

**The Impact of Timing of Adjuvant Radiotherapy
on Disease free survival in neoadjuvantly-treated
breast Cancer patients**

A Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ مَوْلَا

لَسْبَدَانِكَ لَا مَعْلَمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

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✍️ **Asmaa Ali Kortoma**

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List of Abbreviations

Abbr.	Full-term
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Introduction

Breast cancer has become the leading cause of cancer-related mortality among females worldwide, And up to 60% are living in developing countries(*Bray et al., 2011*).

Mostly the patients are diagnosed without metastatic disease in approximately 90% of cases (*Torre et al., 2012*)therefore, the cure becomes the physician's ultimate goal, and a multidisciplinary approach is critical to achieving it. This includes the coordinated and timely administration of systemic therapy, surgery, and postoperative radiation therapy (PORT) (*Kesson et al., 2012*).

Postoperative radiation therapy is a pillar stone in the adjuvant treatment of breast cancer as it improves both disease-free survival (DFS) and overall survival (OS) (*Fisher et al., 2002*).The patient needs to receive the needed dose at the right time; However, the lack of medical health awareness and limited medical infrastructures leads to waiting lists and a delay in the time of initiation of PORT. That is why developing countries women cannot receive radiotherapy's full benefits, they have few radiotherapy centers available and high number of cases who require PORT, and as many of them are unable to afford private centers cost it leads eventually to overload and longer waiting lists at the government-supported centers (*Shaukat et al., 2013*).

The Lancet Radiotherapy Commission in Latin America published a report in 2015 which estimated that premature mortality due to a lack of optimal radiation therapy over the next 20 years in low and middle-income countries would result in a million lives lost(*Atun et al., 2015*).

Trials have been done to estimate the correct order and timing of a multidisciplinary treatment approach and we focused on radiotherapy timing. Some trials proved that patients who have a longer waiting time for radiotherapy have an increased risk of local recurrence of their cancer (*Chen et al., 2008*) but no specific time is set between the different centers in the world. For example, in china a multicentre study revealed that for locally advanced breast cancer patients treated with neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy, radiotherapy should be initiated within 18 weeks after mastectomy(*Huang et al., 2019*).

In Europe, a study reported that PORT started within 8 weeks of surgery was associated with better DFS and OS in locally advanced breast cancer patients submitted to neoadjuvant chemotherapy(*Silva et al., 2018*).

On the other hand, a statistical study was done at Columbia University in America which included 24,833 women, Among those receiving radiotherapy (RT), 97% started treatment within 3 months (older age, black race, advanced

stage, more co-morbidities, and being unmarried were associated with longer time intervals between surgery and RT). There was no benefit to earlier initiation of RT; however, delays > 3 months was associated with higher overall mortality (*Hershman et al., 2006*).

Meanwhile, the National Canadian Clinical Practice Guidelines recommend that radiation treatment be administered within 12 weeks of breast-conserving surgery to reduce the incidence of local relapse (*Whelan et al., 2003*). Therefore, the ideal timing for PORT remains unknown and differs across the globe according to trials, also there were few studies found that specifically evaluated the neoadjuvant scenario, in which theoretically the patients have higher-risk disease, and a treatment-free interval before initiating PORT, which makes them a unique population to test the rule of PORT delay. On that basis, we performed a retrospective study questioning the impact of the time to initiate PORT in patients who received neoadjuvant chemotherapy followed by surgery.

Aim of this Study

As adjuvant radiotherapy (RT) is a cornerstone in treating breast cancer following surgery, but in developing countries, it is difficult to start adjuvant RT to all cases as soon as possible after surgery for patients who received neoadjuvant chemotherapy. This study aims to assess the impact of delaying adjuvant radiotherapy in breast cancer patients who received neoadjuvant chemotherapy and to correlate between the radiotherapy timing and other risk factors as prognostic factors on Disease-free survival.

Chapter (1)

Epidemiology

Breast cancer is the most frequent cancer among women accounting for almost 1 in 4 cancer cases among women impacting 2.1 million women in 2018 globally (24% of all cancers). It is the most frequently diagnosed cancer in the vast majority of the countries (154 of 185), the Incidence rates vary from 92.6 per 100,000 women in Western Europe, greater than 80 per 100,000 in developed regions of the world (except Japan) and less than 40 per 100,000 in most of the developing regions (*Globocan 2018*).

Elevated incidence rates in developed countries are attributed to a higher prevalence of known risk factors such as early age at menarche, later age at menopause, nulliparity, late age at first birth, and fewer children, exogenous hormone intake (oral contraceptive use and hormone replacement therapy), nutrition (alcohol intake), sedentary lifestyle, greater weight, and body fat distribution; whereas breastfeeding and physical activity which is more seen in developing regions are known protective factors (*Brinton et al., 2018*). The incidence rate of breast cancer is estimated to reach 3.2 million by 2050 (*Hortobagyi et al., 2005*).

Incidence rates of breast cancer have been rising for most countries where rates have been historically relatively low

like: South America, Africa, and Asia (*Bray et al., 2004*). as it reflects the combination of demographic factors and the socio-economic development, including the postponement of childbearing and having fewer children, increasing levels of obesity, and lacking physical activity, besides the increase of breast cancer screening and awareness. On the other hand in developed countries, the fall in incidence in the early 2000s was partly attributable to declines in the use of postmenopausal hormonal treatment after the publication of the Women's Health Initiative trial linking postmenopausal hormone use to increased breast cancer risk (*Rossouw et al., 2002*).

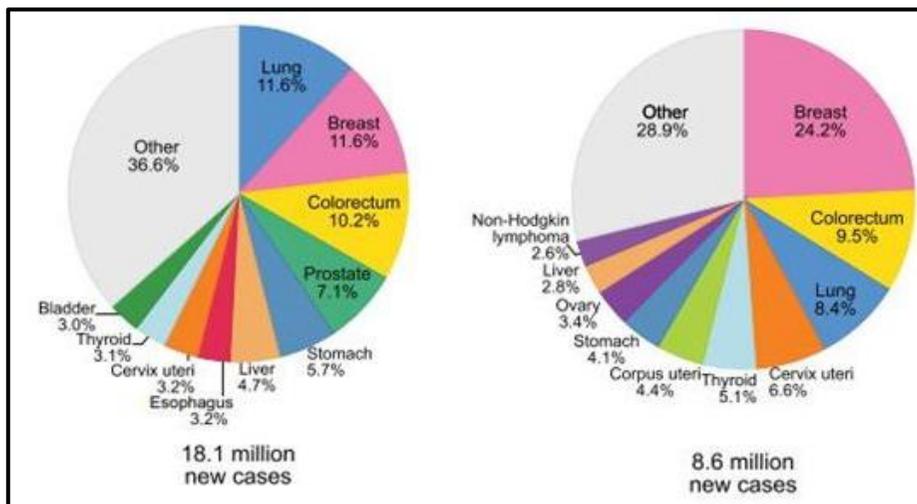


Figure (1): Breast incidence in both sexes (on left) and in female population (on right) (*Globocan, 2018*)

The range of survival estimates is still wide in each continent, North America is first with 5-year net survival approaching 90%, 85% or higher in countries like Japan and

European countries. Survival was in the range 70-79% in other countries such as : Cuba, Kuwait, Croatia, breast cancer survival remains lower in Eastern Europe and Africa (*Zaidi and Adlane, 2019*). Breast cancer causes the greatest number of cancer-related deaths among women in over 100 countries accounting approximately for 15% of all cancer deaths among women, the main exceptions are Australia/New Zealand, Northern Europe, Northern America (where it is preceded by lung cancer) and many countries in Sub-Saharan Africa (because of elevated cervical cancer rates). (*Globocan, 2018*)

It ranks fifth among all cancers in both men and women (6.6%) following lung, colorectal, gastric, and liver cancers, it is estimated that 627,000 women died from breast cancer in 2018 (*Globocan, 2018*).

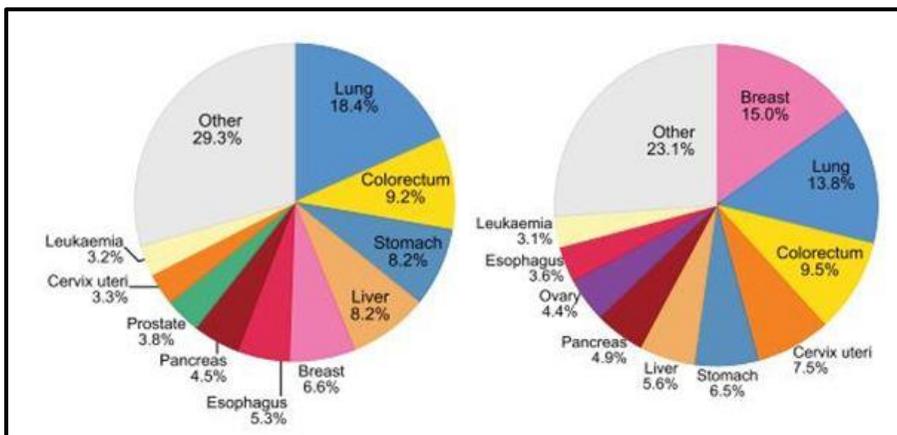


Figure (2): The proportion of the total number of cases and deaths for the 10 most common cancer in 2018 in both sexes on right and in female population on left (*Globocan, 2018*).