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RESEARCH ARTICLE

Predictive Role of Age and Deviant Life Style on Acute Side Effects During Chemoradiotherapy for Breast and Gynecological Cancers

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Abstract

Introduction and Purpose: Chemo- and/or radiation therapy are currently key pillars in cancer care. However, these therapies often induce variable side effects with a strong potential to nuance treatment compliance and effectiveness. This review aims to collate the fragmented evidence on potential predictors of the chemoradiation side effects, providing thus a unified resource for personal treatment planning and counselling.

Materials and Methods: This review analysis secondary data on the predictive role of age and deviant lifestyle factors in acute side effects experienced during chemoradiotherapy for breast and gynecological cancers. A systematic online search was conducted using keywords such as age, smoking, alcohol consumption, and body mass index, and their associations with acute side effects of chemoradiation therapy. A total of six articles were found and subjected to an in-depth analysis as to study's design, sample size, methodology, key findings, strengths and limitations.

Results and Discussion: The current body of evidence indicates that advanced age (particularly 52 years and above), body weight below 60 kilograms, low body mass index, smoking and alcohol consumption during chemotherapy are positive predictors of the development of side effects during chemoradiotherapy. This evidence, however, comes from few studies with small sample sizes, nuanced measurement of age, lack of comparison group(s) and no information on interactive relationships between the variables.

Conclusion: Older age, lifestyle and body weight deviations expose to side effects during chemo- and/or radiation therapy. No study, so far, has investigated the possibility of interactions between these variables. Thus, further studies which focus on interactive effects, in addition to using larger samples, and control group(s) are required.

Keywords: Age, Life Style, Chemoradiotherapy, Acute Side Effects, Breast and Gynecological Cancers

1. Introduction

Cancers impose a tremendous burden of morbidity and mortality worldwide [1,2]. This health problem is currently the second most common cause of mortality in industrialized nations [3] and the fourth most common cause of death in poor countries [4]. In 2020, 19.3 million people worldwide suffered from cancer, and 10 million of them died from it (51.8% of deaths compared to incidence). Furthermore, estimates suggest that, within the coming decades, there will be a significant increase in the worldwide cancer burden [5,6], inferably for both sexes.

In women, endometrial and cervical cancers are among the most common cancers. Specifically, malignancies of the corpus uteri, cervix uteri, vulva, ovary, vagina, fallopian tube, and placenta are ranked

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as the third most common group of cancers [7]. Cervical cancer remains an important public health problem, despite the fact that it is largely preventable [8]. It has, for long, been on record as the leading cause of mortality in women world-wide. A large part of the disease burden is on the less developed countries [9] which unfortunately, have a weak resource-base and dysfunctional health systems in which effective cancer services, and control are still a low priority and hence underfunded [10, 11].

Every nation in the world is making an attempt to treat cancer sufferers. Chemotherapy, radiation, surgery, and hormone therapy are the cornerstones of the treatment. Recent advancements in these therapeutic pillars are responsible for the noticeable decline in mortality, with a resultant rise in the survival rates, which is anticipated to continue increasing in the years ahead [12-14].

The gold-standard treatment for locally advanced cervical cancer (Federation Internationale de Gynecologie et Obstetrique (FIGO) stage IIb to IVa) is Concurrent ChemoRadiotherapy (CCRT), specifically chemotherapy plus external beam radiotherapy (EBRT), followed by brachytherapy [15, 16]. Unfortunately, this gold-standard treatment frequently provokes side effects, or toxic complications. Radiotherapy can cause acute radiation toxicity (ART) within 90 days, from initiation. During treatment for cervical cancer, up to 84% of patients could exhibit some form of ART [17-19]. The most common manifestations are hematologic, gastrointestinal and genitourinary toxicities, whose intensity and severity depend on the radiation dose, the fractionation regime, and the applied radiation technique [19]. The occurrence of these undesirable effects, can lead to treatment interruptions and/or dosage reduction, all of which can lower the effectiveness of the treatment [20, 21].

Radiation and chemotherapy both kill cancerous cells, but can also harm healthy tissues, leading to undesirable side effects and an increased level of discomfort for patients [22, 23]. A number of studies have reported cancer-related fatigue as the most common side effect occurring in 60-99% of patients. When cancer-related fatigue occurs, it leads to overwhelming exhaustion and a reduced capacity for physical and mental work that is not relieved by rest [24-29]. Other frequent side effects include nausea, vomiting, mucositis, constipation, and diarrhea [30]. Their occurrence on the one hand and their intensity on the other hand vary across patients. Knowledge on the possible determinants of the variation may greatly assist in reducing the proportion of poor compliance to treatment, and even abandonment, both of which affect outcomes. Hence the basis of this review which focuses on potential predictors of chemoradiation side effects. The review assembles scattered evidence in the literature to make it available, en bloc, for therapeutic counselling and planning.

2. Materials and Methods

This review examined the existing literature on the role of age and deviant lifestyle factors in the emergence of acute side effects during chemoradiotherapy for breast and gynecological cancers. A systematic online search was conducted using keywords such as age, smoking, alcohol consumption, and body mass index, and their associations with acute side effects of chemoradiation therapy. Retrieved articles were carefully evaluated for relevance, with the primary inclusion criterion being their direct relationship to the review's objectives. Additionally, explanatory articles were identified using a combination of the snowball method and keyword-based searches. An in-depth analysis was then performed on the selected core articles to bring out and synthesize insights, and draw meaningful conclusions.

A total of six core articles were obtained with three (Watard A et al, Goronzl JJ et al and Holmquist A et al) focusing on age, one each (Peppone et al, Zhao et and Radojecci MZ et al) focusing on smoking, alcohol consumption and body mass index respectively. Each core article was subjected to an in-depth analysis. For this, an eight-column table was drawn up, having an analytical parameter per column. The parameters tabulated included the author, research topic, study design, sample size, methodology, key findings, strengths and limitations. Each core article was then studied across the eight columns and findings recorded in a row. The recorded information served as the substrate of the review.

3. Results and Discussion

The exploited articles differentially provided evidence on the predictive role of age, smoking, alcohol consumption, and deviant Body Mass Index (BMI) in the development of Acute side effects during chemoradiation therapy for breast and gynecological cancers.

3.1 Age

Holmqvist et al [31], found in 2022 that patients 52 years or older had significantly higher frequency of

nausea/vomiting, weight loss and hospitalization. In general, the frequency of weight loss and diarrhea was higher, the older the patients. The researchers concluded that age can predict diarrhea and weight loss. This may be so because aging affects both innate and adaptive immune function as well as the incidence /pattern of autoimmune conditions. In addition, an increase in the basal inflammatory process, and an elevated production of autoantibodies have been linked to aging [32,33].

3.2 Smoking

Peppone et al. [34], through a survey research study comparing side effects in smoking and non-smoking breast cancer patients, found a significantly higher total symptom burden among smokers. Specifically, smokers reported greater weight loss and showed trends toward increased severity of skin problems, sleep disturbances, and nausea during treatment. A similar pattern was observed at a six-month follow-up, except for nausea. This study assessed overall treatment effects without isolating the contributions of specific therapies to the observed differences, leaving a gap in understanding the role of individual treatment modalities.

It is posited however, that smoking during cancer treatment does not only disproportionately expose to side effects but also swells other adverse events including greater mortality, and treatment–related complications. This presently unchallenged fact has apparently not impacted on the prevalence of smoking. Smoking rates at time of cancer diagnosis vary from 10->95%, depending on the cancer site, [35-38]. Data from 1999-2001 showed little difference in smoking prevalence between cancer patients and the general population (20 and 24% respectively), even when age is controlled for [35]. Below 40 years of age, about 44% of cancer patients reported smoking whereas this percentage was 27 among those with no reported cancer history [39, 40]. Tobacco is a major component of cigarettes and contains free radicals, carbon monoxide and formaldehyde, which promote inflammatory oxidative stress when inhaled [41]. Cardiovascular disease risk, tooth erosion, decreased pulmonary health and visual problems are other well documented negative effects of tobacco on health [42]. Additionally, cigarette smoking can create a hypoxic environment [43]. Hypoxic environments are unfavorable for radiotherapy, resulting in limited effectiveness of treatment on disease progression and morality [44, 45].

3.3 Alcohol Consumption

Zhao et al [46], conducted a descriptive study involving a cross-sectional analysis of a geographical cohort of patients in 2022. These researchers found that 38.1 % of patients who consumed alcohol during chemotherapy reported side effects. This study however, involved 69 patients, which is a small sample. No comparison was also done with patients who were not consuming alcohol. Another limitation of this study is the fact that the use of alcohol in the past was not investigated.

3.4 Body Mass Index

Radojeci et al [47], conducted a two-nested case-control study on acute radiotherapy toxicity (ART) among 138 cervical cancer patients made up of 54 patients who were treated with 3D-RT and 84 who had 2D-RT. Use of ACE inhibitors concurrently with radiotherapy had a statistically significant effect on the appearance of ART. The study identified the following constitutional characteristics as predictive of the onset of ART: body weight less than 60 kilograms, small waist volume, low BMI, and small pelvic gross volume.

4. Discussion

Currently, there is a notable gap in the existing literature concerning a comprehensive evaluation of age, smoking, alcohol consumption, and body mass index as potential predictors of side effects in the context of chemoradiation. Most studies in the literature have predominantly focused on individual variables, and there is a lack of research that simultaneously considers the interactive effects of these variables on the side effects of chemoradiation. Examining these factors independently has limitations.

Small samples, bias-ridden sampling, lack of comparative group(s) and unclear methodology were other found limitations. For instance, the study that investigated age as a potential predictor used a small sample size of 93 patients, and the methodology lacked clarity regarding how age was measured-whether it was recorded in completed years. Furthermore, the absence of randomization in subject selection raises concerns about the generalizability of the findings. On its part, the study that examined the impact of cigarette smoking on cancer treatment-related side effects was descriptive in nature and lacked a control group. By focusing solely on current smokers and omitting data on the duration, quantity, and intensity of smoking, the study was unable to establish a dose-

response relationship between smoking and symptom burden. Furthermore, the potential confounding effects of substance use were not thoroughly evaluated. To address these limitations, future research should adopt a controlled study design, incorporate larger and randomly selected samples, and comprehensively assess the interactive influences of these variables. In so doing, robustness and external validity of the results will, undoubtedly, be enhanced.

Overall, there is a critical need for more comprehensive studies that jointly assess age, smoking, alcohol consumption, and body mass index as potential predictors of side effects during chemoradiation. The limitations of existing studies underscore the importance of conducting well-designed, randomized investigations with larger sample sizes to provide more conclusive and generalizable insights into the complex interplay of these factors in the context of cancer treatment. A cross-cutting limitation of all the reviewed studies is the finding that none was conducted in Africa. The African reality may be different, given dissimilarities in biological, socio-economic and environmental characteristics.

5. Conclusion

The current body of evidence suggests that certain factors, such as advanced age (particularly 52 years and beyond), smoking, alcohol consumption, body weight below 60 kilograms, and a low Body Mass Index (BMI), are positive predictors of the development of side effects during chemoradiation therapy. This information holds practical relevance in the formulation of policies, strategies, and clinical guidelines for chemoradiation therapy. At the clinical level, targeted interventions and preventive measures can be developed for individuals who, based on these potential predictors, are judged to be at higher risk of experiencing side effects.

However, the need for more comprehensive understanding should not be sidelined. Studies that investigate the interactive influences of smoking and alcoholism levels as well as various body weight-related parameters on the occurrence of chemoradiation side effects are needed. The complexity of the recommended interactive studies is acknowledged, but should not nuance efforts to provide an in-depth understanding of these influences. It is worth emphasizing that such studies should not only be conducted in diverse populations but should necessarily involve the African continent. This emphasis on diverse populations and involvement of the African continent acknowledges the potential variations based on factors such as genetics, lifestyle, and environmental parameters.

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