question of the accessibility and the sharing of these data which are necessarily present in the electronic medical records [13]. Learned societies have recently established recommendations on real-world data studies, the quality of the conclusions of which is directly linked to the quality of the data obtained [14].

However, the effectiveness of big data and digital health hinges on the quality and comprehensiveness of the data. We must not forget the importance of real world data which are complementary to clinical trials [15], particularly on subjects such as the appearance of a second primary cancer for which these patients are often excluded from traditional clinical research studies. It therefore appears fundamental to continue collaboration within, for example, the TriNetX network because the greater the volume and completeness of the data, the greater the confidence in the conclusions of these retrospective studies [16]. For this it seems necessary for each hospital to define its digital data strategy which must include a data collection strategy (by aligning them from the start

with international benchmarks), for the qualification of this data, for their analysis with quality control and a sharing strategy [17]. This entire strategy must of course respect the regulations in force and integrate a priori the question of interoperability to facilitate data sharing and enhancing research outcomes [18, 19].

To maximize the potential of big data and digital health, continued collaboration within networks like TriNetX is essential. The greater the volume and completeness of the data, the higher the confidence in the study conclusions. Recommendations from learned societies on real-world data studies emphasize the importance of data quality, suggesting that the robustness of study conclusions is directly linked to the quality of the data obtained.

In conclusion, our study showed that patients treated with immunotherapy for a first lung cancer had a reduced risk of a SPC and underscores the significant benefits of utilizing big data and digital health in cancer research. The ability to conduct real-life studies on an international network like TriNetX allows for the inclusion of diverse patient populations and the generation of real-world evidence that complements clinical trials. Despite current data limitations, continued network collaborations and strategic data management can enhance the relevance and impact of real-world data studies, ultimately improving patient outcomes and advancing medical knowledge.

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**Table 1**. Characteristics of the population before and after propensity score matching

| | Characteristics before propensity score matching | | | | | | Characteristics after propensity score matching | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ICI cohort (N = 687) | | no-ICI cohort (N = 2,157) | | | | ICI cohort (N = 685) | | no-ICI cohort (N = 685) | | | |
| | Patients / Mean ± SD | % of Cohort | Patients / Mean ± SD | % of Cohort | P-Value | Std diff. | Patients / Mean ± SD | % of Cohort | Patients / Mean ± SD | % of Cohort | P-Value | Std diff. |
| **Demographics** | | | | | | | | | | | | |
| Age at Index | 66.8 +/- 9.7 | 100.0% | 65.4 +/- 11.0 | 100.0% | 0.005 | 0.128 | 66.8 +/- 9.7 | 100.0% | 67.0 +/- 10.0 | 100.0% | 0.734 | 0.018 |
| Male | 385 | 56.0% | 1,073 | 49.7% | 0.004 | 0.126 | 384 | 56.1% | 387 | 56.5% | 0.87 | 0.009 |
| Female | 292 | 42.5% | 1,065 | 49.4% | 0.002 | 0.138 | 292 | 42.6% | 290 | 42.3% | 0.913 | 0.006 |
| White | 396 | 57.6% | 1,082 | 50.2% | 0.001 | 0.15 | 395 | 57.7% | 406 | 59.3% | 0.546 | 0.033 |
| Black or African American | 59 | 8.6% | 144 | 6.7% | 0.09 | 0.072 | 58 | 8.5% | 48 | 7.0% | 0.312 | 0.055 |
| Male | 385 | 56.0% | 1,073 | 49.7% | 0.004 | 0.126 | 384 | 56.1% | 387 | 56.5% | 0.87 | 0.009 |
| Asian | 18 | 2.6% | 126 | 5.8% | 0.001 | 0.161 | 18 | 2.6% | 15 | 2.2% | 0.597 | 0.029 |
| **Diagnosis** | | | | | | | | | | | | |
| Nicotine dependence | 173 | 25.2% | 393 | 18.2% | <0.001 | 0.17 | 171 | 25.0% | 160 | 23.4% | 0.488 | 0.038 |
| Malignant neoplasm of bronchus and | 471 | 68.6% | 1,373 | 63.7% | 0.019 | 0.104 | 469 | 68.5% | 478 | 69.8% | 0.599 | 0.028 |
| Problems related to care provider dependency | 10 | 1.5% | 21 | 1.0% | 0.289 | 0.044 | 10 | 1.5% | 10 | 1.5% | 1 | <0.001 |
| **Treatment** | | | | | | | | | | | | |
| Radiotherapy | 234 | 33.5% | 491 | 22.7% | <0.001 | | 231 | 33.7% | 157 | 22.9% | <0.001 | |
| Loco-regional surgery | 41 | 5.9% | 173 | 8.0% | 0.63 | | 41 | 6.0% | 35 | 5.1% | 0.479 | |
| Systemic chemotherapy | 687 | 100.0% | 1,785 | 82.4% | <0.001 | | 684 | 99.9% | 562 | 82.0% | <0.001 | |
| Targeted treatment other than ICI | 77 | 11.0% | 557 | 25.7% | <0.001 | | 75 | 10.9% | 166 | 24.2% | <0.001 | |

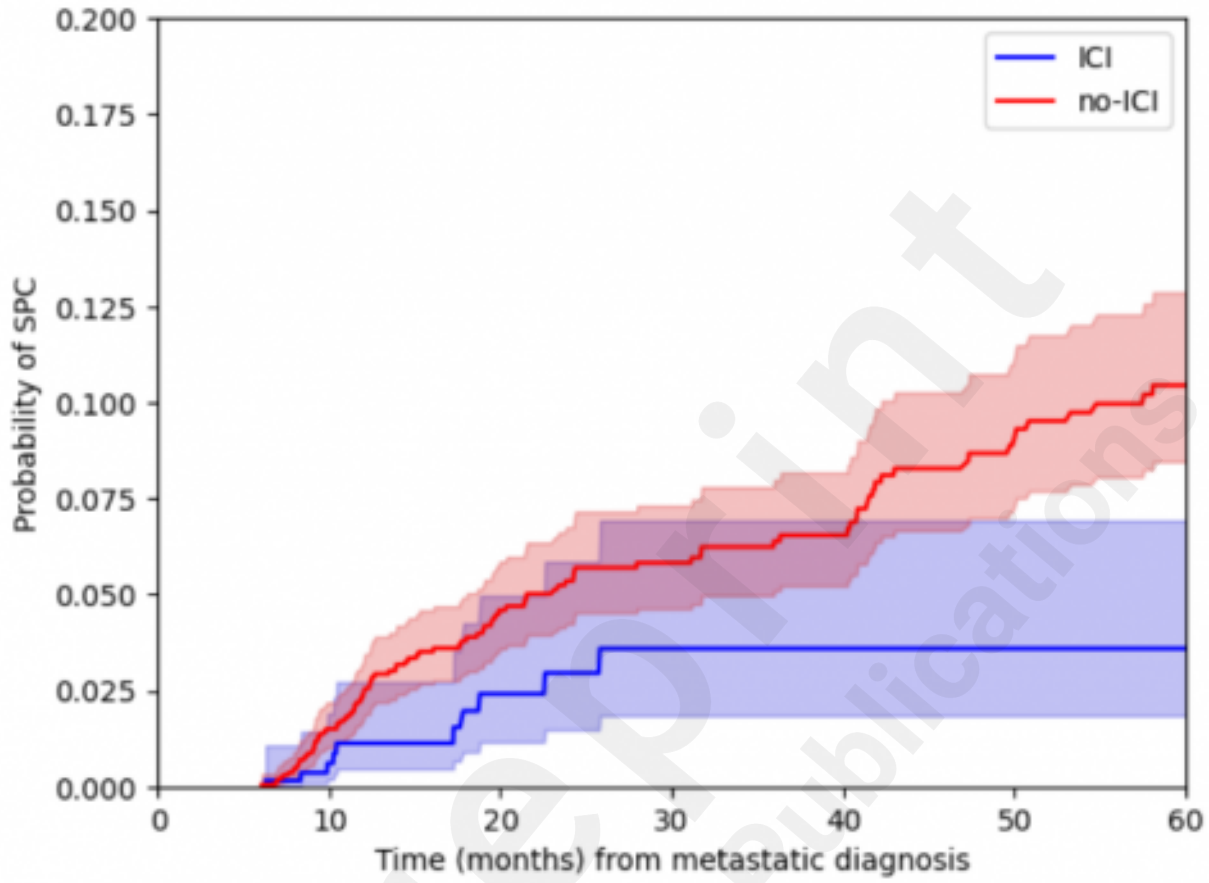
Figure 1. Kaplan-Meier curve to second primary cancer
Figure 2. Kaplan-Meier survival curve to death or second primary cancer

# Supplementary Files

# Figures

Untitled.

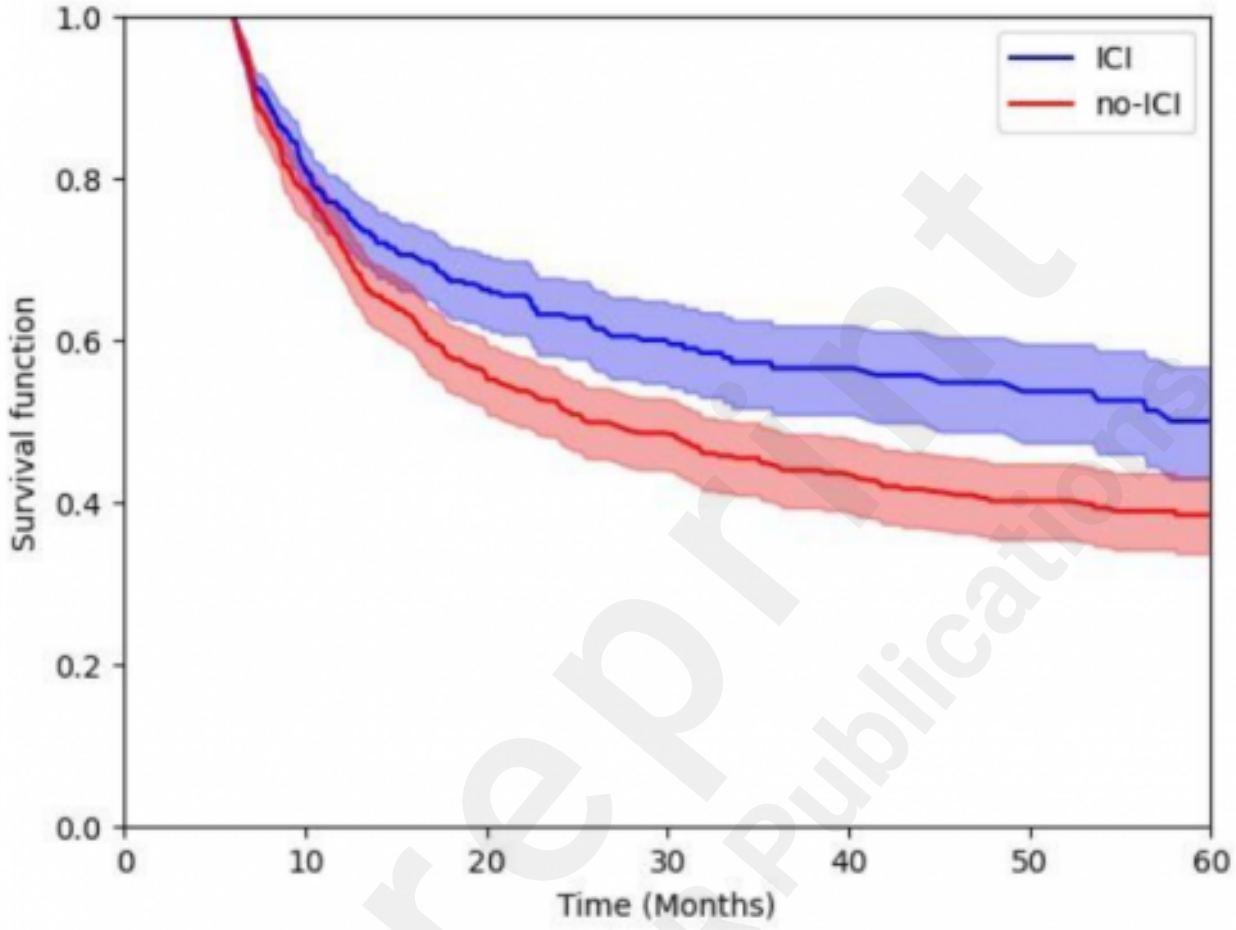
**Figure 1**. Kaplan-Meier curve to SPC




| Months | 0 | 10 | 20 | 30 | 40 | 50 | 60 |
|---|---|---|---|---|---|---|---|
| ICI | 685 | 388 | 211 | 146 | 146 | 146 | 146 |
| No-ICI | 685 | 476 | 284 | 240 | 172 | 133 | 107 |

Untitled.

**Figure 2.** Kaplan-Meier survival curve to death or SPC




Patients at risk

| Months | 0 | 10 | 20 | 30 | 40 | 50 | 60 |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| ICI | 685 | 365 | 187 | 127 | 82 | 50 | 40 |
| No-ICI | 685 | 437 | 243 | 187 | 136 | 107 | 87 |

# Multimedia Appendixes

Untitled.
URL: http://asset.jmir.pub/assets/fe75019810bc8a97ad2b8241ab65706a.docx

Untitled.
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