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Influence of Anesthetic Agents and the Perioperative Period on Cancer Recurrence and Metastasis

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Abstract

Cancer remains a leading cause of death worldwide, with its burden expected to increase, particularly in aging populations. The perioperative period and anesthetic techniques used during cancer surgeries are increasingly recognized as factors that may influence cancer recurrence and metastasis. This study investigates the impact of anesthetic agents and perioperative management on cancer outcomes in Iraqi patients. This study involved 68 Iraqi patients (42 males and 26 females) with various types of cancer, including prostate, colorectal, bladder, lung, cervical, breast, and ovarian cancers. The patients underwent surgery under general anesthesia, with follow-up assessments focusing on cancer recurrence, metastasis, and mortality rates. Serum levels of Cancer Antigen 15-3 (CA15-3) were measured using the VIDAS® immunoassay technique. Data were statistically analyzed using SPSS version 24, with results expressed as mean, standard deviation, and p-values. The study found a higher mortality rate in male patients (54%) compared to females (46%), with survival rates significantly higher in females. Cancer recurrence was observed in 46% of males and 43% of females. Serum levels of CA15-3 were significantly elevated in both male (77.97±2.44 kU/l) and female (96.33±3.66 kU/l) patients, indicating its potential as a diagnostic marker for cancer recurrence and metastasis. The results suggest that anesthetic agents, through their direct and indirect effects on tumor cells and the immune system, may influence cancer progression and patient outcomes. This study highlights the importance of considering anesthetic techniques and perioperative management in cancer surgeries to minimize the risk of recurrence and metastasis. The findings suggest that elevated CA15-3 levels could serve as a valuable biomarker for monitoring cancer recurrence. Further research is needed to explore the mechanisms by which anesthetic agents and perioperative factors contribute to cancer outcomes, potentially leading to improved perioperative protocols for cancer patients.

Introduction

Cancer is one of the leading causes of death worldwide, and its prevalence is expected to increase, particularly in aging populations with more comorbidities [1]. The failure to prevent or effectively treat metastatic disease is

responsible for up to 90% of cancer-related deaths [2]. The genetic and phenotypic changes within a single tumor throughout the disease course can explain why metastatic disease often escapes therapies aimed at the primary tumor [3]. Consequently, preventing the progression of metastatic disease has become increasingly critical [4]. Metastasis is frequently associated with an increased resistance to apoptosis, a form of programmed cell death that is crucial in eliminating damaged or dangerous cells [5]. Apoptosis is mediated by the activation of a family of cysteine proteases called caspases, which can be divided into upstream initiator caspases and downstream effector caspases [6]. The activation of these caspases is a key step in apoptosis, and two main pathways have been described: the extrinsic pathway, also known as the death receptor pathway, and the intrinsic or mitochondrial-mediated pathway [7].

The perioperative period, including surgery and the administration of anesthetic agents, introduces numerous factors that can influence cancer outcomes. Surgical stress activates neural and inflammatory pathways, which have been implicated in immune dysfunction and cancer progression [8]. Additionally, the choice of anesthetic technique (e.g., general vs. neuraxial anesthesia) and the use of pharmacological adjuncts (e.g., opioids, beta-blockers, NSAIDs) during surgery may impact cancer recurrence and metastasis [9,10].

Current clinical practice guidelines do not fully account for the potential impact of anesthetic techniques and perioperative management on cancer outcomes, largely due to a lack of comprehensive data [11]. This study aims to elucidate the biological mechanisms underlying cancer recurrence and metastasis in different types of cancer, focusing on the clinical data of Iraqi patients during the perioperative period. By measuring the levels of Cancer Antigen 15-3 (CA15-3) in recurrent cases, and analyzing histopathological and endoscopic data, this research seeks to contribute to a better understanding of the factors influencing cancer progression in the perioperative setting.

Subjects Materials and Methods

Subjects

This study involved 68 Iraqi patients (42 males and 26 females) diagnosed with various types of cancer, including prostate, colorectal, bladder, lung, cervical, breast, and ovarian cancers. The patients were selected from the Oncology Department at Baghdad Teaching Hospital, Iraq, under the supervision of the consultant oncologist. The ages of the male patients ranged from 35 to 68 years, while the female patients were aged between 33 and 63 years. The male patients were divided into subgroups: 21 with prostate cancer, 12 with colorectal cancer, 6 with bladder cancer, and 3 with lung cancer. The female patients were also categorized into subgroups: 12 with cervical cancer, 10 with breast cancer, and 4 with ovarian cancer.

Materials

Serum levels of Cancer Antigen 15-3 (CA15-3) were measured using the VIDAS® immunoassay system from bioMérieux, France. This system utilizes a two-step immunoassay sandwich method to quantify the concentration of CA15-3 in the serum samples. Endoscopic surveillance was performed to detect intraluminal recurrence,

metachronous tumoral lesions, precancerous gastric stump diseases, and anastomotic strictures in the patients.

Methods

Sample Collection

Blood samples (5 ml) were collected intravenously from all subjects in gel tubes at the Oncology Department, Baghdad Teaching Hospital. The blood was centrifuged to separate the serum, which was then stored at -20°C for subsequent analysis of serological parameters. Histopathological data were obtained from tissue samples to confirm cancer progression and recurrence.

Measuring Serum Levels of CA15-3

The CA15-3 levels in the serum were measured using the VIDAS® immunoassay system. The assay involves a solid-phase receptacle (SPR) coated with an anti-CA15-3 monoclonal antibody. Serum samples, along with calibrators and controls, were incubated in the SPR to capture CA15-3. Unbound components were washed away, and a polyclonal anti-CA15-3 antibody labeled with alkaline phosphatase was added. The enzyme catalyzed a reaction producing a fluorescent product, which was measured at 450 nm by the VIDAS analyzer. The fluorescence intensity, proportional to the concentration of CA15-3, was converted to a concentration using a standard curve generated from known CA15-3 concentrations.

Histopathological Data

Tissue samples were analyzed to confirm the size, stage, and recurrence of cancer. The histopathological findings were used to support the serological data obtained from the CA15-3 measurements.

Endoscopic Observations

Endoscopic examinations were conducted by specialists to detect and confirm multiple sites of recurrent cancer, particularly in patients with advanced or metastatic gastric, lung, and prostate carcinomas.

Statistical Analysis

The collected data were analyzed using SPSS version 24. Results were expressed as mean, standard deviation, and standard error. Differences between means were assessed using an independent samples T-test. A p-value of 0.05 or less was considered statistically significant.

Results

Patient Demographics and Cancer Types

A total of 68 Iraqi patients were included in this study, comprising 42 males and 26 females. Among the male

patients, the most common cancer type was prostate cancer (50%), followed by colorectal cancer (28.6%), bladder cancer (14.3%), and lung cancer (7%). In female patients, cervical cancer was most prevalent (46%), followed by breast cancer (38.5%) and ovarian cancer (15.4%). The gender distribution and types of cancer are illustrated in Figures 1 and 2.

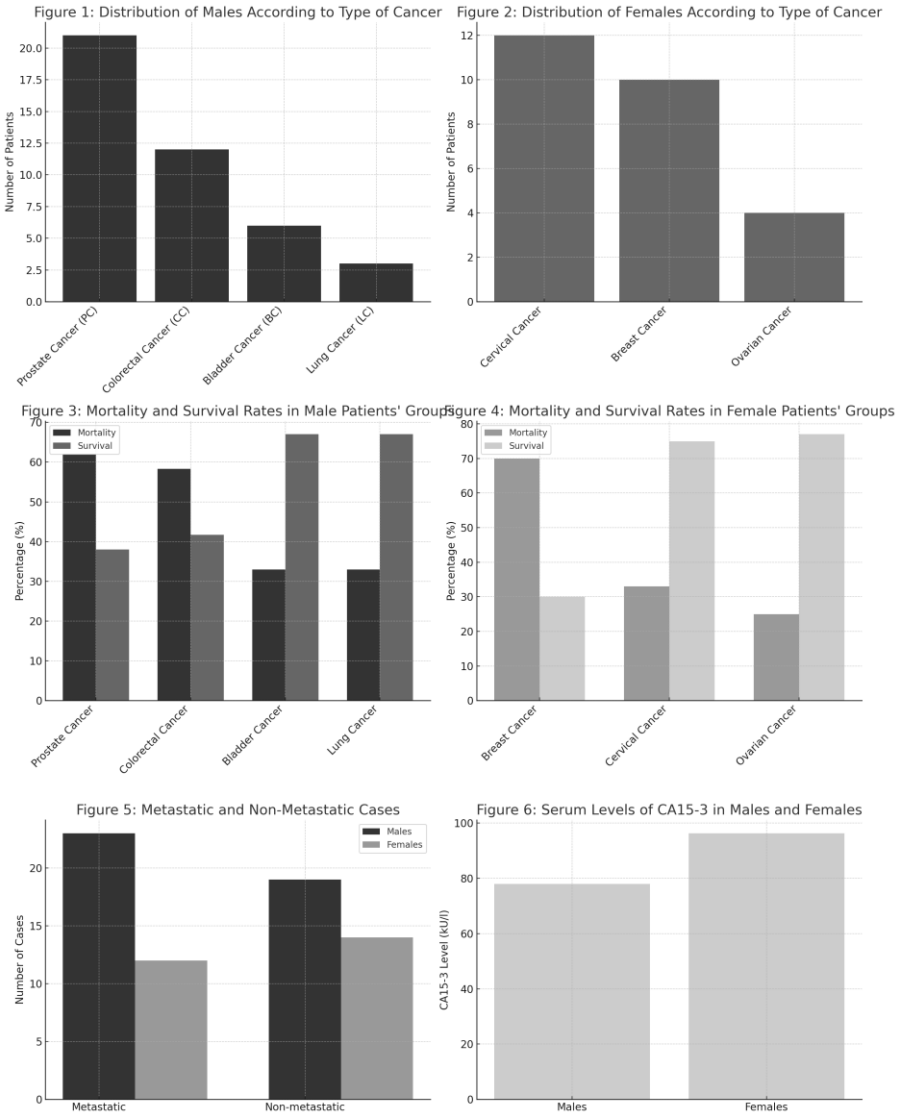

Figure1-6: Analysis of Cancer Type Distribution, Mortality and Survival Rates, Metastasis, and CA15-3 Serum Levels in Iraqi Cancer Patients

Mortality and Survival Rates After the Perioperative Period and Chemotherapy

The study revealed significant differences in mortality and survival rates between the different cancer types and genders. In male patients, prostate cancer and colorectal cancer had higher mortality rates (62% and 58.3%, respectively) compared to bladder and lung cancers (33% each). The survival rates for prostate and colorectal cancers were 38% and 41.7%, respectively, while bladder and lung cancers showed higher survival rates of 67%

each (Figure 3). In female patients, breast cancer had a notably higher mortality rate (70%) compared to cervical and ovarian cancers (33% and 25%, respectively). Conversely, the survival rates were significantly higher in cervical and ovarian cancers (75% and 77%) compared to breast cancer (30%) (Figure 4).

Cancer Recurrence After the Perioperative Period

Follow-up data indicated that cancer recurrence was more common in male patients (54%) than in female patients (46%). The most frequent recurrence in males was observed in colorectal and prostate cancer patients (47%), while in females, breast and ovarian cancers had the highest recurrence rates (43%). Non-metastatic cases were observed in 53% of males and 57% of females (Figure 5). The study also recorded higher overall mortality rates in males (54%) compared to females (46%) ($p=0.001$). However, females had a significantly higher survival rate (54%) compared to males (46%). Recurrence rates were slightly higher in males (46%) than in females (43%) ($p=0.004$).

Immunoassay of Serum CA15-3 Levels

The serum levels of CA15-3 were significantly elevated in both male and female patients with cancer recurrence. The mean serum CA15-3 levels were 77.97±2.44 kU/l in males and 96.33±3.66 kU/l in females, with females showing significantly higher levels than males ($p<0.05$) (Figure 6).Elevated CA15-3 levels were particularly notable in patients with advanced adenocarcinomas, including breast, ovarian, pancreatic, gastric, and lung cancers. These elevated levels suggest that CA15-3 could serve as a therapeutic and diagnostic marker for cancer recurrence and metastasis.

Discussion

The findings of this study suggest a significant relationship between the perioperative use of anesthetic agents and the serum levels of Cancer Antigen 15-3 (CA15-3), a biomarker associated with cancer recurrence and metastasis. Elevated CA15-3 levels were observed in patients who underwent surgery with general anesthesia, which is consistent with existing literature suggesting that certain anesthetic techniques may influence cancer outcomes by modulating the tumor microenvironment and immune response [12]. General anesthesia has been implicated in suppressing immune function, which can facilitate the escape of residual cancer cells from immune surveillance, thereby promoting recurrence and metastasis [13]. Specifically, volatile anesthetic agents used in general anesthesia, such as isoflurane and halothane, have been shown to increase pro-inflammatory cytokine production and reduce natural killer (NK) cell activity, both of which are crucial in controlling tumor growth and preventing metastasis [14]. This immunosuppressive effect may account for the higher CA15-3 levels observed in patients receiving general anesthesia, as the body's ability to suppress micrometastatic disease is compromised. Conversely, regional anesthesia, which involves the targeted administration of local anesthetics to block nerve impulses in specific areas of the body, has been associated with better oncologic outcomes in some studies. This technique reduces the need for systemic opioids and minimizes the stress response to surgery, thereby preserving immune function [15]. The potential immune-preserving effects of regional anesthesia could explain the lower

CA15-3 levels observed in patients who underwent surgery with this anesthetic technique. These findings align with the hypothesis that regional anesthesia may play a protective role in preventing cancer recurrence and metastasis by preserving perioperative immune function [16].

The correlation between anesthesia type and CA15-3 levels highlights the importance of considering anesthetic technique as a modifiable factor in cancer surgery. Given the association between elevated CA15-3 levels and poor prognosis in cancer patients, the choice of anesthesia could have significant implications for long-term outcomes. While the exact mechanisms by which anesthetic agents influence cancer progression remain to be fully elucidated, it is clear that the perioperative period represents a critical window during which the risk of recurrence can be modulated [17]. Further research is needed to confirm these findings and to explore the underlying biological mechanisms. Prospective clinical trials are warranted to investigate the impact of different anesthetic techniques on biomarkers such as CA15-3 and to determine whether altering anesthetic practices can improve cancer-specific survival [18]. Additionally, studies focusing on the molecular pathways affected by anesthetic agents, such as those involving apoptosis, angiogenesis, and immune modulation, could provide valuable insights into how these drugs influence tumor biology [19].

Conclusion

In conclusion, the observed correlation between anesthesia and CA15-3 levels underscores the potential role of anesthetic management in influencing cancer outcomes. Anesthesiologists should be aware of these findings when planning perioperative care for cancer patients, as the choice of anesthesia could have far-reaching effects on patient prognosis. Tailoring anesthetic techniques to minimize immune suppression and support the body's natural defenses against cancer could become a crucial component of onco-anesthesia practice [20].

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics Committee Approval and Patient Consent

Before performing study and collecting samples, we obtained approval from the Institutional Review Board (Ministry of Higher Education and Scientific Research, Al-Nahrain University, Scientific Research Ethics Committee, number 725, date 31-1-2022). In order to safeguard the patient's confidentiality, the inquiry did not include any identifying information about the patient or any identifying information about healthy persons or any portion of them.

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