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RESEARCH PAPER

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# Changes in thyroid function in prostate cancer patients receiving docetaxel chemotherapy at Haji Adam Malik Hospital, Indonesia

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## ABSTRACT

**Background:** Prostate cancer treatment is determined based on several factors, namely tumor grading, staging, co-morbidity, patient preferences, life expectancy at diagnosis. Today, taxanes are commonly prescribed to treat several types of cancer and have been shown to have antitumor effects in many cancers. This research has never been done in prostate cancer patients but similar studies have been done before in breast cancer patients.

**Materials and methods:** The research design was observational analytic where this type of research was a prospective cohort where data was collected to record prostate cancer patients who received docetaxel chemotherapy which were then examined for thyroid function in cancer patients at the Adam Malik Hospital, Medan, Indonesia.

**Result:** In this study, data were collected regarding the thyroid function of the study sample in the form of free thyroxine (fT4) and thyroid-stimulating hormone (TSH) levels before chemotherapy with the docetaxel regimen. The mean of fT4 in all research subjects was 1.05 with a standard deviation of 0.26. The mean TSH in all study subjects was 1.52 with a standard deviation of 1.21. Thyroid function was examined after 3 cycles of docetaxel chemotherapy. The mean of fT4 in all research subjects was 0.91 with a standard deviation of 0.23. The mean TSH in all study subjects was 1.69 with a standard deviation of 1.09.

**Conclusion:** There are traces of the use of docetaxel chemotherapy in prostate cancer patients on decreased thyroid function at the Adam Malik Hospital in the form of decreased fT4 levels and increased TSH.

**Key word:** docetaxel; prostate cancer; thyroid function

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## Introduction

Prostate cancer is the most common malignancy and leading cause of death in men in Western countries, causing 94,000 deaths in Europe in 2008 and more than 28,000 deaths in the United States in 2012. Data in the United States shows that more than 90% of prostate cancer is found at an early stage and regional, with a 5-year survival rate close to 100%. This figure is much better compared to 25 years ago which only reached 69%. The main key to the success of cancer treatment is the discovery of cancer at an early stage. But unfortunately, in Indonesia, most patients are already in an advanced stage when they come for treatment. According to data from the 2011 Indonesian Society of Urologic Oncology (ISUO) during the 2006–2010 period, there were 971 prostate cancer patients in Indonesia, with most of them being stage 4 (50.5%) [1, 2].

Prostate cancer treatment is determined based on several factors, namely tumor grading, staging, co-morbidity, patient preferences, life expectancy at diagnosis. Determination of prostate cancer treatment should be done through a multidisciplinary team discussion and after discussing with the patient in considering the benefits and side effects that can occur with each treatment [1].

There have been only a few cancer treatment options for patients for decades which include surgery, radiation, and chemotherapy as a single treatment or in combination [3, 4]. Recently, however, many of the pathways involved in the development of cancer therapy and targeted therapy have been enhanced dramatically, with combinatorial strategies, involving several targeted therapies or "traditional" chemotherapy, such as taxanes and platinum, which were found to have synergistic effects [5]. Chemotherapy is considered the most effective and widely used modality in treating cancer, either alone or in combination with radiotherapy [6].

Chemotherapy is a well-known and effective treatment for many types of cancer, but chemotherapy has not been as efficient at eradicating all cancer cells as one might hope. The mechanism of this failure has not yet been fully clarified. Chemotherapy drugs can activate several signaling pathways and increase the secretion of inflammatory mediators. Inflammation can serve two opposing roles in the microtumor environment. On the one hand, inflammation, as an innate immune response tries to suppress tumor growth but on the other hand, it is not strong enough to eradicate cancer cells and can even provide suitable conditions for cancer growth and recurrence. Therefore, administration of mild anti-inflammatory drugs during chemotherapy may result in more successful clinical outcomes [7].

Taxanes, a class of chemotherapy drugs including paclitaxel and docetaxel, have been widely used in various systemic chemotherapy regimens for advanced gastric cancer. This was initially shown to have an effect on microtubule proteins that interfere with cell division and proliferation. After being isolated from the needle leaves of European Taxus baccata, docetaxel is characterized by a tricyclic taxane framework and antineoplastic activity similar to that of paclitaxel. Today, taxanes are commonly prescribed to treat several types of cancer and have been shown to have antitumor effects in lung cancer, gastric cancer, breast cancer, and ovarian cancer. Additionally, taxane has been consistently used in combination with other systemic chemotherapeutic agents including 5-fluorouracil, cisplatin, bevacizumab, and S-1 [8].

Treatment of cancer with chemotherapy and radiation can damage healthy tissue and cause secondary tumors. Thyroid tissue is very sensitive to radiation. External beam radiotherapy to the neck area can cause thyroid dysfunction, reducing tumor size and thyroid gland, and increase the risk of thyroid nodules and thyroid cancer. Several studies have described how radiation and chemotherapy for the treatment of malignancies located outside the head and neck area affect the size and function of the thyroid gland [9].

This research has never been done in prostate cancer patients but similar studies have been done before in breast cancer patients. Groot et al. study in 2015 showed a decrease in free thyroxine (fT4) levels and an increase in thyroid-stimulation hormone (TSH) levels with a significance $p < 0.05$. The decreased fT4 concentration and increased TSH concentration during chemotherapy observed in our study may reflect chemotherapy-induced thyroid gland damage. Alternatively, the observed increase in TSH could also be explained in the context of recovery from "non-thy-

roidal disease" (NTI), an adaptive response to (chemotherapy-induced) cell damage. In critically ill patients, the hypothalamic–pituitary–thyroid axis decreases as an adaptation to adverse physical conditions [10].

Because this has never been done before, the researchers are interested in conducting a study to determine changes in thyroid function after docetaxel administration in patients with prostate cancer.

## Materials and methods

The research design was observational analytic, prospective cohort study where data was collected to record prostate cancer patients who received docetaxel chemotherapy and were then examined for thyroid function at Adam Malik Hospital, Medan, Indonesia.

The population in this study were patients diagnosed with prostate cancer who received docetaxel chemotherapy. The patients who made up the sample in this study were diagnosed with prostate cancer, received docetaxel chemotherapy from August 2022 to January 2023 and were treated at the Adam Malik Hajj Center General Hospital in Medan. The research sample was taken using the consecutive sampling method where the determination of the sample was carried out with certain considerations, namely inclusion and exclusion criteria.

## Results

### Characteristics of the research sample

This study was conducted on 24 patients diagnosed with prostate cancer who received docetaxel chemotherapy for 3 cycles from December 2021 to December 2022. The mean age of the patients was 62.7 years with a standard deviation of 8.51 years. The median age of the patients was 60 years with the youngest being 50 years and the oldest being 78 years. In this study, data were collected regarding the thyroid function of the study sample in the form of fT4 and TSH levels before chemotherapy with the docetaxel regimen. The mean of fT4 in all research subjects was 1.05 with a standard deviation of 0.26. The mean TSH in all study subjects was 1.52 with a standard deviation of 1.21. In this study, data were collected regarding the thyroid function of the study sample in the form of fT4 and TSH levels after docetaxel chemotherapy for 3 cycles. The mean of fT4 in all research subjects was 0.91 with a standard deviation of 0.23. The mean TSH in all study subjects was 1.69 with a standard deviation of 1.09. This is shown in Table 1.

**Table 1.** Characteristics of the research sample

| Parameter | Value |
|---|---|
| **Usia** | |
| Mean ± SD | 62.7 ± 8.51 |
| Median (Min–Max) | 60 (50–78) |
| **Parameter before chemotherapy** | |
| **fT4** | |
| Mean ± SD | 1.05 ± 0.26 |
| **TSH*** | |
| Mean ± SD* | 1.52 ± 1.21 |
| Median (Min–Max)* | 1.14 (0.03–4.33) |
| **Parameters after chemotherapy** | |
| **fT4** | |
| Mean ± SD | 0.91 ± 0.23 |
| **TSH*** | |
| Mean ± SD* | 1.69 ± 1.09 |
| Median (Min–Max)* | 1.65 (0.01 – 3.6) |

SD — standard deviation; fT4 — free thyroxine; TSH — thyroid-stimulating hormone

### Comparison of thyroid function pre and post chemotherapy

After all the data was obtained, an analysis was carried out to compare thyroid function before and after chemotherapy with the docetaxel regimen. Because the sample was < 50, the Shapiro Wilk test was carried out to test the normality of the data. The results showed that the fT4 parameters before and after chemotherapy and the TSH parameters after chemotherapy to be tested were normally distributed with $p > 0.05$. TSH parameters before chemotherapy were found to be abnormally distributed. Then a paired t-test was chosen to determine the difference between the two pre- and post-intervention groups. The results showed that there was a significant difference between fT4 levels before and after chemotherapy with a p value of 0.001. There also appears to be a significant difference between TSH levels before and after chemotherapy with a p value of 0.001. From the visualization of graph 4.1 and the calculations, it was found that fT4 levels decreased by 13.3% while TSH levels increased by 10.05%. This can be seen in Table 2 and Figure 1.

**Table 2.** Comparison of thyroid function pre and post chemotherapy

| | Pre-chemotherapy | Post-chemotherapy | p-value |
|---|---|---|---|
| Mean fT4 | 1.05 ± 0.26 | 0.91 ± 0.23 | 0.001[a] |
| Mean TSH | 1.52 ± 1.2 | 1.69 ± 1.09 | 0.001[a] |

[a]paired t-test; fT4 — free thyroxine; TSH — thyroid-stimulating hormone

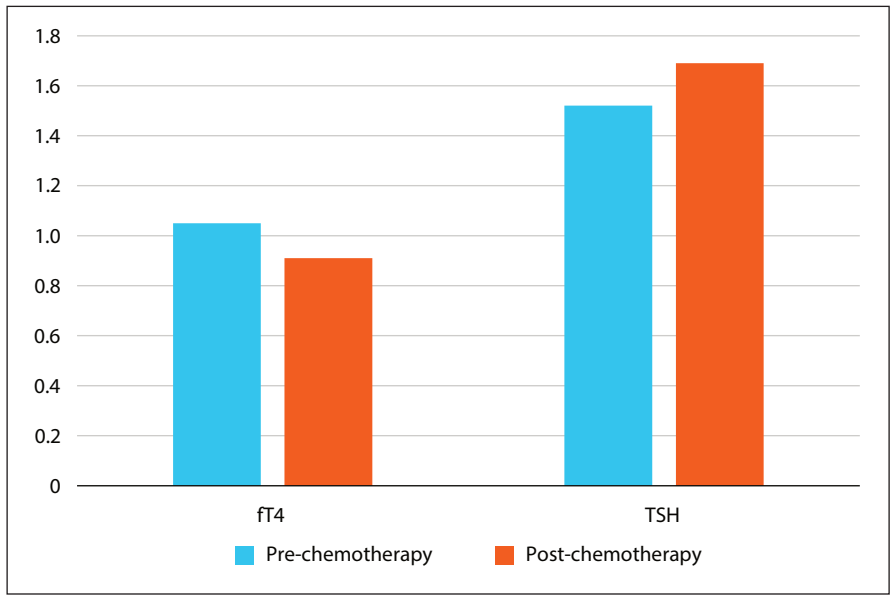


**Figure 1.** Comparison of thyroid function pre and post chemotherapy. fT4 — free thyroxine; TSH — thyroid-stimulating hormone

## Discussion

This study was conducted on 24 patients diagnosed with prostate cancer who received docetaxel chemotherapy during the study period. This research was conducted at the Adam Malik Hajj Center General Hospital in Medan with the approval of the USU FK Research Ethics Commission. Research and data collection were carried out from August 2022 to January 2023, followed by processing and analysis of the data that had been collected. The patients in this study were diagnosed with prostate cancer, received docetaxel chemotherapy from August 2022 to January 2023 and were treated at the Adam Malik Hajj Center General Hospital in Medan.

The mean age of the patients was 62.7 years with a standard deviation of 8.51 years. The median value of the patients' age was 60 years with the youngest being 50 years and the oldest being 78 years. These results are in accordance with the study of Godtman et al where it was found that the median of prostate cancer patients at the University of Gothenburg was 65 years.[11] There has been an increase in the incidence of prostate cancer since prostate cancer screening with the introduction of prostate-specific serum antigen (PSA) [12].

In this study, data were collected regarding the thyroid function of the study subjects in the form of fT4 and TSH levels before chemotherapy with the docetaxel regimen. The mean of fT4 in all research subjects was 1.05 with a standard deviation of 0.26. The mean TSH in all study subjects was 1.52 with a standard deviation of 1.21. These results are consistent with the study of Lee et al. at the Seoul National Police Hospital. Their research results found that the fT4 level of the study sample was 1.05 with a standard deviation of 0.14 and the study TSH was 1.44. The median analysis found a figure of 1.97 which indicates that this result is consistent with Lee's research [13].

In this study, thyroid function was examined after 3 cycles of docetaxel chemotherapy. This is something new and has never been studied before.

The mean of fT4 in all research subjects was 0.91 with a standard deviation of 0.23. The mean TSH in all study subjects was 1.69 with a standard deviation of 1.09. Although it has not been studied in prostate cancer, similar studies on the use of docetaxel in breast cancer can be used as a comparison. In Groot's 2015 study of breast cancer patients, it was found that the fT4 level was 1.06 ug/dL after being converted from pmol/L. TSH level was 1.47 ug/dL [10].

In this study, a paired t-test was conducted to assess whether there was a difference between thyroid levels before and after docetaxel chemotherapy. The results showed that there was a significant difference between fT4 levels before and after chemotherapy with a p value of 0.001. There also appears to be a significant difference between TSH levels before and after chemotherapy with a p value of 0.001. This is consistent with a study by Groot et al. in 2015 which showed a decrease in fT4 levels and an increase in TSH levels with a significance $p < 0.05$. However, it should be underlined that Groot's research was conducted on breast cancer and no studies have examined this effect on prostate cancer [10].

The decreased fT4 concentration and increased TSH concentration during chemotherapy observed in our study may reflect chemotherapy-induced thyroid gland damage. Alternatively, the observed increase in TSH could also be explained in the context of recovery from "non-thyroidal disease" (NTI), an adaptive response to (chemotherapy-induced) cell damage. In critically ill patients, the hypothalamic–pituitary–thyroid axis decreases as an adaptation to adverse physical conditions [10].

In the study conducted by Rivas in 2020, a total of 318 patients were reviewed, and 281 patients were excluded from the study after initial screening. Most patients received alkylating agents (n 33, 89%), about half received docetaxel (n 19, 51%), and nearly half received a topoisomerase II inhibitor (n = 16, 43%). The most common treatment combinations are alkylating agents and taxanes, and alkylating agents and topoisomerase II inhibitors, with or without radiation. Of the 37 patients, 29 had a clinical appointment record 3 months after the second CT scan; Death at 3 months or loss-to-follow up occurred in 13 patients (45%). After treatment, there was a statistically significant reduction in thyroid gland size by all measurements. Rivas' results demonstrated that in patients treated with external radiotherapy and/or chemotherapy for malignancies located outside the head and neck area, and living in West Texas, thyroid gland volume decreased by 14% to 17% at 6 months. Decreased thyroid gland volume after cancer treatment has been associated with the development of hypothyroidism. Additionally, studies have suggested that the development of thyroid dysfunction may be a marker of an increased likelihood of response to therapy. In addition, decreased thyroid hormone can cause proliferative arrest of G0–G1 in cancer cells, with a possible influence on their sensitivity to chemotherapeutic agents [9].

Retrospective study by Kiyomatsu et al. in 2022 studied thyroid function in 61 patients undergoing conventional chemotherapy for breast cancer. Of the 61 patients, 17 (28%) had thyroid dysfunction, including subclinical hypothyroidism and hypothyroidism after chemotherapy, and 9 (15%) had clinical hypothyroidism. Eight of the nine patients required thyroid hormone replacement therapy with levothyroxine (L-T4). Taxane-based regimens tended to reduce free T4 levels and increase TSH levels more markedly than non-taxane-based regimens. This study suggests that conventional chemotherapy may cause hypothyroidism and may require evaluation of thyroid function during chemotherapy. Thyroid hormone replacement therapy should be considered if the patient shows clinical features of hypothyroidism [14].

The important role of docetaxel in cancer management must nevertheless be emphasized. Study by Balcazar in 2020 revealed that the initiation of treatment within the first 45 days of diagnosis of breast cancer in women portends better survival compared with those who began treatment longer than 45 days from diagnosis [15]. Thus, mayhaps follow up would be a much more appropriate solution in handling this problem as specified by Zaluska-Kusz in which they concluded that there is a need to educate both physicians and patients on the principles of follow up check-ups [16]. This result was also reflected in study regarding prostate cancer similar to ours in which in several cases, docetaxel administration remained imperative [17].

## Study limitation

The limitation of this study is that it is a single-center study, which makes the sample size not so large. Even though the sample size is statistically appropriate, multi-center research will be able to help better capture the phenomena that occur. This study also did not look at the symptoms and side effects that might arise due to hypothyroidism. In fact, regardless of the cause of the chemotherapy-related decrease in fT4 observed in the Groot and Hamnvik study a large reduction in fT4 concentrations over 6 cycles of docetaxel was associated with fewer (cumulative) side effects in terms of neuropathy, vomiting, and nausea of CTC grade II or higher. This is thought to be due to lower fT4 levels during chemotherapy, which is an adaptive response, protecting the body from tissue damage by regulating cell metabolism. The weakness of this study is that thyroid function tests were not carried out after 6 cycles of docetaxel, which can only be declared complete. However, considering that the effect has been seen in 3 cycles, it is likely that this effect will also be seen in 6 cycles [10, 18].

## Conclusion

This study was conducted on 24 patients diagnosed with prostate cancer who received docetaxel chemotherapy during the study period with an average age of 62.7 years with a standard deviation of 8.51 years. In this study, data were collected regarding the thyroid function of the study sample in the form of fT4 and TSH levels before chemotherapy with the docetaxel regimen. The mean of fT4 in all research subjects was 1.05 with a standard deviation of 0.26. The mean TSH in all study subjects was 1.52 with a standard deviation of 1.21.

Thyroid function was examined after 3 cycles of docetaxel chemotherapy. This is something new and has never been studied before. The mean of fT4 in all research subjects was 0.91 with a standard deviation of 0.23. The mean TSH in all study subjects was 1.69 with a standard deviation of 1.09.

There are traces of the use of docetaxel chemotherapy in prostate cancer patients on decreased thyroid function at the Adam Malik Hospital in the form of decreased fT4 levels and increased TSH levels.

### Conflict of interest

The author declare no conflict of interest.

### Funding

None declared.

### Authors contribution

Al Firman, Syah Mirsya Warli, Bungaran Sihombing and Aznan Lelo was acknowledged for conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published.

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