Prescription Pattern of Immunotherapy in the Management of Solid Cancers: A Retrospective Study

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Abstract

Solid cancers are abnormal tissues in organ systems without liquid or cysts. Immunotherapy, an advanced treatment option, stimulates the host immune system to destroy cancer cells. Immune Checkpoint Inhibitors (ICIs) are the main class of immunotherapy, used as direct anti-cancer agents or supportive therapy alone or in combination with other treatments. The trend of immunotherapy use in solid cancers may vary by geographical region and ethnicity.

Objective: The goal of the study was to assess the drug use pattern of immunotherapy in patients diagnosed with solid cancers in the Indian clinical setting.

Methodology: This was a retrospective study carried out in the Department of Oncology, ESIC MC-PGIMSR, and Model Hospital, Rajajinagar, Bengaluru, for 6 months by collecting the data in the patient medical records from June 2021 to May 2023. A total of 40 samples were collected and statistically analyzed using Microsoft Excel.

Results: A total of 40 solid cancer patients received immunotherapy. The majority of the patients were in the 56–65year age category and were male. Lung cancer was the most common solid cancer (20%), followed by oral cancer (17.5%). Metastasis was present in the majority (67.5%) of the study population, with more lymph node metastasis (42.5%). PD-1 inhibitors were used mostly (72.5%), with Nivolumab being the primary drug of choice. Atezolizumab was the major PD-L1 inhibitor drug used in the study population. A statistically significant association between immunotherapy and metastasis of solid cancers was observed in the Chi-square test for independence.

Conclusion: The immunotherapy drugs were used according to international professional guidelines and the findings agree with the various global experiences and are helpful in similar clinical settings where immunotherapy is used.

Keywords: Solid Cancers, Immunotherapy, Drug use pattern, Retrospective, PD-1 inhibitors

1. Introduction

Cancer, also called neoplasia or malignancy, is a group of diseases that may begin in any tissue or organ of the body in which the cells multiply without control due to genetic changes. [1,2] On a global basis, malignancy is accountable for nearly 10 million deaths in 2020, which makes cancer the second-leading cause of death in the world. In 2020, 18.1 million new cases of cancer were estimated globally.[3] 9.3 million of these cases involved men, and 8.8 million involved women. According to the Globacon report

2020, 1324413 new cancer cases were detected in India in which 646030 were males & 678383 were females. Total 851678 deaths happened due to cancers. [4-7]

Solid cancers represent the malignancy of single or multiple masses of abnormal cells that do not contain any liquid or cysts. [7-10] Based on the histology, they can be categorised into carcinomas, sarcomas, lymphomas, melanomas, mixed and other type cancers. [11-14] Solid cancers can be classified or named based on the primary sites of cancer origin. [15]

Solid cancers are treated using the various modalities, which may be used singly, sequentially, or concurrently. Treatment modalities of solid cancer involve surgery, radiation therapy and systemic anticancer agents such as chemotherapy, targeted therapy, and immunotherapy. Systemic anticancer agents are used to eradicate cancerous cells and this therapeutic approach can be applied either alone or in combination with other modalities to all forms of solid cancer. [7,16-19]

Immunotherapy is an advanced, revolutionary cancer treatment option that started and developed in the past few decades, and its use has risen in recent years for treating various advanced forms of solid cancer. [20,21] It stimulates the host immune system of natural defence in the body to destroy cancer cells by training the immune system to attack and kill the tumour cells or by administering the components of the immune system to generally stimulate immunity. [7,22] It can be used as a direct anti-cancer agent or supportive therapy alone or in combination with other traditional cancer treatments. [23] The most commonly used immunotherapy treatment is immune checkpoint inhibitors (ICIs), that involves CTLA-4 inhibitors, PD-1 inhibitors and PD-L1 inhibitors. Other options are cytokines, therapeutic vaccines, and CAR T-cell therapies. [24- 26]

The main objective of the study was to assess the drug use pattern of immunotherapy drugs in the patients diagnosed with solid cancers. This study was conducted to have a better insight into the current immunotherapy trend and its usage for the different types of solid cancers in the Indian hospital settings.

2. Materials And Methods

This retrospective study was conducted in the Department of Oncology, ESIC MC-PGIMSR and Model Hospital, Rajajinagar, Bengaluru for 6 months in the patients who had taken immunotherapy in the management of solid cancers. Patients of age above 18 years were included in the study. The data present in the old case files and medical records of patients from June 2021 and May 2023 was collected. Self-designed data collection form containing demographic details, social details, medical and medication histories, diagnostic details, and treatment details of patients was used for study.

2.1. Study procedure

The study commenced after the approval of the Institutional Ethics Committee. The investigator had chosen the study subjects based on the inclusion and exclusion criteria from the old case files and medical records available in the Department of Oncology. Relevant data from the files was obtained and recorded on the data collection form or entered into an electronic data collection form and then in a Microsoft Excel sheet. The data so obtained was segregated in a Microsoft Excel sheet, assessed, and appropriate statistical analysis was performed.

2.2. Statistical analysis

All recorded data were entered using MS Excel software and analyzed using the same method for determining statistical significance. Descriptive statistics such as mean and standard deviation were computed for quantitative variables, and frequencies and percentages were calculated for categorical variables. Bar diagrams and pie charts were plotted to determine the nature of the data distribution. A chi-

square test for independence was performed to find out the significant association between immunotherapy and metastasis in solid cancers.

3. Results

A total of 40 patient samples were gathered and used for analysing the results. Distribution of patients was done based on baseline characteristics depicted in Table 1. It shows the patients distribution based on their age, gender, and social histories.

Mean age of the patients was found to be 56.77 years, with a Standard Deviation (SD) of 11.3 year. The patients were categorised based on age and the highest number of patients were in the 56–65year age category (n=12, 30%) followed by 46-55year category (n=11, 27.5%). Out of 40 patients, 30 were males (75%) and 10 females (25%). The patients were categorised based on their social habits. Smoking was the most common social habit, with 45% (n=18) of patients involved followed by alcohol consumption at 32.5% (n=13).

Table 1. Distribution of patients based on baseline characteristics

Baseline Characteristics	Frequency (n)	Percentage (%)
Age (years):		
36-45	8	20
46-55	11	27.5
56-65	12	30
>65	9	22.5
Gender:		
Male	30	75
Female	10	25
Social History:		
Smoking	18	45
Tobacco chew	3	7.5
Alcohol consumption	13	32.5

The patients collected had various comorbidities, in which Type-2 Diabetes Mellitus was the most common comorbidity (n=8, 20%) followed by Hypertension (n=7, 17.5%). Distribution of patients based on comorbidities present with the solid cancer is represented in Figure1.
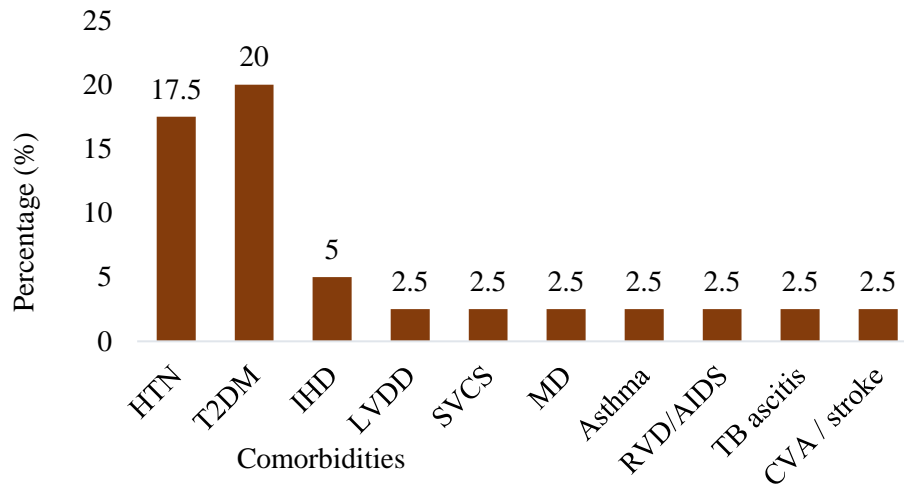
Figure 1: Distribution of patients based on comorbidities

Distribution of type of cancers, metastasis and extent of metastasis are represented in Figure 2, Figure 3 and Figure 4 respectively. Out of 40 patients, the most prevalent cancer was lung cancer (n=8, 20%) followed by oral cancer (n=7, 17.5%), renal cancer (n=5, 12.5%) and liver cancer (n=5, 12.5%). Patients showed metastasis were 27 (67.5%) and the most common sites of metastasis were lymph nodes (n=17, 42.5%), lung (n = 8, 20%) and bone (n = 7, 17.5%).
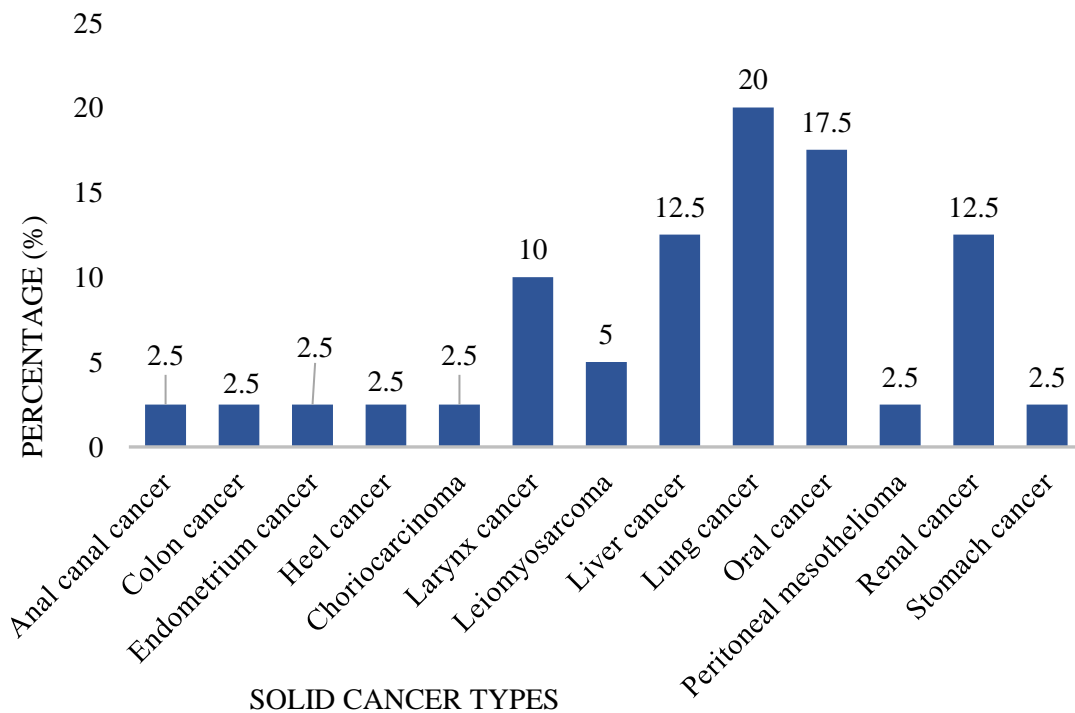

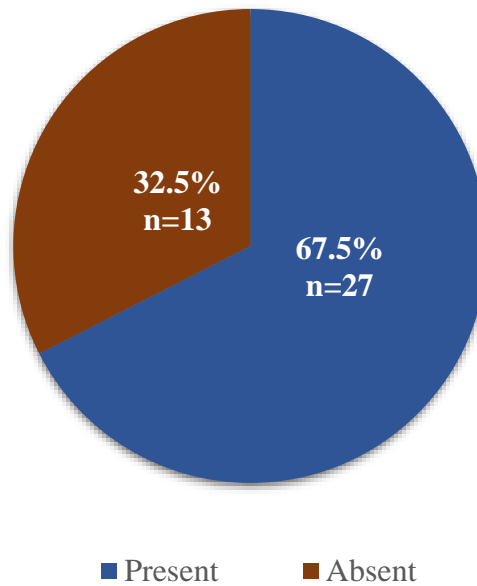**Figure 2: Distribution of patients based on types of solid cancer**

Figure 3: Distribution of patients based on metastasis of solid cancer
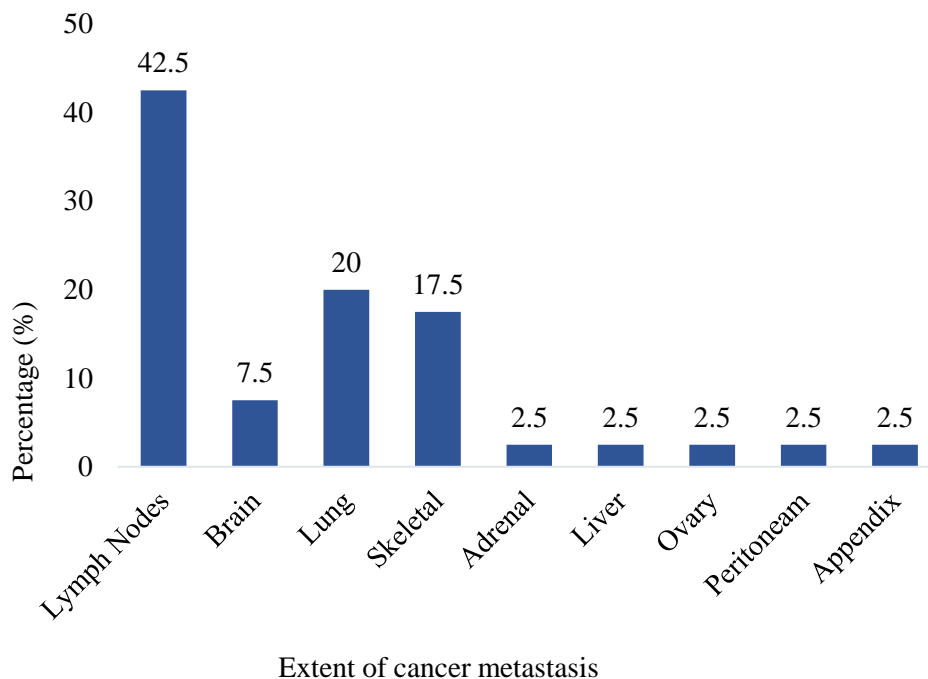

Figure 4: Distribution of patients based on extent of metastasis in solid cancer

Categorisation of patients based on type of immunotherapy was done in the study that is represented in Table 2. İn this summary of patients taking PD-1 inhibitor and PD-L1 inhibitor taking patients is depicted clearly. Total 29 (72.5%) patients were given PD-1 inhibitors, followed by 11 (27.5%) PD-L1 inhibitors. Nivolumab was the major PD-1 inhibitor (n=24, 82.8%) followed by pembrolizumab (n=5, 17.2%) and Atezolizumab was the major PD-L1 inhibitor (n=10, 90.9%) followed by avelumab (n=1, 9.1%).

Table 2: Distribution of Patients based on Types of Immunotherapies

Type of immunotherapy	Frequency (n)	Percentage (%)
PD-1 Inhibitors	29	72.5
PD-L1 Inhibitors	11	27.5
Total	40	100
PD-1 Inhibitors:		
Nivolumab	24	82.8
Pembrolizumab	5	17.2
Total	29	100
PD-L1 Inhibitors:		
Atezolizumab	10	90.9
Avelumab	1	9.1
Total	11	100

Patients were categorised consecutively based on metastasis of solid cancer and immunotherapy drugs. The cross table of immunotherapy types and metastasis of solid cancer is represented in Table 3. In metastatic cancers nivolumab was the major drug of choice (n=19, 70.4%) and in non-metastatic cancers both atezolizumab (n=6, 46.1%) and nivolumab (n=5, 38.5%) were major drugs. PD-1 inhibitor (n=23, 85.5%) was more commonly prescribed in metastatic cancers.

Table 3. Distribution of patients based on immunotherapy drugs and solid cancer metastasis

Immunotherapy drugs	Frequency (n)	Percentage (%)
Metastatic cancer patients:		
Nivolumab	19	70.4
Pembrolizumab	4	14.8
Atezolizumab	4	14.8
Avelumab	0	0
Total	27	100
Non- metastatic cancer patients:		
Nivolumab	5	38.5
Pembrolizumab	1	7.7
Atezolizumab	6	46.1
Avelumab	1	7.7
Total	13	100

The comparison between immunotherapy and metastasis of solid cancers was statistically analysed using Chi-square test for independence with the significance level 0.05 which is depicted in Table 4. After applying formula for the test, the Chi-square score was found to be 6.705 with 1 degrees of freedom (DF). The P-value was found to be 0.0096 which was less than the significance level 0.05. This showed the statistically significant association between immunotherapy and metastasis of solid cancers.

Table 4. Chi-square distribution of patients based on immunotherapy drugs and solid cancer metastasis

Immunotherapy types	Metastasis		Total	χ2 value	P-value
	yes	no			
PD-1 Inhibitors	23	6	29		
PD-L1 Inhibitors	4	7	11	6.705	0.0096
Total	27	13	40		

Distribution of patients taking PD-1 inhibitors and PD-L1 inhibitors in various solid cancers are represented in Table 5 and Table 6 respectively. In the study, it was found that, out of 24 nivolumab prescriptions, 7 (29.2%) were oral cancers followed by 4 (16.7%) lung cancers and 3 (12.5%) larynx cancer. Out of 5 pembrolizumab prescriptions, 2 (40%) were renal cancers and one (20%) patient each of larynx cancer, uterine cancer, and anal canal cancers.

Table 5. Distribution of PD-1 Inhibitors in patients of solid cancers

Solid cancer types	Nivolumab		Pembrolizumab	
	n	%	n	%
Oral cancer	7	29.2	0	0
Lung cancer	4	16.7	0	0
Larynx cancer	3	12.5	1	20
Renal cancer	2	8.3	2	40
Cancer of Unknown origin	2	8.3	0	0
Leiomyosarcoma	2	8.3	0	0
Peritoneal mesothelioma	1	4.2	0	0
Stomach cancer	1	4.2	0	0
Uterine cancer	1	4.2	1	20
Heel cancer	1	4.2	0	0
Anal canal cancer	0	0	1	20
Total	24	100	5	100

Table 6. Distribution of PD-L1 Inhibitors in patients of solid cancers

Solid cancer types	Atezolizumab		Avelumab	
	n	%	n	%
Liver cancer	5	50	0	0
Colon cancer	1	10	0	0
Lung cancer	4	40	0	0
Renal cancer	0	0	1	100
Total	10	100	1	100

4. Discussion

Out of 40 patients in our study, 30% were in the 56–65 age group and 27.5% were in the 46–55 age group. These results were similar to a systemic review and meta-analysis conducted by **Conforti F *et al.,* (May 2018)** using 20 different RCTs from 2010–2018, which revealed that patients receiving immunotherapy had a median age range of 56–66 years. [27]

Our study depicted that the majority of patients who received immunotherapy were males (75%), compared to females (25%), which was similar to the retrospective study conducted by **Gunturu KS *et al.,* (January 2022).** This immunotherapy utilisation study showed the majority of patients were male (58%). [28]

From our study, it was revealed that, among patients undergoing immunotherapy, lung cancer (20%) was the most prevalent type. This finding lined up with a study by **Alanazi MQ *et al.,* (April 2020)** that found 27.8% of patients had lung cancer. [29]. In contrast to the retrospective study by **Wahli MN *et al.,* (2023)**, which indicated that lung cancer was the most common cancer in both genders, the majority of men in our current study had lung cancer and the majority of women had oral cancer. [30]

Metastasis was present in 67.5% of solid cancer patients in our study. This result was in line with the study done by **Wahli MN *et al.,* (2023),** in which 65.4% of patients had metastasis. [30] Contrary to the results we got, the retrospective study carried out by **Raphael J *et al.,* (May 2022)** showed 39.3% metastasis. [20]

In our study, PD-1 inhibitors were used more frequently than PD-L1 Inhibitors. Nivolumab was the most often used PD-1 inhibitor, and atezolizumab was the most often used PD-L1 inhibitor. These findings were similar to two distinct worldwide retrospective studies. The first was a study conducted in Canada by **Raphael J *et al.* (May 2022)**, which showed that 78% of cancer patients used PD-1 inhibitors. [20] Another study was done by **Wahll MN *et al.,* (August 2022)** in Switzerland, which showed 79% use of PD-1 inhibitors out of 798 cancer patients taking ICIs. According to both studies, nivolumab was the main PD-1 inhibitor, and atezolizumab was the main PD-L1 inhibitor. [30]

The results of our study indicated that nivolumab was most frequently used in oral cancers (29.2%), pembrolizumab in renal cancers (40%), and atezolizumab in liver cancers (50%). These found conflict with the research that **Kaushik MR *et al.,* (September 2023)** conducted. Their study found that 23%, 40%, and 60% of patients received nivolumab, pembrolizumab, or atezolizumab primarily for the treatment of lung cancer, respectively. [31]

In this study, of the 40 patients, 12 (30%) received immunotherapy drugs alone, and 28 (70%) received combination therapies including targeted agents and/or chemotherapeutic agents. This finding agreed with that of the study by **Sun M *et al.,* (2022)** which found that 11% of patients received immunotherapy alone and 89% received immunotherapy in combination with chemotherapy and/or targeted therapy. [32]

Within the 40 patients in our study with solid cancer, PD-1 inhibitors were primarily used for metastatic cancers (n = 23, 85.2%) and PD-L1 inhibitors for non-metastatic cancers (n = 7, 53.8%). Using statistical tests to compare immunotherapy and solid cancer metastases, it was found that there was a significant association between the two.

In this study, in accordance with international professional guidelines, the immunotherapy drugs nivolumab, pembrolizumab, atezolizumab, and avelumab were used. Nivolumab was prescribed in the current study at various doses, including 20, 40, 200, and 240 mg. The following immunotherapy medications were prescribed in fixed dosages: 200 mg of pembrolizumab, 1200 mg of atezolizumab, and

200 mg of avelumab. The intravenous route was used to administer all immunotherapy agents once every three weeks.

The patients with metastatic cancer received 6 of the 12 monotherapies, while patients without metastatic cancer received 6 of the 28 combination therapies containing chemotherapeutic agents and/or targeted agents; 21 of the combination therapies were administered to patients with metastatic cancer, and 7 to patients without metastatic cancer.

In order to treat solid cancers, chemotherapy was administered to 16 patients (40%) and targeted therapy was administered to 15 patients (37.5%) along with immunotherapy. Treatment of solid cancers involved the use of immunotherapy medications in several combinations of various chemotherapeutic and targeted agents. Carboplatin was the most often used chemotherapy drug in 11 (27.5%) of the patients, while paclitaxel was used in 10 (25%) of them. In 6 (15%) and 5 (12.5%) of the patients, bevacizumab and erlotinib were the two main targeted medications used. Atezolizumab+bevacizumab was the most commonly prescribed combination, with 4 patients receiving it, and 3 patients receiving nivolumab+methotrexate+endoxan+erlotinib.

5. Conclusion

In the study, all the immunotherapy drugs were used in accordance with international professional guidelines and the study offers practical insights into the use of immunotherapy for Indian patients with various solid cancers. In this study, it was concluded that nivolumab was the drug of choice for most of the patients with solid cancers followed by other immunotherapy drugs. It also showed the significant association between metastasis of cancer and immunotherapy use in the solid cancer treatment. The findings agree with experiences across the world and may be helpful in similar clinical settings where immunotherapy drugs are used.

6. Acknowledgement

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