Indonesian Journal of Global Health Research
Volume 6 Number 4, August 2024
e-ISSN 2715-1972; p-ISSN 2714-9749
http://jurnal.globalhealthsciencegroup.com/index.php/IJGHR

EFFECTIVENESS OF ENDOCRINE THERAPY IN LUMINAL-A BREAST CANCER PATIENTS: A LITERATURE REVIEW

Jeremiah Nugraha Mai[1]*, M. Rizky Ferdiaananda[2], Muhammad Nur Hidayah Rayhan Wiradiharja[3], Shabrina Nur Afiati[4], Muhammad Alif Fahren Subangkit[5]

[1]School of Medicine and Health Sciences, Universitas Katolik Indonesia Atma Jaya, Jl. Jend. Sudirman No.515, Karet Semanggi, Setiabudi, Jakarta Selatan, Jakarta 12930, Indonesia

[2]Faculty of Medicine, Universitas HKBP Nommensen, Jl. Sangnawaluh No.4, Siopat Suhu, Siantar Timur, Pematang Siantar, North Sumatra 21136, Indonesia

[3]Faculty of Medicine, Universitas Padjadjaran, Jl. Raya Bandung Sumedang KM.21, Hegarmanah, Jatinangor, Sumedang, West Java 45363, Indonesia

[4]Faculty of Medicine, Universitas Trisakti, Jl. Lt. Gen. S. Parman No.1 Campus A, Grogol, Grogol Petamburan, Jakarta Barat, Jakarta 11440, Indonesia

[5]Faculty of Medicine, Universitas Jambi, Jl. Jambi - Muara Bulian No.KM. 15, Mendalo Darat, Jambi Luar Kota, KMuaro Jambi, Jambi 36361, Indonesia

*jeremiahmai1607@gmail.com

ABSTRACT

Breast cancer ranks as one of the primary causes of mortality in women worldwide, with Southeast Asia, particularly Indonesia, witnessing a notable prevalence. Objective: To elaborate the endocrine therapy in breast cancer patients. Method: A comprehensive literature search was done across PubMed, Medline, ProQuest, Sage, and Google Scholar. Breast cancer, carcinoma mammae, luminal A, endocrine therapy, and recurrence rate, were used as the keywords. Inclusion criteria were studies on endocrine therapy in breast cancer. Initial search using title and abstract was conducted, then followed by full-text screening. Results: From 415 studies, 11 articles published between 2003 and 2022 were retrieved [RCT (n=8), clinical trial (n=1), cohort (n=1), cross-sectional (n=1)]. Endocrine therapy, also known as hormone therapy, could inhibit the growth of tumor cells by slowing down the ability of those cells to replicate. Fulvestrant and aromatase inhibitors (AI) such as anastrozole and letrozole have shown high survival and low recurrence rates. Conclusions: Adjuvant endocrine or hormonal therapy had shown remarkable outcomes for luminal A breast cancer patients, with high survival rates and very low recurrence rates. Further research was still needed to further understand the development of future treatments and to extend the research on long-term survival rates.

Keywords: breast cancer; endocrine; luminal A; therapy

First Received	Revised	Accepted
01 March 2024	16 March 2024	27 March 2024
Final Proof Received		**Published**
28 May 2024		01 August 2024

How to cite (in APA style)
Mai, J. N., Ferdiaananda, M. R., Wiradiharja, M. N. H. R., Afiati, S. N., & Subangkit, M. A. F. (2024). Effectiveness of Endocrine Therapy in Luminal-A Breast Cancer Patients: A Literature Review. Indonesian Journal of Global Health Research, 6(4), 2297-2306. https://doi.org/10.37287/ijghr.v6i4.3083.

INTRODUCTION

National Cancer Institute's Surveillance, Epidemiology, and End Result Program showed that the incidence of breast cancer has increased rapidly in the fourth decade, leading to elevated mortality rates (Acheampong et al., 2020). Currently, Southeast Asian countries have recorded the highest increase in breast cancer prevalence in the world. According to GLOBOCAN 2008, Singapore had a breast cancer incidence rate of 59.9% per 100,000 population, and Indonesia showed the highest mortality rate (18.6% per 100,000). According to data from the International Agency for Research on Cancer in 2012, Indonesia had an incidence rate of 43.3% and a mortality rate of 12.9% for breast cancer (Widiana & Irawan,

2020). Presently, various classifications were employed to delineate the types and attributes of breast cancer. One popular classification used in the medical community is the molecular subtype, which is identified based on the role of hormonal receptors in patients, such as the progesterone receptor, estrogen receptor, and HER2. There are subgroups of this molecular subtype which also known as triple-negative: basal-like tumor, luminal A, luminal B, and HER2 (Eliyatkin et al., 2015).

In Indonesia, luminal A breast cancer ranks first in incidence, accounting for 50-60% of all breast cancer cases, followed by luminal B (15-20%). The HER2 type, accounting for 10-20% of cases, has a worse prognosis than luminal B. Lastly, the basal type, which does not express ER, PR, and HER2, has the worst prognosis (Widiana & Irawan, 2020) Currently, numerous therapeutic modalities are available for cancer patients, particularly those with breast cancer. These include chemotherapy, surgery, radiotherapy, targeted therapy, and endocrine (hormonal) therapy. These therapy modalities can also serve as adjuvant therapy to the primary treatment performed, such as additional radiotherapy after surgery, or endocrine therapy after surgery and radiotherapy (Nounou et al., 2015). Endocrine therapy, as a treatment modality, aligns with breast cancer's nature, which relies on estrogen and progesterone hormones. A commonly utilized adjuvant treatment for postoperative patients with luminal A type breast cancer is endocrine therapy, aimed at hormonal regulation in patients. Several endocrine therapy options exist, including aromatase inhibitor (letrozole, exemestane, anastrozole), ER downregulators (fulvestrant), and selective ER modulators (tamoxifen) (Li et al., 2022).

This article seeks to elucidate the role of endocrine therapy as adjuvant therapy in breast cancer, with a particular emphasis on those with low-risk features and early onset. Given the pivotal role of endocrine therapy as a cornerstone of breast cancer treatment, particularly in hormone-receptor-positive cases, it is essential to grasp its efficacy, considering the disease's hormone-focused mechanism. The primary goal of providing adjuvant therapy to cancer patients is to prevent recurrence and improve the patient's wellbeing and survivability. Therefore, the author wanted to provide a comprehensice review regarding this issue on endocrine therapy as a management for patients with luminal-A breast cancer.

METHOD

The design of this study is literature review. The authors conducted a comprehensive literature search to assess the role of endocrine therapy in Luminal-A breast cancer. The keywords used were: breast cancer, carcinoma mammae, luminal A, endocrine therapy, and recurrence rate. Articles were searched across various databases such as PubMed, Medline, ProQuest, Sage, and Google Scholar. The inclusion criteria were: (1) assessed the role of endocrine therapy in breast cancer patients (2) written in English, (3) available in full text. Literature search was done without time limitation. The exclusion criteria were: (1) articles that had similarities with articles that had already been used as data sources (2) repeated publications (3) reviews, letter to editor, and case reports. Five authors independently extracted the articles that have been included. An initial search and screening process was conducted according to their title and abstract. Then, full-text screening was done and information needed was extracted. The extracted data were: (1) author (references), (2) publication year, (3) study design, (4) results of the study.

RESULTS

The studies included for this literature review were published between 2003 and 2022. All of which were randomized controlled trial (RCT), cohort or cross-sectional. An initial search

was conducted, and 415 articles were retrieved. After full-text screening was done, 11 articles were included [RCT (n=8), clinical trial (n=1), cohort (n=1), cross-sectional (n=1)].

Table 1.
Primary studies of endocrine therapy in breast cancer patients

Author (Ref)	Year	Study Design	Results
International Breast Cancer Study Group (IBCSG) (International Breast Cancer Study Group (IBCSG), 2003)	2003	RCT	In patients with estrogen receptor-positive disease, goserelin alone and chemotherapy alone yielded similar outcomes (5-year DFS for both therapy groups = 81%, 95% CI = 76% to 87%). However, sequential treatment showed a statistically non-significant enhancement over the combined use of the two modalities (5-year DFS = 86%, 95% CI = 82% to 91%), especially in younger women.
Regan MM, et al. (Regan et al., 2011)	2011	RCT	In postmenopausal women with early endocrine-responsive breast cancer, letrozole monotherapy reduced mortality and recurrence when compared to tamoxifen monotherapy. However, sequential treatment did not improve outcomes when compared to letrozole monotherapy.
Francis PA, et al. (Francis et al., 2018)	2018	RCT	When combined with tamoxifen, ovarian suppression significantly improved the overall and DFS of breast cancer in premenopausal patients, over an 8-year period compared to tamoxifen alone. Higher recurrence-free rates were obtained when exemestane was used in conjunction with ovarian suppression.
Robertson JF, et al. (Robertson et al., 2016)	2016	RCT	Fulvestrant was considered a more effective option compared to third-generation AI, which were typically used as the first line of treatment for hormone receptor-positive breast cancer.
Howell A, et al. (Howell et al., 2005)	2005	RCT	Fulvestrant and anastrozole were comparable in terms of overall survival when used as a postmenopausal woman's second-line therapy with advanced breast cancer.
Nielsen TO, et al. (Nielsen et al., 2017)	2017	RCT	Adjuvant cyclophosphamide-based chemotherapy did not prove beneficial for patients with luminal A breast cancer.
Pan H, et al. (Pan et al., 2016)	2016	Clinical trial	After five years of endocrine therapy, there is a 5 to 14 years risk of ER+ recurrence. Recurrence was less common in patients with good TN status and grade, but was still very possible in patients with low-grade T1N0 disease.
Jung SU, et al. (Jung et al., 2019)	2019	Retrospective cohort	Patients with clinicopathologically hormone-positive and HER2-negative responses could avoid chemotherapy and achieve low recurrence rates and good survivability, even in cases with lymph node metastasis.
Huang G, et al. (G. Huang et al., 2022)	2022	Cross-sectional	The prevalence of BRCA1 and BRCA2 mutations in early-onset breast cancer did not differ significantly (20.7% vs. 17.1%, P = 0.35). Among patients with a family history of breast cancer, BRCA2 mutations were more common than BRCA1 (54.3% vs. 44.8%, P = 0.01). BRCA1 mutations were more prevalent in patients with triple-negative breast cancer than BRCA2 (34.5% vs. 28.6%, P = 0.04).
Regan MM, et al (Regan et al., 2016)	2016	RCT	Premenopausal patients who received chemotherapy showed an increase of 5% or more in 5-year breast cancer-free interval (BCFI) with exemestane with ovarian function suppression (OFS) compared

Author (Ref)	Year	Study Design	Results
			to tamoxifen with OFS or tamoxifen alone (10% to 15%) in the intermediate to high combined risk group. Exemestane combined with OFS vs tamoxifen plus OFS in 5-year BCFI ranged from 5% to 15%.
Water W, et al (Water et al., 2012)	2012	RCT	In a cohort of 3,142 postmenopausal breast cancer patients, 1,682 were younger than 65 years old, 951 were aged 65-74 years old, and 509 were 75 years old or older. Older age was linked to a higher proportion of non-persistence in the first year of the study. Among patients younger than 65 years old, those who were non-persistent had a lower probability of survival. However, in patients aged 65-74 years and those aged 75 years or older, the survival time for both persistent and non-persistent patients was similar.

The comprehensive care of cancer patients worldwide typically includes chemotherapy, which is aimed at systemically eliminating cancer cells following surgery. However, chemotherapy is associated with systemic toxic side effects that are generally disliked by both patients and treating doctors. In cases of early-onset breast cancer with low-risk types such as luminal A and B, chemotherapy is often not routinely administered, taking into account the risks and benefits. Meanwhile, endocrine therapy, also known as hormone therapy, could inhibit the growth of tumor cells by slowing down the ability of those cells to replicate. Tamoxifen was initially used as breast cancer treatment. In recent studies, fulvestrant and aromatase inhibitors (AI) such as anastrozole and letrozole were used. Studies have shown that fulvestrant was more effective than third-generation AI. These drugs could reduced the mortality rates in breast cancer patients. Recurrence rates were also reduced in patients with endocrine therapy (table 1).

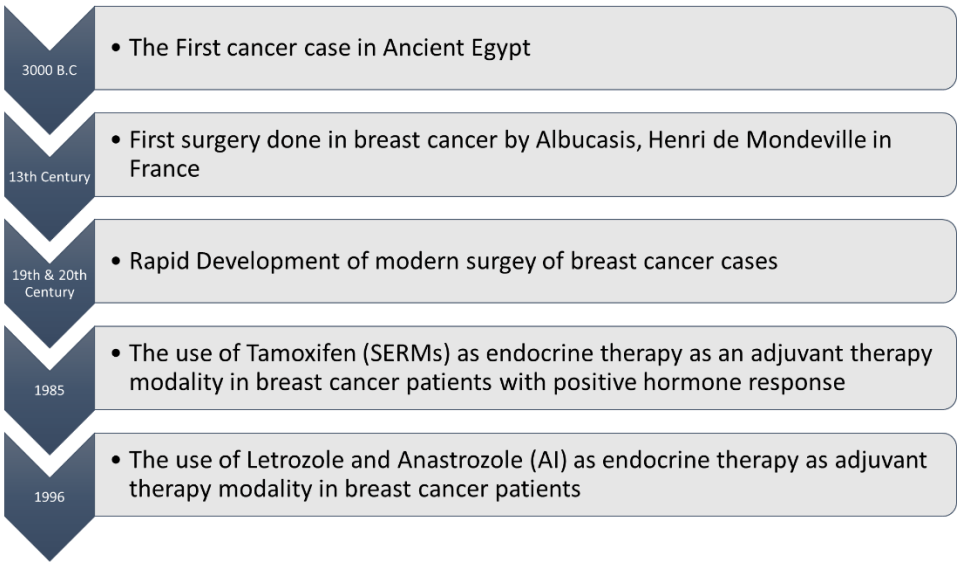

Figure 1. Endocrine therapy's development in breast cancer

The history of endocrine therapy's development in breast cancer was shown in Figure 1 (Acheampong et al., 2020; Eliyatkin et al., 2015; Harbeck & Gnant, 2017; Li et al., 2022; Nounou et al., 2015; Widiana & Irawan, 2020). It is established that taking tamoxifen for 5 years reduced the risk of mortality from breast cancer and the likelihood of recurrence within the following 15 years (Trayes & Cokenakes, 2021). In some cases, women begin taking aromatase inhibitors after two to three years of tamoxifen therapy, totaling ≥5 years on endocrine treatment (Gao & Swain, 2018; Mauri et al., 2006). Studies have indicated that AI

were preferred over tamoxifen in postmenopausal women (G. Huang et al., 2022; Paterni et al., 2014). AI with ovarian suppression combination for breast cancer in premenopausal women has been proven to be more effective than using tamoxifen combined with ovarian suppression or tamoxifen alone (H. Huang et al., 2021).

DISCUSSION

Overview Breast Cancer Treatment Modalities

The most frequent disease in the world and the primary cause of mortality for women globally is breast cancer. This chronic disease is a multifaceted ailment that is categorized as heterogeneous cancer according to clinical and histological criteria. This includes human receptor-positive breast cancer, triple-negative breast cancer (TNBC), and breast cancer that is overexpressed in human epidermal growth factor receptor-2 (HER2+) (Harbeck & Gnant, 2017). Advancements in breast cancer therapy have been rapid in recent years, with several treatment modalities ranging from conventional surgery to hormonal therapy. The basis of breast cancer therapy today is also based on the cancer staging. Currently, for breast cancer types that are triple-negative and HER2-positive, adjuvant therapy is recommended over conventional surgery. The backbone of the therapy currently consists of several components, including endocrine therapy, anti-HER2 targeting, and chemotherapy (Trayes & Cokenakes, 2021).

Breast Cancer Subtypes and Recurrence Patterns

Research suggests that the presence of progesterone receptor (PR) and estrogen receptor (ER) is crucial in determining response to therapy and patients' prognosis. Additionally, the status of HER2 is a significant prognostic factor. Evaluating the expression of ER, PR, and HER2 combination could improve the accuracy of prognosis. Breast tumor classification includes HER2 positive, luminal A, luminal B, and triple-negative subtypes (Mauri et al., 2006). Among breast cancer patients, the HER2-positive subtype had the highest rate of local recurrence at 7.5%, followed by triple-negative at 7.1%, luminal B at 5.0%, and luminal A at 3.7%. Regional recurrence within 10 years was most common in triple-negative breast cancer (TNBC) at 5.2%, compared to 4.5% in luminal B, 4.0% in HER2-positive, and 1.7% in luminal A subtypes (Gao & Swain, 2018).

Metastasis cases within 10 years were most common in patients with HER2-positive breast cancer (25.6%), followed by approximately 23.2% in triple-negative and 20.0% in luminal B, with around 9.5% in luminal A. These differences between subtypes were statistically significant. Luminal A showed the lowest incidence of all types of recurrence. The findings were further analyzed based on the trastuzumab administration in HER2-positive patients subtype and some patients in the luminal B subtype. The recurrence rate increased when trastuzumab was not administered to luminal B HER2-positive or HER2-positive patients (Gao & Swain, 2018). Some studies have shown that the highest rates of recurrence and metastasis were observed in triple-negative subtypes and HER2-positive within the first 2 years. However, in the subsequent 4 years, a higher rate of metastasis was found in the luminal subtypes, particularly luminal B. Luminal A subtype exhibited the lowest recurrence rate. Based on the research data, the percentage of patients per breast cancer subtype is 74.0% (luminal A), 67.0% (luminal B), 64.3% (HER2 Positive), and 61.4% (Triple Negative). However, the percentage of patients free from recurrence per breast cancer subtype is 87.5% (luminal A), 76.6% (luminal B), 70.0% (HER2 Positive), and 73.4% (triple negative) (G. Huang et al., 2022).

Overview of Endocrine Therapy in Breast Cancer

Estrogen and progesterone, produced in the ovaries, are key regulators of cell growth in breast tissue. These hormones bind to Progesterone Receptor (PR) and Estrogen Receptor (ER), respectively. Upon binding, these receptors become activated and initiate cell transcription. ER α and ER β are the two primary estrogen receptors, with ERα playing a major role in gene expression in breast cancer, for at about 70% of cases (Paterni et al., 2014). Estrogen has diverse functions in the immune system, including polarization, cytokine production, proliferation, and macrophage activity. Estrogen can initiate the formation of another type of macrophage known as M2, which can promote tumor progression. Hormonal therapy aims to disrupt the relationship between estrogen and estrogen-related cell formation through two mechanisms (H. Huang et al., 2021). The first mechanism involves inhibiting estrogen production, while the second one involves blocking estrogen's effects using selective estrogen receptor modulators (SERMs) on tumor cells, which act as an agonists of estrogen depending on the target cells, and selective estrogen receptor degraders (SERDs), which work by inhibiting estrogen receptor activity (Drăgănescu & Carmocan, 2017).

Following the discovery of estrogen's role in breast cancer regulation, tamoxifen was initially used as a treatment for postmenopausal breast cancer patients. Following this, aromatase inhibitors (AI) like anastrozole and letrozole have also been utilized in breast cancer treatment. These drugs among breast cancer patients, lead to reduced mortality rates and favorable outcomes (Tremont et al., 2017). Aromatase inhibitors have been shown to reduce recurrence rates by 30% compared to tamoxifen. Letrozole reduces recurrence compared to tamoxifen-based therapy (84% vs. 81%, P=0.001), and letrozole demonstrates superior DFS compared to anastrozole (84.9% vs. 82.9%, P=0.3150).The inclusion of AI with OFS improved breast cancer-free interval (BCFI) by 10-15%. However, for individuals unable to tolerate aromatase inhibitors, the use of tamoxifen still led to a favorable 5-year BCFI of 96.1% (Regan et al., 2016).

Advancements and Considerations in Adjuvant Endocrine Therapy for Breast Cancer

Adjuvant therapy regimens was used to prolong the survival of breast cancer patients. Currently, ASCO has established the use of aromatase inhibitors like letrozole or anastrozole as standard endocrine treatment for low-risk breast cancer. Tamoxifen was more commonly used in the past, but numerous studies conducted have shown that recurrence rates and DFS of aromatase inhibitors were better than SERMs. Low-risk breast cancer patients with ER-positive (luminal A) status could be given aromatase inhibitors like letrozole 2.5 mg, anastrozole 1 mg, or exemestane 25 mg for 5-10 years. Tamoxifen could be an alternative choice with a dose of 20 mg for 5-10 years. The duration of endocrine therapy depends on several factors such as the cancer risk level, menopausal status, and the side effects experienced by each individual (Shien & Iwata, 2020). There were several studies and recommendations for this therapy modality (Table 1), including single therapy and combination therapy with two different types of drugs. Most of these studies stated that patients receiving aromatase inhibitors have better DFS and recurrence rates compared to tamoxifen. However, this does not mean that tamoxifen was a poor choice for luminal A breast cancer patients. In some cases, aromatase inhibitors may cause more musculoskeletal side effects than SERMs, and tamoxifen tends to be more cost-effective than aromatase inhibitors (Tremont et al., 2017). Tamoxifen remains an option for patients with metastatic or advanced-stage breast cancer. Other therapies, like fulvestrant, may benefit postmenopausal women who have not received endocrine therapy previously or have already undergone it. Some studies suggested that compared to other endocrine therapies, AI could enhance the survival rate of patients with metastases (Drăgănescu & Carmocan, 2017).

Genetic Mutations and Breast Cancer Risk Factors

Among mutations in genes associated with familian cancer (BRCA1, BRCA2, p53, hMLH1, and hMSH2), BRCA1 and BRCA2 mutations were the most common (80-90%) and represent the highest risk factor. Breast cancer associated with BRCA gene mutations is typically invasive, occurs at a young age, and is often bilateral (90-95%). Approximately 5-10% of breast cancer cases are influenced by familial factors and mutations in BRCA1 and BRCA2 genes (G. Huang et al., 2022). Research conducted by Machackova E from 1999 to 2018 reported that most of the family samples (7,400) had a high risk of BRCA mutations [BRCA1 (n=1,021); BRCA2 (n=497)] with a 20.5% detection rate, unique variants of BRCA1 (n=96) and BRCA2 (n=126) with the potential to become malignant (Machackova et al., 2019). Research conducted by Huang G also revealed that 128 of 368 individuals had the possibility of developing breast cancer in the age under 40s, with patients having BRCA mutations [BRCA1 (n=58); BRCA (n=70)]. There was no difference in the prevalence of BRCA1 and BRCA2 mutations in patients with early-onset breast cancer (20.7% vs. 17.1%, P = 0.35). However, in individuals with a family history of breast cancer, BRCA2 mutations being more common than BRCA1 mutations (54.3% vs. 44.8%, P = 0.01). In triple-negative breast cancer patients, the prevalence of BRCA1 mutations was higher than BRCA2 mutations (34.5% vs. 28.6%, P = 0.04). A study by Huang G also noted that several factors influenced BRCA1 mutations, such as cancer diagnosed at <40 years, tumor size >2 cm, and lymph node metastasis. Meanwhile, age, triple-negative breast cancer, and tumor size >2 cm could influence the BRCA2 mutations (G. Huang et al., 2022).

According to Sung et al., in a retrospective study involving 18,000 early-onset breast cancer receiving chemotherapy along with endocrine therapy had a lower 5-year recurrence-free rate (94%) compared to those receiving only endocrine therapy (96.1%). Additionally, there was no significant difference in the 10-year overall survival rate between the chemotherapy and endocrine therapy group (98.8%) compared to the endocrine therapy alone group (98.7%) (p = 0.731) (Jung et al., 2019). Another comparison was made between chemotherapy management and a placebo in a clinical trial by The Danish Breast Cancer Cooperative Group 77B. These premenopausal women with breast cancer were either given radiotherapy (without endocrine therapy), chemotherapy (levamisole), chemotherapy (cyclophosphamide), chemotherapy (cyclophosphamide-methotrexate-fluorouracil), or received no chemotherapy. It was found that patients with luminal A breast cancer did not respond well to chemotherapy, but chemotherapy was effective for patients with other breast cancer subtypes. Another study stated cyclophosphamide-based chemotherapy was not beneficial for luminal A breast cancer (Nielsen et al., 2017).

Numerous studies have also compared placebo therapy with endocrine therapy. Administering aromatase inhibitors and/or adjuvant tamoxifen for 5 years reduced mortality in breast cancer cases with positive estrogen receptors and potential for surgical intervention by one-third in years 0 to 4 and years 5 to 14. Although it carries additional side effects, prolonging adjuvant endocrine therapy can further reduce mortality in years 5 to 14 (Pan et al., 2016). When it comes to recurrence in estrogen receptor-positive breast cancer, one important consideration was the time elapsed since surgery, especially in the first 20 years of follow-up. In years 5 through 14, the recurrence rate was influenced by factors such as grade (high vs. low: RR = 2.02, 95% CI 1.44 – 2.83), T-stage (T2N0 vs. T1N0: RR = 1.73, 95% CI 1.53 – 1.95), N-stage (N1-3 vs. N0: RR = 2.08, 95% CI 1.87 – 2.32), and Ki67 (≥ 20% vs. 0-13%: RR = 1.63, 95% CI 1.23 – 2.16). In low, moderate, and high-risk T1N0 disease, the respective risk values for distant recurrence were 5%, 8%, and 10% in years 5 to 14, and for all types of recurrence, they were 12%, 15%, and 17% (Pan et al., 2016).

In today's age of precision medicine, the aim is to provide patients with the appropriate level of treatment, avoiding both over- and under-treatment, understanding the unique features of each tumor is crucial for selecting the appropriate personalized therapy. Chemotherapy is not recommended for low-risk breast cancer patients, who can instead receive more comfortable and optimally effective endocrine therapy. This strategy could aid in lowering the adverse effects and expenses linked to the treatment of low-risk breast cancer, while also avoiding potential complications and additional costs from chemotherapy in the future. In this article, several challenges faced by the author were evident, including the limited representation of patient population characteristics with luminal A breast cancer, which was often limited to specific age groups. Primary research studies conducted to collect data were also confined to research centers in developed countries with limited samples. Research specifically focusing on the efficacy of hormonal treatment in luminal A breast cancer cases was still scarce, especially in Indonesia. The author suggested strengthening the breast cancer database in Indonesia to ensure more accurate results in future research and to provide a comprehensive overview of breast cancer cases in the country. Ongoing research was essential to continually improve treatment regimens to help maximize the benefits of therapy while minimizing side effects, ultimately enhancing the quality of life for breast cancer patients.

CONCLUSION

Breast cancer, particularly the luminal A subtype, was the most common type of breast cancer in Indonesia. Despite having a relatively favorable prognosis compared to other subtypes, optimal treatment for luminal A breast cancer was crucial to maximize the quality of life for survivors. Adjuvant endocrine or hormonal therapy had shown remarkable outcomes for luminal A breast cancer patients, with high survival rates and very low recurrence rates. However, ongoing research was still needed to further understand the development of future treatments and to extend the research on long-term survival rates.

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