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Comparison of Chemotherapy Effectiveness Between Cancer Patients with and without Dependent Dose of Radiotherapy

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ABSTRACT

Aims Cancer is now known to be one of the most important health issues people face. So, we looked into what makes cancer grow. This research aimed to compare the effect of chemotherapy in the presence and absence of radiotherapy in cancer patients.

Materials & Methods In this experimental study, which took place at Al-Hussein Teaching Hospital in Kerbala from October 2023 to February 2024, 94 cancer patients between 30 and 50 years old were divided into two radiotherapy (n=48) and non-radiotherapy (n=46) groups according to the expert's opinion. An enzyme-linked immunosorbent assay was used to identify serum tumor markers. Spectrophotometric analysis was used to detect calcium and phosphorus levels in the sera. The data were evaluated using the student's t-test in SPSS 26 software.

Findings There were significant differences in CA15-3, AFP, and CA19-9, calcitonin, carcinoembryonic antigen, calcium, and phosphorus levels between the chemotherapy and non-chemotherapy groups.

Conclusion Using chemotherapy alone is not enough to treat cancer, and it makes the cancer spread when used without radiation treatment. To save the bone, chemotherapy must be used with dose-dependent radiation.

Keywords Chemotherapy; Radiotherapy; Tumor Markers

CITATION LINKS

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Introduction

Chemical materials known as carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), carbohydrate antigen 15-3 (CA15-3), and alpha-fetoprotein (AFP) have been found on the surfaces of some cells [1]. Throughout the embryo's development, gastrointestinal tract cells release a glycoprotein called CEA [2]. Very little CEA is secreted after delivery. CA15-3, CA19-9, CEA, and AFP levels in the blood are comparatively lower unless certain conditions, such as cancer with obvious symptoms, are present [3]. The majority of these tumor markers were tested in blood. Additionally, biopsy tissues and bodily fluids can diagnose cancer [4]. As tumor markers, CA15-3, CA19-9, CEA, and AFP were preferred, especially for gastrointestinal tract cancers [5].

It was possible to get rid of all the cancer after the surgery [2]. The CA15-3, CA19-9, CEA, and AFP levels were seriously messed up before malignant organ resection or other treatment could restore normalcy. Levels of AFP, CA19-9, CEA, and CA15-3 were extremely important for reported cancer development or recurrences. These need to be guaranteed because the tumor marker exam was insufficiently specific to demonstrate a cancer recurrence on its own [6]. Assessing the concentration of specific tumor markers in serum is crucial for various clinical purposes, including screening, diagnosing, managing therapy, and monitoring the progression of advanced diseases, particularly in gastrointestinal cancers [7-8]. For example, in colorectal cancer, the presence of CEA holds significant prognostic value, with elevated CEA levels often correlating with worse outcomes before surgery [9]. Additionally, CEA plays a key role in diagnosing and monitoring postoperative patients, helping to detect any disease recurrence early [10].

Furthermore, before therapy, levels greater than 20ng/ml can be associated with metastatic illness or cancer that has already spread [11]. Patients with benign (harmless) and malignant (cancerous) tumor indicators were able to increase their levels together. However, CEA is not suitable for screening due to its limited sensitivity during the early stages of cancer and its relatively low occurrence in asymptomatic individuals. While CEA is a vital marker for colorectal cancer, it can also be raised in non-cancerous conditions [12]. In general, recurrent cancers such as colon and rectal cancer raise the tumor marker [13]. Malignancies of the pancreas, breast, lung, stomach, and ovaries, and thyroid and ovarian cancers. Smoking, infections, inflammatory bowel disorders, liver cirrhosis, pancreatitis, and other benign tumors in the same organs that increase CEA imply cancer are among the conditions that might cause benign tumor patients to have elevated CEA levels [14].

In liver cancer, alpha-fetoprotein (AFP) serves as an effective screening tool, particularly for those at high risk of developing hepatocellular carcinoma, and is also useful for assessing prognosis, monitoring after surgery, and tracking disease progression. AFP levels may be elevated not only in hepatocellular carcinoma but also in a variety of benign and malignant conditions [15]. In the case of gastric cancer, no specific tumor marker has been recommended for screening or diagnosis [16]. CA19-9 is an established marker in pancreatic cancer and remains the gold standard for post-surgery follow-up. However, its diagnostic utility in detecting pancreatic cancer is still debated [17]. CA19-9 levels tend to rise in both advanced gastrointestinal cancers and benign gastrointestinal disorders. It's important to note that individuals with the Lewis (a-b-) phenotype do not express CA19-9, necessitating alternative tumor markers for these patients [8, 18].

Radiation therapy and chemotherapy have the potential to kill or destroy tumor cells, which release CEA into the blood vessels and cause a preliminary increase in CEA levels [19]. The CEA levels that altered due to cancer treatment typically need to be linked to additional clinical outcomes. Research has shown that temporary fluctuations in CEA levels can occur even when a patient responds positively to treatment. For example, studies have found that variations in CEA levels during chemotherapy are linked to tumor response and overall survival (OS). Patients who experienced a significant decrease in CEA levels early in their treatment tended to have more favorable prognoses than those whose CEA levels remained high or continued to rise [20, 21].

Nonetheless, interpreting rising CEA levels after treatment is a complex issue. Although an increase could signal disease progression, it might also reflect the tumor's biological response to the treatment. Some studies have suggested that temporary increases in CEA levels during adjuvant chemotherapy could be associated with better survival outcomes than consistent elevations, underscoring the importance of careful monitoring and accurate interpretation of these biomarkers [22].

However, it is concerning because the progression of the malignancy was not recognized based on changes in CEA levels [23]. Monitoring CEA levels provides far more than just detection; it is essential for assessing the effectiveness of treatment and helping guide clinical decision-making. For instance, a noticeable rise in CEA levels following the initial stages of treatment can act as an early indicator of possible disease progression. Studies have shown that when CEA levels increase beyond specific thresholds after therapy, it often correlates with unfavorable outcomes, prompting the need for further assessment or additional therapeutic actions [24, 25]. For example, one study revealed that an increase of at least 120% from the lowest observed level (nadir) could effectively predict disease control status after the first round of treatment, helping clinicians avoid

unnecessary imaging procedures in many situations [24, 26].

However, challenges arise in differentiating between disease progression and benign variations that might result from the treatment. Given the individual differences in how patients respond to treatment, it is crucial to interpret CEA levels in conjunction with other diagnostic tools, such as imaging and overall clinical evaluations. Research has demonstrated that there can be discrepancies between CEA levels and the results of imaging studies, which suggests that relying solely on CEA data can lead to misinterpretations of a patient's health status. This emphasizes the importance of a comprehensive, multi-faceted approach when using biomarkers like CEA for monitoring cancer progression and treatment outcomes [22, 25].

It was proven that C cells from the thyroid gland, located frontally inside the human lower neck, made the calcitonin hormone. Calcitonin is attributed to the metabolism of calcium, followed by the breakdown (catabolism) and reconstruction (anabolism) of bone [12]. The blood's calcium content directly influences the release of this calcitonin hormone [6]. As calcium levels rise, the body reacts by producing increased calcitonin levels. Calcitonin levels fall in tandem with a drop in calcium levels [12].

This research aimed to compare the effect of chemotherapy in the presence and absence of radiotherapy in cancer patients.

Materials and Methods

In this experimental study at Al-Hussein Teaching Hospital in Kerbala from October 2023 to February 2024, 94 cancer patients between 30 and 50 years old who suffered from colon cancer (n=47), rectum cancer (n=20), and gastric cancer (n=27) were selected by oncologists by the available sampling method. The patients were divided into two radiotherapy (n=48) and non-radiotherapy (n=46) methods (the researchers had no interference in the selected method), which were selected according to the expert's opinion. Assigned several cancer patients to the oncology unit to get the right care, we discovered that patients in the early stages of the disease were initially given chemotherapy (Zoladex) roughly 10-15 times over nearly two years to lower the cancer level. The chemotherapy drug will be switched to another medication, such as Zometa or Taxotere (docetaxel), if the patient does not respond to the current one. This will stop the cancer from spreading to other tissues, including bone tissue. On the other hand, some patients, especially those with advanced cancer, were given a straight dose of chemotherapy to stop the cancer cells from spreading to nearby tissue and killing it.

Following an overnight period of fasting from food, patients underwent a venipuncture procedure to extract and monitor 5ml of blood in the early morning (it was the routine treatment and nothing more than needed). The samples were spun at 3000 rpm for 15 minutes. The serum was then separated and stored at -20 until it was time to be analyzed.

An enzyme-linked immunosorbent assay (ELISA) (CUSABIO; China) was used to identify serum tumor markers (Human CEA, CA19-9, CA15-3, AFP, and Calcitonin). Spectrophotometric analysis was used to detect calcium and phosphorus levels in the sera using calcium and phosphorus kits (Mannheim; Germany).

The data were evaluated using the student's t-test in SPSS 26 software. P-values of less than 0.05 were regarded as significant.

Findings

There were significant increases in CA15-3, AFP, and CA19-9 in the chemotherapy group compared to the non-chemotherapy group. Calcitonin levels were slightly lower in the chemotherapy group than in the non-chemotherapy group. In contrast, the CEA level was significantly increased in the chemotherapy group compared to the non-chemotherapy group (Table 1).

Table 1. Comparing the levels of parameters in cancer patients with (n=48) and without (n=46) chemotherapy

Parameter	Non-chemotherapy	Chemotherapy	p-Value
CA15-3 (U/ml)	19.27±2.45	100.30±12.96	0.0001
AFP (ng/ml)	3.82±2.55	327.25±68.24	0.0001
CA19-9 (U/ml)	202.71±17.63	339.20±53.66	0.003
Calcitonin (ng/ml)	8.90±0.01	7.52±2.10	0.004
CEA (ng/ml)	2.88±1.18	4.16±1.18	0.004

The calcium (Ca+2) level was significantly higher in the chemotherapy group than in the non-chemotherapy group. The phosphorus (PO_4^{-3}) level was also elevated in the chemotherapy group compared to the non-chemotherapy group (Table 2).

Table 2. Comparing the levels of calcium and phosphorus in cancer patients with (n=48) and without (n=46) chemotherapy

Parameter	Non-chemotherapy	Chemotherapy	p-Value
Ca^{+2} (mg/dl)	4.78±1.28	6.16±1.18	0.0001
PO_4^{-3} (mg/dl)	9.80±1.11	10.52±1.10	0.002

Discussion

The results emphasize the critical role of Carcinoembryonic Antigen (CEA) as a highly valuable tumor marker for both staging and monitoring the efficacy of cancer treatment. Carcinoembryonic antigen (CEA) has long been recognized as one of oncology's most widely used biomarkers, particularly in colorectal and gastric cancers. Previous research by Lee & Oesterling established CEA as an excellent marker for these types of cancer, highlighting its utility for staging and tracking treatment responses and early detection of recurrence. As a glycoprotein expressed in various malignant tissues, CEA's presence and concentration

correlate well with the extent of disease progression. It is an invaluable tool for clinicians to monitor tumor burden and assess how well treatments work [27]. In particular, studies have shown that CEA is effective in assessing treatment outcomes, especially when combined with imaging and clinical evaluations.

In a study comparing individuals with benign gastric tumors to those diagnosed with gastric cancer, CEA demonstrated high sensitivity, specificity, and positive predictive value. These qualities make CEA an indispensable biomarker for distinguishing between benign and malignant gastric lesions. High specificity and sensitivity make CEA a robust diagnostic tool, allowing for more accurate early detection of cancerous growths. Additionally, the positive predictive value of CEA makes it highly reliable for identifying patients who are more likely to develop complications or experience disease recurrence, contributing to better clinical outcomes by guiding early therapeutic intervention [28].

In chemotherapy, the primary objective is to halt the proliferation and spread of cancer cells while monitoring the overall treatment efficacy. The study's findings underscore the dynamic role of tumor markers, such as CEA, in this process. When patients show increased levels of tumor markers while undergoing hormone therapy, it does not necessarily indicate failure; rather, it suggests the need to explore other systemic treatments. These may include a shift to more aggressive therapies like chemotherapy, targeted therapies, or alternative hormonal treatments that aim to prevent the cancer from metastasizing to other tissues [29]. This approach allows clinicians to tailor treatment to the patient's evolving needs, improving long-term survival outcomes.

Concerning chemotherapy-induced changes in tumor markers, the study also found a significant increase in calcium (Ca^{+2}) and phosphorus (PO_4^{-3}) levels in the chemotherapy group. These findings are consistent with the observations made by Thuret *et al*., who conducted a preliminary study on prostate cancer patients. Thuret *et al*. [30] observed an initial increase in serum PSA levels during the first eight weeks of chemotherapy. This phenomenon, often referred to as the PSA surge syndrome, is particularly common in patients receiving both first and second-line chemotherapy, including treatment regimens with docetaxel and other chemotherapeutic agents. The most widely accepted explanation for this transient rise in PSA levels is tumor cell lysis, which releases tumor markers like PSA into the bloodstream, indicating the cytotoxic effects of chemotherapy [30]. A decline typically follows this initial rise in PSA levels as the chemotherapy takes effect, bringing the marker levels in line with clinical stabilization or response as per consensus guidelines.

While transient, this surge in PSA levels holds important implications for interpreting treatment responses. Despite its temporary nature, the PSA surge phenomenon has been associated with prolonged survival in certain patients, although its prognostic significance remains unclear. In contrast to other tumor markers, the rise in PSA in prostate cancer patients can last for up to eight weeks before showing signs of decline. This pattern highlights the importance of careful monitoring of tumor markers, as early increases may not necessarily signal poor prognosis but rather represent a chemotherapy-related effect. In germ-cell tumors, the rise in tumor markers is often short-lived, further supporting the unique dynamics of marker kinetics in different cancer types.

Additionally, Thuret *et al*. [30] demonstrated that tracking the kinetics of tumor markers as early as three weeks after chemotherapy begins provides an independent predictive value for high-risk disease. This finding is crucial for informing clinical decisions, particularly in advanced cancer stages, where the ability to predict response to chemotherapy can guide adjustments in treatment plans. The patterns of tumor marker behavior observed in this study, such as the calcium and phosphorus surges, further underscore the systemic effects chemotherapy has on cancer patients, particularly in cases involving metastasis to bone and other vital tissues. Therefore, the rise in tumor markers following chemotherapy in your study may be understood as part of a broader phenomenon similar to the PSA surge in prostate cancer, reflecting the intense interaction between chemotherapy and the body's metabolic and immune responses. These changes may serve as critical markers for the initial phase of treatment and indicate potential pathways for monitoring long-term survival and treatment efficacy.

In a different trial, Fizazi *et al.* demonstrated that serum tumor markers would rise, which has been previously documented to happen very often to people who are taking consolidation docetaxel following induction chemotherapy and after a response or stabilization [31].

An earlier study by Banfi *et al.* looked at the bone mineral density (BMD) of 26 patients and discovered that high-dose chemotherapy sped up the rate of bone resorption (deoxypyridinoline (DPD), pyridinoline (PYD), calcium phosphate, $PO4^{3-}$, and other bone contents) and a loss of 20% in trabecular bone and 10% in cortical bone. As a mechanism separate from and summable to hypogonadism, this is thought to be because chemotherapy doesn't use dose-dependent radiation, which is harmful to bone marrow stromal osteoprogenitors and can cause osteopenia by killing osteoblasts directly [32].

Zhang *et al.* reported in a recent study that following therapy with zoledronic acid (Zometa) at week 2, the mean level of bone-specific alkaline phosphatase (B-ALP), a measure of bone growth, dropped by 12.9% from baseline. Bone-specific alkaline phosphatase (B-ALP) levels in the blood were higher in people with breast cancer that had spread to the bones, multiple

myeloma, prostate cancer, and lung cancer. The administration of zoledronic acid significantly reduced these levels, and the decline in levels persisted as long as the medication was used [33].

Conclusion

Chemotherapy alone is insufficient to treat cancer. A dependent dose of radiation must be used in conjunction with it to preserve the bone and bone marrow. Calcitonin stops stomach acid from working, which is good for people with stomach cancer.

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