Octogenarians’ Breast Cancer Is Associated with an Unfavorable Tumor Immune Microenvironment and Worse Disease-Free Survival

Maiko Okano 1,2,4,†, Masanori Oshi 1,3,†, Swagoto Mukhopadhyay 1, Qianya Qi 4, Li Yan 4, Itaru Endo 3, Toru Ohtake 2 and Kazuaki Takabe 1,2,3,5,6,7,*,†

1 Breast Surgery, Department of Surgical Oncology, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263, USA; omaiko@hospitdail.jp (M.O.); masanori.oshi@roswellpark.org (M.O.); swagoto.mukhopadhyay@roswellpark.org (S.M.)
2 Department of Breast Surgery, School of Medicine, Fukushima Medical University, Fukushima 960-1295, Japan; trcyin@fmu.ac.jp
3 Department of Gastroenterological Surgery, Graduate School of Medicine, Yokohama City University, Yokohama 236-0004, Japan; endoir@yokohama-cu.ac.jp
4 Department of Biostatistics & Bioinformatics, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263, USA; qianya.qi@roswellpark.org (Q.Q.); li.yan@roswellpark.org (L.Y.)
5 Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences, Niigata 951-8510, Japan
6 Department of Breast Surgery and Oncology, Tokyo Medical University, Tokyo 160-8402, Japan
7 Department of Surgery, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, Buffalo, NY 14263, USA

* Correspondence: kazuaki.takabe@roswellpark.org; Tel.: +1-716-845-55-540; Fax: +1-716-8451-668
† These authors contributed equally to this work.

Abstract: Elderly patients are known to have a worse prognosis for breast cancer. This is commonly blamed on their medical comorbidities and access to care. However, in addition to these social issues, we hypothesized that the extreme elderly (octogenarians—patients over 80 years old) have biologically worse cancer with unfavorable tumor immune microenvironment. The Cancer Genomic Atlas (TCGA) and the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) breast cancer cohorts were analyzed. The control (aged 40–65) and octogenarians numbered 668 and 53 in TCGA and 979 and 118 in METABRIC, respectively. Octogenarians had significantly worse breast cancer-specific survival in both cohorts (p < 0.01). Octogenarians had a higher ER-positive subtype rate than controls in both cohorts. Regarding PAM50 classification, luminal-A and -B subtypes were significantly higher in octogenarians, whereas basal and claudin-low subtypes were significantly lower (p < 0.05) in octogenarians. There was no difference in tumor mutation load, intratumor heterogeneity, or cytolytic activity by age. However, the octogenarian cohort was significantly associated with high infiltration of pro-cancer immune cells, M2 macrophage, and regulatory T cells in both cohorts (p < 0.05). Our results demonstrate that octogenarians’ breast cancer is associated with worse survival and with an unfavorable tumor immune microenvironment.

Keywords: breast cancer; elderly; octogenarian; GSEA; CIBERSORT; tumor microenvironment; macrophage; geriatric oncology
1. Introduction

The aging population is an increasingly central health and social issue in many developed countries—the health and quality of life of the elderly present unforeseen challenges to health systems. The risk of breast cancer increases with age, with approximately 20% of women diagnosed with breast cancer being over the age of 80 in the US [1]. Breast cancer screening and treatment have made remarkable progress in recent decades, and survival rates from breast cancer have improved remarkably throughout the world [2–4]. However, the outcomes in elderly breast cancer patients have not improved proportionally to the progress seen in younger patients [5]. There is speculation that octogenarians (patients greater than 80 years of age) may lack access to care or their comorbidities and frailty may prevent them from achieving similar progress.

Some reports indicate that, even when elderly patients have breast cancer with favorable characteristics, they suffer worse prognosis than younger patients [6]. Being aged 60 and older was demonstrated as an independent negative prognostic factor [6]. Furthermore, older age was associated with early mortality in the metastatic setting [7]. Conflictingly, some have reported that early-stage breast cancer in octogenarian women has similar breast cancer characteristics to younger women [8]. In fact, Muss et al. reported age is not an independent prognostic factor for outcomes [9]. Thus, it is difficult to conclude that medical comorbidities and worse access to care are primarily why elderly breast cancer has worse survival with such contradicting evidence. Further assessments for an underlying biological etiology are necessary to address the gap in age-based outcomes for breast cancer.

With advances in technology, it is now possible to study cancer biology utilizing comprehensive transcriptomes. Analysis using intrinsic subtype (e.g., luminal, basal-like, and HER-2 like) has become routine [10,11], and gene expression profiling is now common [12]. Furthermore, improved transcriptome and gene sequencing technologies have deepened our understanding of the tumor microenvironment [13–15]. Our group has recently elucidated the clinical relevance of stromal cells [16–20] and infiltrating immune cells [21–31] in the tumor microenvironment utilizing an in silico translational approach to multiple large patient cohorts. Using these various modalities, it has become clear that breast tumors differ at the DNA level depending on the age group [32].

This study hypothesized that the extreme elderly, octogenarians, have biologically worse cancers determined by the tumor immune microenvironment.

2. Materials and Methods

2.1. The Data of Breast Cancer Patient Cohorts

Two completely independent breast cancer cohorts, The Cancer Genome Atlas (TCGA) and the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC), were used in the current study. It is essential to analyze cohorts with a reasonable number of octogenarian breast cancer patients to obtain statistically meaningful results, and these were the largest cohorts that we had access to. TCGA is a joint collaboration project of the National Cancer Institute (NCI) and the National Human Genome Research Institute of the National Institute of Health that includes 1084 breast cancer patients [33]. The METABRIC cohort was collected from tumor banks in the UK and Canada and includes 2509 breast cancer patients [34]. Both cohorts consist of treatment naïve primary cancer samples with clinical profiles, survival data, and gene expression data. They are de-identified publicly available databases; thus, Institutional Review Board (IRB) approval was waived. Our group has used both of these databases previously to demonstrate and unravel the tumor biology of breast cancer [16–31,35–49].

2.2. Statistical Analysis

In order to compare the biology between elderly and the most common age breast cancer patients, this study defined the control group as patients aged 40–65 and octogenarians (age over 80) at the time of breast cancer diagnosis. We used the Kaplan–Meier method with log-rank testing. Both the TCGA and the METABRIC cohorts provide the information
on specifically breast cancer as the cause of death. To this end, the survival curve obtained from this information is Breast Cancer-Specific Survival (BCSS) following DATECAN guidelines [50]. Overall Survival (OS) indicates death by all causes. Fisher’s exact tests and one-way ANOVA tests were used to compare the differences between groups. In all analyses, p-values less than 0.05 were considered statistically significant. All statistical analyses were performed using Microsoft Excel 2010, R software (http://www.r-project.org/, accessed on 1 April 2019), and Bioconductor (http://bioconductor.org/, accessed on 1 April 2019).

2.3. Gene Set Enrichment Analysis (GSEA)

Gene Set Enrichment Analysis (GSEA) was conducted to investigate what biology is associated with octogenarians’ breast cancer compared to common age. GSEA was calculated by the Broad Institute software (http://software.broadinstitute.org/gsea/index.jsp, accessed on 1 April 2019) [51], as previously described [35,36]. As recommended by GSEA software, a False Positive Rate (FDR) of 0.25 was defined as statistically significant.

2.4. The Immune Cytolytic Activity (CYT) Score, the Mutant-Allele Tumor Heterogeneity (MATH), and CIBERSORT

To substantiate our hypothesis that octogenarians’ breast cancer has worse biology, the following three analyses were performed. The immune Cytolytic Activity (CYT) score is a new indicator of cancer immunity developed by Rooney et al. [13]. It is acquired by calculating mRNA expression levels of Granzyme A (GZMA) and Perforin (PRF1) in the tumor and used to predict the level of immune-mediated elimination associated with Cytotoxic T Cell (CTL) markers. We previously demonstrated that CYT score reflects immune cell antitumor activity and its clinical relevance in several articles [17,18,22,24,26–29,31,35–37,41,43,44,46–49,52–54].

Intratumor heterogeneity is the clonal variation between individual cancer cells within a patient’s tumor. It has recently drawn attention as an important underlying mechanism of therapeutic failure. Our group utilized Mutant Allele Tumor Heterogeneity (MATH) out of the multiple computational algorithms that assess intratumor heterogeneity based on the exome sequencing of tumors [14]. Our prior work assessed intratumor heterogeneity and demonstrated that it is associated with cancer biology and patient outcomes [30,36,37,41,42,55].

Recently, the tumor immune microenvironment has been found to plays an important role in cancer biology, and the profiling of the infiltrating immune cells is critical to assess the characteristics of a tumor [56]. CIBERSORT deconvolution algorithm was utilized by Newman et al. to estimate tumor-infiltrating immune cells in the tumor microenvironment using gene expression profiles [15]. The 22 cell fractions were calculated via their online calculator (https://cibersort.stanford.edu/, 1 April 2019). We have already illustrated that CIBERSORT analysis could provide the clinical significance and the prediction of outcomes in some cancers in several articles [21,27–31,35,36,41,48,52,57].

3. Results

3.1. Octogenarians Have a Significantly Higher Rate of Luminal Type Cancers Than the Control Group in Both Cohorts

We assessed the trend of luminal subtype breast cancers in our data to see if our cohorts followed the known tendency that breast cancer in the elderly has a higher ratio of luminal subtypes compared than younger patients. In total, 1081 patients with age information were available in TCGA and 1866 in METABRIC. These cohorts were separated into the control and the octogenarian groups, numbering 668 and 53 in TCGA and 979 and 118 in METABRIC, respectively. We examined clinical factors for each patient group and the distribution of breast cancer subtypes in octogenarians’ breast cancer (Table 1). The American Joint Committee on Cancer (AJCC) pathological stage, histology, and Nottingham grade had no statistical difference between the age groups in either of the cohorts. Estrogen Receptor (ER) expression determined by immunohistochemistry was significantly higher in the octogenarian group than in the control group in both the METABRIC and the TCGA cohorts. However, there was no difference in Progesterone Receptor (PR) expression between the age groups in either cohort (Figure 1). Assessment of the intrinsic subtypes
by gene expression showed that Luminal-A and -B subtypes were significantly higher, and basal and claudin-low subtypes were significantly lower in octogenarians in both cohorts, analogous to previous reports (Figure 1, both $p < 0.013$).

**Figure 1.** Expression rate of receptors and intrinsic subtype in TCGA and the METABRIC cohorts. (A) Comparison of the positive expression rate of receptors in the control group versus the octogenarian group. (B) Comparison of the PAM50 intrinsic subtypes by gene expression in the control group versus the octogenarian group. There was a statistically significant difference between the control group and the octogenarians.
Table 1. Clinical factors of each patient group.

| Variable          | TCGA Age Group | METABRIC Age Group |
|-------------------|----------------|-------------------|
|                    | Total Control (40, ≤ 60 years) | Octogenarian (>80 years) | p-Value | Total Control (40, ≤ 60 years) | Octogenarian (>80 years) | p-Value |
|                    | N % | N % | N % | | N % | N % | |
| pTMN stage        |     |     |     |     |     |     |     |
| I                 | 181 | 16.7| 108 | 16.2| 11  | 20.8| 0.113|
| II                | 611 | 56.5| 391 | 58.5| 22  | 41.5|      |
| III               | 246 | 22.8| 140 | 21  | 17  | 32.1|      |
| IV                | 19  | 1.8 | 14  | 2.1 | 1   | 1.9 |      |
| Unknown           | 24  | 2.2 | 15  | 2.2 | 2   | 3.8 |      |
| estrogen receptor |     |     |     |     |     |     |     |
| positive          | 794 | 73.5| 478 | 71.6| 45  | 84.9| 0.062|
| negative          | 237 | 21.9| 159 | 23.8| 7   | 13.2|      |
| Unknown           | 50  | 4.6 | 31  | 4.6 | 1   | 1.9 |      |
| progesterone receptor |       |       |       |       |       |       | 0.973|
| positive          | 688 | 63.6| 418 | 62.6| 34  | 64.2|      |
| negative          | 340 | 31.5| 219 | 32.8| 18  | 34  |      |
| Unknown           | 53  | 4.9 | 31  | 4.6 | 1   | 1.9 |      |
| HER2              |     |     |     |     |     |     | 0.649|
| positive          | 179 | 16.6| 109 | 16.3| 8   | 15.1|      |
| negative          | 762 | 70.5| 477 | 71.4| 42  | 79.2|      |
| Unknown           | 140 | 13  | 82  | 12.3| 3   | 5.7 |      |
| histology         |     |     |     |     |     |     | 0.195|
| infiltrating ductal | 771 | 71.3| 482 | 72.2| 34  | 64.2|      |
| infiltrating      | 203 | 18.8| 130 | 19.5| 13  | 24.5|      |
| lobular           | 107 | 9.9 | 56  | 8.4 | 6   | 11.3|      |
| histological grade | 450 | 41.6| 258 | 38.6| 20  | 37.7|      |
| pAM50 subtype     |     |     |     |     |     |     | 0.008|
| luminal A         | 303 | 28  | 179 | 26.8| 21  | 39.6| 0     |
| luminal B         | 244 | 22.6| 133 | 19.9| 16  | 30.2|      |
| HER2              | 144 | 13.3| 98  | 14.7| 6   | 11.3|      |
| basal-like        | 227 | 21  | 154 | 23.1| 12  | 22.6|      |
| normal-like       | 136 | 12.6| 88  | 13.2| 2   | 3.8 |      |
| Unknown           | 27  | 2.5 | 16  | 2.4 | 0   | 0   |      |
| race              |     |     |     |     |     |     | 0.626|
| white             | 745 | 68.9| 476 | 71.3| 33  | 62.3|      |
| black             | 180 | 16.7| 108 | 16.2| 6   | 11.3|      |
| other             | 156 | 14.4| 84  | 12.6| 14  | 26.4|      |
3.2. Octogenarians Have Worse Overall Survival and Higher Recurrence Rates in Two Independent Cohorts

By the very nature of aging, we could likely predict that octogenarians have worse OS compared to younger patients; however, to address our hypothesis, we assessed for any difference in Breast Cancer Specific Survival (BCSS) to reflect the aggressiveness of breast cancer in each age group. The ER-positive subtype was of particular interest since the octogenarians appeared to have that subtype more commonly.

Octogenarians demonstrated significantly worse BCSS overall and in ER-positive subtypes in both the TCGA and the METABRIC cohorts (Figure 2, all \( p < 0.015 \)). As expected, the OS Kaplan–Meier curve of the octogenarians was significantly worse than the control group in both the whole cohorts and ER-positive subtypes in TCGA (Figure 2, both \( p < 0.001 \)). These results show that octogenarians have worse outcomes from breast cancer than the control group, which could be due to worse biology or differences in management.

![Figure 2](image-url)

**Figure 2.** Survival analyses. (A) Kaplan–Meier survival curves for breast cancer specific survival (BCSS) and overall survival (OS) between the octogenarian group and the control group in the TCGA cohort. (B) Kaplan–Meier survival curves for BCSS between the octogenarian group and the control group in the METABRIC cohort.

3.3. There Is No Significant Difference in Tumor Mutation Load, Intratumor Heterogeneity, or Cytolytic Activity between the Age Groups

Given that octogenarians demonstrated poorer survival within the whole cohorts and in the ER-positive subtypes, we expected them to have worse cancer biology, which could be reflected in a higher mutation load, intratumor heterogeneity by Mutant Allele Tumor Heterogeneity (MATH), or Cytolytic Activity Score (CYT). Surprisingly, there was no difference between the age groups in mutation load, intratumor heterogeneity, or cytolytic activity (Figure 3).
3.4. The Octogenarian Group Was Not Associated with Any Gene Set Related to Cancer Aggressiveness by Gene Set Enrichment Analysis (GSEA) in Both the TCGA and the METABRIC Cohorts

GSEA of the Hallmark collection was conducted to investigate any specific pathways associated with octogenarians’ breast cancer. Unexpectedly, octogenarians’ breast cancer was not associated with any gene set associated with cancer aggressiveness, such as angiogenesis, epithelial–mesenchymal transition, KRAS signaling pathway, PI3K-AKT signaling pathway, MYC targets, or mitotic spindle in either the TCGA or the METABRIC cohort (Figure 4, showing only results for TCGA).
3.5. Octogenarians’ Tumors Had High Infiltration of Pro-Cancer Immune Cells M2 Macrophage and Regulatory T Cells While Having Lower Infiltration of Anti-Cancer Immune Cells M1 Macrophage and Activated Memory CD4 T Cells

Given the GSEA result that octogenarians did not enrich tumor aggressiveness pathways, we investigated the tumor immune microenvironment of octogenarians’ breast cancers to explain the poorer outcomes. We performed CIBERSORT analysis to estimate the immune cell composition infiltrating the tumors. We found that infiltration of pro-cancer immune cells, the M2 macrophage, was significantly higher in the octogenarian group across both the TCGA and the METABRIC cohorts (Figure 5, both \( p < 0.001 \)). Additionally, regulatory T cells, another pro-cancer immune cell, also highly infiltrated octogenarians’ breast cancers in TCGA. There was a similar trend in METABRIC (\( p = 0.023 \) and \( p = 0.054 \), respectively). Conversely, anti-cancer immune cells, M1 macrophages, and activated memory CD4 T cells both had lower infiltration in octogenarians in the METABRIC cohort (both \( p < 0.05 \)). Together with the survival outcomes, mutation data, and GSEA results, we concluded that octogenarians’ breast cancer was associated with worse survival than younger patients. Our findings suggest that this is because octogenarians’ breast cancers may not inherently have more aggressive cancer biology, but it may have a worse tumor immune microenvironment.

3.6. Analyses by Subtype

Given the fact that cancer biology differs significantly by subtype, survival, mutation load, intratumor heterogeneity, cytolytic activity, and immune cell infiltration were individually assessed by the subtype. As shown in Figure S1, octogenarians demonstrated significantly worse BCSS only in Luminal-A. Octogenarians showed no difference in mutational load, intratumor heterogeneity, or cytolytic activity in any of the subtypes except mutational load in Her2 subtype (Figure S2). No significant infiltration in any macrophages, CD4, CD8, or Regulatory T cells were seen in octogenarians in any subtypes (Figure S3).
4. Discussion

We found that the octogenarian cohort had more luminal type breast cancer, which is known to have a relatively good prognosis. However, their overall survival and, perhaps more importantly, their disease-free and disease-specific survival were worse than the younger control group. We found no difference in cancer cell biology, such as tumor mutation load, intratumor heterogeneity, cytolytic activity, and tumor aggravating pathways of cancer cells and stromal cells. However, we found that octogenarians’ breast cancer had a significantly higher infiltration of pro-cancer immune cells, M2 macrophage, and regulatory T cells and a lower infiltration of anti-cancer immune cells, M1 macrophage, and activated memory CD4 T cells compared to younger controls. We concluded that octogenarians’ breast cancer was associated with worse survival, possibly explained by an unfavorable tumor immune microenvironment but not necessarily with a more aggressive cancer cell biology.

M2 macrophages have anti-inflammatory properties and are found in the tumor development phase [58,59], promote angiogenesis in vivo [60], and correlate with poor prognosis in breast cancer [61,62]. Multiple studies show increased M2 macrophage infiltration in elderly patients’ bone marrow, lymph nodes, spleen, lung, and muscles [63–66]. M2 macrophages release cytokines and suppress cytotoxic lymphocytes through PD-L1 expression and recruitment of Tregs [67]. Our results align with previous reports that tumors with an increased presence of M2 macrophages have a poorer prognosis and that octogenarians have more M2 macrophages than younger patients. Furthermore, an increased number of Tregs is associated with immune deficiency in aged animals [68] and promotes tumor growth. Based upon our results, we speculate that the prognosis of octogenarians’ breast cancer is worse than breast cancer in the young not only because of inadequate access to care or increased medical comorbidities but also because of an unfavorable tumor immune microenvironment.

In clinical practice, octogenarians are more likely to receive nonstandard care or be undertreated [69–71] because of their medical comorbidities, frailty, concern for treatment toxicity, or social determinants of health. Often performance status and comorbidities rather than cancer biology dictate the management strategy in elderly patients [72]. About half of
early-stage breast cancer patients over 70 years old were reported to have sarcopenia [73]. Further, data on the effect and toxicity of newer drugs are often limited for elderly patients since patients over 70 years old are typically excluded from clinical trials [74]. Although the importance of comprehensively evaluating elderly patients before any treatment cannot be overemphasized, there is evidence that elderly patients tolerate and benefit from standard therapy [75]. However, the cited cohort includes elderly patients under 80 years old. For example, a surgical approach with hormone therapy also clearly improves survival in elderly breast cancer patients with early-stage hormone-receptor-positive disease compared to hormone therapy alone [76].

It should be noted that the elderly are more likely to have suboptimal adherence to hormone therapy, which can increase the risk of cancer recurrence [77,78]. Our findings show that the tumor microenvironment of the octogenarian is significantly different and worse than younger patients. Some studies report that patient immune profiles in elderly breast cancer patients are changed with chemotherapy, and these profiles can predict the clinical frailty of patients [79]. The need for such studies is paramount given the rapid aging of society with increasing longevity. In fact, a combined approach investigating appropriate therapies for elderly patients with breast cancer, along with standardized assessments of frailty and comorbidities, is in urgent need. This would allow for evidence-based treatment decisions founded upon a holistic assessment of the patient, including their tumor biology, treatment goals, life expectancy, and physical and mental condition.

This study is not free of limitations. The largest limitation is that, although we retrospectively demonstrated the association between octogenarians’ breast cancer and the infiltration of immune cells, the presented data do not show causality. Another limitation is that all the patients included in the TCGA and the METABRIC cohorts underwent surgical resection of their tumor in order to be included in these databases. To this end, breast cancer treated exclusively with endocrine therapy, which can be the case especially in older women, may have been excluded, resulting in a selection bias. In addition, some key clinical information that would have been helpful for this study, such as comorbidities or geriatric characteristics, were missing in these cohorts. In addition, it would have been ideal to group the patients by menopausal status; however, that information was lacking in both of the analyzed cohorts, and the sample size would be too small for meaningful analyses if we limited the control group to those aged 55–65. Menopause significantly changes the internal environment of women and causes various symptoms [80]. It is well known that menopause by itself has a major impact on breast cancer biology. Medication for hormone-sensitive breast cancer differs in premenopausal and postmenopausal patients [81]. It has also been reported that zoledronic acid has different therapeutic effects before and after menopause [82]. However, few studies have compared the cancer biology by the menstruation status instead of age. To this end, it would be interesting to investigate the difference among premenopausal, postmenopausal under 70 years old, and older patients, since we were unable to do this due to the lack of menstruation information in our cohorts. By comparing the biology of pre- and postmenopausal cancer at the genetic level and clarifying the characteristics of each, it could be possible to contribute to the prevention and treatment of breast cancer.

5. Conclusions

Our results demonstrate that octogenarians’ breast cancer is associated with an unfavorable tumor immune microenvironment that may explain its biologically worse behavior.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/cancers13122933/s1, Figure S1: Kaplan–Meier survival curves of breast cancer specific survival (BCSS) and overall survival (OS) analyses between the Octogenarian (red line) and the control group (blue line) by subtypes in TCGA cohort, Figure S2: Boxplots of comparison of the control group and the Octogenarians in mutation load, Intratumor heterogeneity (MATH score), and Cytolytic Activity Score (CYT) by the subtypes in TCGA cohort, Figure S3: Fraction of Macrophage (M0), M1, M2
activated memory CD4 T cell, CD8 T cell and Regulatory T cell in control group and Octogenarian by the subtypes in TCGA cohort.

Author Contributions: Conceptualization, M.O. (Maiko Okano) and K.T.; Methodology, M.O. (Maiko Okano) and K.T.; Formal Analysis, M.O. (Maiko Okano), M.O. (Masanori Oishi), and Q.Q.; Writing—Original Draft Preparation, M.O. (Maiko Okano); Writing—Review and Editing, S.M. and K.T.; Supervision, I.E., T.O., L.Y., and K.T.; and Project Administration, K.T. All authors have read and agreed to the published version of the manuscript.

Funding: K.T. is supported by US NCI/NIH grant R01CA160688, R01CA250412, R37CA248018, as well as Department of Defense—BCRP grant W81XWH-19-1-0674. Roswell Park Comprehensive Cancer Center is supported by NCI/NIH grant P30-CA016056.

Data Availability Statement: All data were from previous studies.

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Society, A.C. Breast Cancer Facts & Figures 2017–2018. Available online: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf (accessed on 10 April 2021).
2. Berry, D.A.; Cronin, K.A.; Plevritis, S.K.; Fryback, D.G.; Clarke, L.; Zelen, M.; Mandelblatt, J.S.; Yakovlev, A.Y.; Habbema, J.D.; Feuer, E.J. Effect of screening and adjuvant therapy on mortality from breast cancer. N. Engl. J. Med. 2005, 353, 1784–1792. [CrossRef]
3. Allemani, C.; Weir, H.K.; Carreira, H.; Harewood, R.; Spika, D.; Wang, X.S.; Bannon, F.; Ahn, J.V.; Johnson, C.J.; Bonaventure, A.; et al. Global surveillance of cancer survival 1995–2009: Analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet 2015, 385, 977–1010. [CrossRef]
4. Cossetti, R.J.; Tyldesley, S.K.; Speers, C.H.; Zheng, Y.; Gelmon, K.A. Comparison of breast cancer recurrence and outcome patterns between patients treated from 1986 to 1992 and from 2004 to 2008. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2015, 33, 65–73. [CrossRef] [PubMed]
5. Smith, B.D.; Jiang, J.; McLaughlin, S.S.; Hurria, A.; Smith, G.L.; Giordano, S.H.; Buchholz, T.A. Improvement in breast cancer outcomes over time: Are older women missing out? J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2011, 29, 4647–4653. [CrossRef]
6. Chen, H.L.; Zhou, M.Q.; Tian, W.; Meng, K.X.; He, H.F. Effect of Age on Breast Cancer Patient Prognoses: A Population-Based Study Using the SEER 18 Database. PLoS ONE 2016, 11, e0165409. [CrossRef] [PubMed]
7. Vaz-Luis, I.; Lin, N.U.; Keating, N.L.; Barry, W.T.; Winer, E.P.; Freedman, R.A. Factors Associated with Early Mortality Among Patients with De Novo Metastatic Breast Cancer: A Population-Based Study. Oncologist 2017, 22, 386–393. [CrossRef]
8. Schonberg, M.A.; Marcantonio, E.R.; Li, D.; Silliman, R.A.; Ngo, L.; McCarthy, E.P. Breast cancer among the oldest old: Tumor characteristics, treatment choices, and survival. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2010, 28, 2038–2045. [CrossRef]
9. Jenkins, E.O.; Deal, A.M.; Anders, C.K.; Prat, A.; Perou, C.M.; Carey, L.A.; Muss, H.B. Age-specific changes in intrinsic breast cancer subtypes: A focus on older women. Oncologist 2014, 19, 1076–1083. [CrossRef]
10. Morrison, D.H.; Rahardja, D.; King, E.; Peng, Y.; Sarode, V.R. Tumour biomarker expression relative to age and molecular subtypes of invasive breast cancer. Br. J. Cancer 2012, 107, 382–387. [CrossRef] [PubMed]
11. Azim, H.A., Jr; Partridge, A.H. Biology of breast cancer in young women. Breast Cancer Res. 2014, 16, 427. [CrossRef]
12. Azim, H.A., Jr; Michiels, S.; Bedard, P.L.; Singhal, S.K.; Crisciuttiolo, C.; Ignatiadis, M.; Haibe-Kains, B.; Piccart, M.J.; Sotiriou, C.; Loi, S. Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 2012, 18, 1341–1351. [CrossRef]
13. Rooney, M.S.; Shukla, S.A.; Wu, C.J.; Getz, G.; Hacohen, N. Molecular and genetic properties of tumors associated with local immune cytolytic activity. Cell 2015, 160, 48–61. [CrossRef]
14. Mroz, E.A.; Rocco, J.W. MATH, a novel measure of intratumor genetic heterogeneity, is high in poor-outcome classes of head and neck squamous cell carcinoma. Oral Oncol. 2013, 49, 211–215. [CrossRef] [PubMed]
15. Newman, A.M.; Liu, C.L.; Green, M.R.; Gentles, A.J.; Feng, W.; Xu, Y.; Hoang, C.D.; Diehn, M.; Alizadeh, A.A. Robust enumeration of cell subsets from tissue expression profiles. Nat. Methods 2015, 12, 453–457. [CrossRef] [PubMed]
16. Katsuta, E.; Rashid, O.M.; Takabe, K. Clinical relevance of tumor microenvironment: Immune cells, vessels, and mouse models. Hum. Cell 2020, 33, 930–937. [CrossRef] [PubMed]
17. Oshi, M.; Huyser, M.R.; Le, L.; Tokumaru, Y.; Yan, L.; Matsuyama, R.; Endo, I.; Takabe, K. Abundance of Microvascular Endothelial Cells Is Associated with Response to Chemotherapy and Prognosis in Colorectal Cancer. Cancers 2021, 13, 1477. [CrossRef] [PubMed]
18. Oshi, M.; Newman, S.; Tokumaru, Y.; Yan, L.; Matsuyama, R.; Endo, I.; Nagahashi, M.; Takabe, K. Intra-Tumoral Angiogenesis Is Associated with Inflammation, Immune Reaction and Metastatic Recurrence in Breast Cancer. Int. J. Mol. Sci. 2020, 21, 6708. [CrossRef] [PubMed]
19. Tokumaru, Y.; Oshi, M.; Katsuta, E.; Yan, L.; Huang, J.L.; Nagahashi, M.; Matsuhashi, N.; Futamura, M.; Yoshida, K.; Takabe, K. Intratumoral Adipocyte-High Breast Cancer Enrich for Metastatic and Inflammation-Related Pathways but Associated with Less Cancer Cell Proliferation. *Int. J. Mol. Sci.* 2020, 21, 5744. [CrossRef]

20. Katsuta, E.; Rashid, O.M.; Takabe, K. Fibroblasts as a Biological Marker for Curative Resection in Pancreatic Ductal Adenocarcinoma. *Int. J. Mol. Sci.* 2020, 21, 3880. [CrossRef]

21. Le, L.; Tokumaru, Y.; Oshi, M.; Asaoka, M.; Yan, L.; Endo, I.; Ishikawa, T.; Futamura, M.; Yoshida, K.; Takabe, K. Th2 cell infiltrations predict neoadjuvant chemotherapy response of estrogen receptor-positive breast cancer. *Gland Surg.* 2021, 10, 154–165. [CrossRef]

22. Oshi, M.; Newman, S.; Tokumaru, Y.; Yan, L.; Matsuyama, R.; Kalinski, P.; Endo, I.; Takabe, K. Plasmacytoid Dendritic Cell (pDC) Infiltration Correlate with Tumor Infiltrating Lymphocytes, Cancer Immunity, and Better Survival in Triple Negative Breast Cancer (TNBC) More Strongly than Conventional Dendritic Cell (cDC). *Cancers* 2020, 12, 3342. [CrossRef]

23. Oshi, M.; Asaoka, M.; Tokumaru, Y.; Angarita, F.A.; Yan, L.; Matsuyama, R.; Zsirós, E.; Ishikawa, T.; Endo, I.; Takabe, K. Abundance of Regulatory T Cell (Treg) as a Predictive Biomarker for Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer. *Cancers* 2020, 12, 3038. [CrossRef] [PubMed]

24. Takeshita, T.; Torigoe, T.; Yan, L.; Huang, J.L.; Yamashita, H.; Takabe, K. The Impact of Immunofunctional Phenotyping on the Malfunction of the Cancer Immunity Cycle in Breast Cancer. *Cancers* 2020, 13, 110. [CrossRef] [PubMed]

25. Oshi, M.; Tokumaru, Y.; Asaoka, M.; Yan, L.; Satyananda, V.; Matsuyama, R.; Matsuhashi, N.; Futamura, M.; Ishikawa, T.; Yoshida, K.; et al. M1 Macrophage and M1/M2 ratio defined by transcriptional signatures resemble only part of their conventional clinical characteristics in breast cancer. *Sci. Rep.* 2020, 10, 16554. [CrossRef] [PubMed]

26. Oshi, M.; Asaoka, M.; Tokumaru, Y.; Yan, L.; Matsuyama, R.; Ishikawa, T.; Endo, I.; Takabe, K. CD8 T Cell Score as a Prognostic Biomarker for Triple Negative Breast Cancer. *Int. J. Mol. Sci.* 2020, 21, 6968. [CrossRef] [PubMed]

27. Chouliaras, K.; Tokumaru, Y.; Asaoka, M.; Oshi, M.; Attwood, K.M.; Yoshida, K.; Ishikawa, T.; Takabe, K. Prevalence and clinical relevance of tumor-associated tissue eosinophilia (TATE) in breast cancer. *Surgery* 2020, 169, 1234–1239. [CrossRef]

28. Gandhi, S.; Elkhanany, A.; Oshi, M.; Dai, T.; Opyrchal, M.; Mohammadpour, H.; Repasky, E.A.; Takabe, K. Contribution of Immune Cells to Glucocorticoid Receptor Expression in Breast Cancer. *Int. J. Mol. Sci.* 2020, 21, 4635. [CrossRef]

29. Takehashi, H.; Kawaguchi, T.; Yan, L.; Peng, X.; Qi, Q.; Morris, L.G.T.; Chan, T.A.; Tsung, A.; Otsuji, E.; Takabe, K. Immune Cytotylic Activity for Comprehensive Understanding of Immune Landscape in Hepatocellular Carcinoma. *Cancers* 2020, 12, 1221. [CrossRef]

30. Narayanan, S.; Kawaguchi, T.; Peng, X.; Qi, Q.; Liu, S.; Yan, L.; Takabe, K. Tumor Infiltrating Lymphocytes and Macrophages Improve Survival in Microsatellite Unstable Colorectal Cancer. *Sci. Rep.* 2019, 9, 13455. [CrossRef]

31. Narayanan, S.; Kawaguchi, T.; Yan, L.; Peng, X.; Qi, Q.; Takabe, K. Cytolytic Activity Score to Assess Anticancer Immunity in Colorectal Cancer. *Ann. Surg. Oncol.* 2018, 25, 2323–2331. [CrossRef]

32. Azim, H.A., Jr.; Nguyen, B.; Brohié, S.; Zoppoli, G.; Sotiriou, C. Genomic aberrations in young and elderly breast cancer patients. *BMC Med.* 2015, 13, 266. [CrossRef]

33. Hoadley, K.A.; Yau, C.; Hinoue, T.; Wolf, D.M.; Lazar, A.J.; Drill, E.; Shen, R.; Taylor, A.M.; Cherniack, A.D.; Thorsson, V.; et al. Cell-of-Origin Patterns Dominate the Molecular Classification of 10,000 Tumors from 33 Types of Cancer. *Cell* 2018, 173, 291–304. [CrossRef]

34. Curtis, C.; Shah, S.P.; Chin, S.F.; Turashvili, G.; Rueda, O.M.; Dunning, M.J.; Speed, D.; Lynch, A.G.; Samarakoju, S.; Yuan, Y.; et al. The genomic and transcriptomic architecture of 2000 breast tumours reveals novel subgroups. *Nature* 2012, 486, 346–352. [CrossRef] [PubMed]

35. Okano, M.; Oshi, M.; Butash, A.L.; Asaoka, M.; Katsuta, E.; Peng, X.; Qi, Q.; Yan, L.; Takabe, K. Estrogen Receptor Positive Breast Cancer with High Expression of Androgen Receptor has Less Cytolytic Activity and Worse Response to Neoadjuvant Chemotherapy but Better Survival. *Int. J. Mol. Sci.* 2019, 20, 2655. [CrossRef] [PubMed]

36. Okano, M.; Oshi, M.; Butash, A.L.; Katsuta, E.; Tachibana, K.; Saito, K.; Okayama, H.; Peng, X.; Yan, L.; Kono, K.; et al. Triple-Negative Breast Cancer with High Levels of Annexin A1 Expression Is Associated with Mast Cell Infiltration, Inflammation, and Angiogenesis. *Int. J. Mol. Sci.* 2019, 21, 4197. [CrossRef] [PubMed]

37. Asaoka, M.; Patnaik, S.K.; Zhang, F.; Ishikawa, T.; Takabe, K. Lymphovascular invasion in breast cancer is associated with gene expression signatures of cell proliferation but not lymphangiogenesis or immune response. *Breast Cancer Res. Treat.* 2020, 181, 309–322. [CrossRef] [PubMed]

38. Katsuta, E.; Qi, Q.; Peng, X.; Hochwald, S.N.; Yan, L.; Takabe, K. Pancreatic adenocarcinomas with mature blood vessels have better overall survival. *Sci. Rep.* 2019, 9, 1310. [CrossRef]

39. Kawaguchi, T.; Yan, L.; Qi, Q.; Peng, X.; Edge, S.B.; Young, J.; Yao, S.; Liu, S.; Otsuji, E.; Takabe, K. Novel MicroRNA-Based Risk Score Identified by Integrated Analyses to Predict Metastasis and Poor Prognosis in Breast Cancer. *Ann. Surg. Oncol.* 2018, 25, 4037–4046. [CrossRef]

40. Kawaguchi, T.; Yan, L.; Qi, Q.; Peng, X.; Gabriel, E.M.; Young, J.; Liu, S.; Takabe, K. Overexpression of suppressive microRNAs, miR-30a and miR-200c are associated with improved survival of breast cancer patients. *Sci. Rep.* 2017, 7, 15945. [CrossRef] [PubMed]

41. McDonald, K.A.; Kawaguchi, T.; Qi, Q.; Peng, X.; Asaoka, M.; Young, J.; Opyrchal, M.; Yan, L.; Patnaik, S.; Otsuji, E.; et al. Tumor Heterogeneity Correlates with Less Immune Response and Worse Survival in Breast Cancer Patients. *Ann. Surg. Oncol.* 2019, 26, 2191–2199. [CrossRef] [PubMed]
42. Oshi, M.; Kim, T.H.; Tokumaru, Y.; Yan, L.; Matsuyma, R.; Endo, I.; Cherkassky, L.; Takabe, K. Enhanced DNA Repair Pathway is Associated with Cell Proliferation and Worse Survival in Hepatocellular Carcinoma (HCC). *Cancers* 2021, 13, 323. [CrossRef]

43. Oshi, M.; Tokumaru, Y.; Angarita, F.A.; Yan, L.; Matsuyma, R.; Endo, I.; Takabe, K. Degree of Early Estrogen Response Predict Survival after Endocrine Therapy in Primary and Metastatic ER-Positive Breast Cancer. *Cancers* 2020, 12, 3557. [CrossRef]

44. Oshi, M.; Tokumaru, Y.; Patel, A.; Yan, L.; Matsuyma, R.; Endo, I.; Katz, M.H.G.; Takabe, K. A Novel Four-Gene Score to Predict Pathologically Complete (R0) Resection and Survival in Pancreatic Cancer. *Cancers* 2020, 12, 5635. [CrossRef]

45. Takahashi, H.; Katsuta, E.; Yan, L.; Dasgupta, S.; Takabe, K. High expression of Annexin A2 is associated with DNA repair, metabolic alteration, and worse survival in pancreatic ductal adenocarcinoma. *Surgery* 2019, 166, 150–156. [CrossRef] [PubMed]

46. Takahashi, H.; Asaoka, M.; Yan, L.; Rashid, O.M.; Oshi, M.; Ishikawa, T.; Nagahashi, M.; Takabe, K. Biologically Aggressive Phenotype and Anti-cancer Immunity Counterbalance in Breast Cancer with High Mutation Rate. *Sci. Rep.* 2020, 10, 1852. [CrossRef]

47. Takeshita, T.; Asaoka, M.; Katsuta, E.; Photiadis, S.J.; Narayanan, S.; Yan, L.; Takabe, K. High expression of polo-like kinase 1 is associated with TP53 inactivation, DNA repair deficiency, and worse prognosis in ER positive Her2 negative breast cancer. *Am. J. Transl. Res.* 2019, 11, 6507–6521.

48. Takeshita, T.; Yan, L.; Asaoka, M.; Rashid, O.; Takabe, K. Late recurrence of breast cancer is associated with pro-cancerous immune microenvironment in the primary tumor. *Sci. Rep.* 2019, 9, 16942. [CrossRef] [PubMed]

49. Tokumaru, Y.; Oshi, M.; Katsuta, E.; Yan, L.; Satyananda, V.; Matsuhashi, N.; Futamura, M.; Akao, Y.; Yoshida, K.; Takabe, K. KRAS signaling enriched triple negative breast cancer is associated with favorable tumor immune microenvironment and better survival. *Am. J. Cancer Res.* 2020, 10, 897–907.

50. Gourgou-Bourgade, S.; Cameron, D.; Poortmans, P.; Asselain, B.; Azria, D.; Cardoso, F.; A’Hern, R.; Bliss, J.; Bogaerts, J.; Bonnefoi, H.; et al. Guidelines for time-to-event end point definitions in breast cancer trials: Results of the DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials). *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* 2015, 26, 873–879. [CrossRef]

51. Subramanian, A.; Tamayo, P.; Mootha, V.K.; Mukherjee, S.; Ebert, B.L.; Gillette, M.A.; Paulovich, A.; Pomeroy, S.L.; Golub, T.R.; Globus, T.R.; Lander, E.S.; et al. Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression profiles. *Proc. Natl. Acad. Sci. USA* 2005, 102, 15545–15550. [CrossRef] [PubMed]

52. Takahashi, H.; Oshi, M.; Asaoka, M.; Yan, L.; Endo, I.; Takabe, K. Molecular Biological Features of Nottingham Histological Grade 3 Breast Cancers. *Ann. Surg. Oncol.* 2020, 27, 4475–4485. [CrossRef]

53. Asaoka, M.; Ishikawa, T.; Takabe, K.; Patnaik, S.K. APOBEC3-Mediated RNA Editing in Breast Cancer is Associated with Heightened Immune Activity and Improved Survival. *Int. J. Mol. Sci.* 2019, 20, 5621. [CrossRef]

54. Katsuta, E.; Maawy, A.A.; Yan, L.; Takabe, K. High expression of bone morphogenetic protein (BMP) 6 and BMP7 are associated with higher immune cell infiltration and better survival in estrogen receptor-positive breast cancer. *Oncol. Rep.* 2019, 42, 1413–1421. [CrossRef]

55. Satyananda, V.; Oshi, M.; Endo, I.; Takabe, K. High BRCA2 Gene Expression is Associated with Aggressive and Highly Proliferative Breast Cancer. *Ann. Surg. Oncol.* 2021, 1–10. [CrossRef]

56. Zhang, Y.; Zhang, Z. The history and advances in cancer immunotherapy: Understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. *Cell. Mol. Immunol.* 2020, 17, 807–821. [CrossRef]

57. Tokumaru, Y.; Oshi, M.; Patel, A.; Tan, W.; Yan, L.; Matsuhashi, N.; Futamura, M.; Yoshida, K.; Takabe, K. Organoids Are Limited in Modeling the Colon Adenoma-Carcinoma Sequence. *Cells* 2021, 10, 488. [CrossRef] [PubMed]

58. Ohmori, Y.; Hamilton, T.A. IL-4-induced STAT6 suppresses IFN-gamma-stimulated STAT1-dependent transcription in mouse macrophages. *J. Immunol.* 1997, 159, 5474–5482. [PubMed]

59. Satoh, T.; Takeuchi, O.; Vandenbon, A.; Yasuda, K.; Tanaka, Y.; Kumaigai, Y.; Miyake, T.; Matsuhashi, K.; Okazaki, T.; Saiioh, T.; et al. The JmjD3-If4 axis regulates M2 macrophage polarization and host responses against helminth infection. *Nat. Immunol.* 2010, 11, 936–944. [CrossRef]

60. Jetten, N.; Verbruggen, S.; Gijbels, M.J.; Post, M.J.; De Winther, M.P.; Donners, M.M. Anti-inflammatory M1 macrophages promote angiogenesis in vivo. *Angiogenesis* 2014, 17, 109–118. [CrossRef]

61. Leek, R.D.; Lewis, C.E.; Whitehouse, R.; Greenall, M.; Clarke, J.; Harris, A.L. Association of macrophage infiltration with angiogenesis and prognosis in invasive breast carcinoma. *Cancer Res.* 1996, 56, 4625–4629.

62. Lin, E.Y.; Li, J.F.; Gnatovskiy, L.; Deng, Y.; Zhu, L.; Grzesik, D.A.; Qian, H.; Xue, X.N.; Pollard, J.W. Macrophages regulate the inflammatory response after lipopolysaccharide exposure. *Crit. Care Med.* 2007, 35, 246–251. [CrossRef] [PubMed]

63. Gomez, C.R.; Hirano, S.; Cuto, B.T.; Birjandi, S.; Baila, H.; Nomellini, V.; Kovacs, E.J. Advanced age exacerbates the pulmonary inflammatory response after lipopolysaccharide exposure. *Ageing Cell* 2013, 12, 345–357. [CrossRef]

64. Jackaman, C.; Dye, D.E.; Nelson, D.J. IL-2/CD40-activated macrophages rescue age and tumor-induced T cell dysfunction in elderly mice. *Aging Cell* 2014, 36, 9655. [CrossRef] [PubMed]

65. Wang, Y.; Wehling-Henricks, M.; Samengo, G.; Tidball, J.G. Increases of M2a macrophages and fibrosis in aging muscle are influenced by bone marrow aging and negatively regulated by muscle-derived nitric oxide. *Aging Cell* 2015, 14, 678–688. [CrossRef]
67. Kitamura, T.; Qian, B.Z.; Pollard, J.W. Immune cell promotion of metastasis. Nat. Rev. Immunol. 2015, 15, 73–86. [CrossRef]
68. Sharma, S.; Dominguez, A.L.; Lustgarten, J. High accumulation of T regulatory cells prevents the activation of immune responses in aged animals. J. Immunol. 2006, 177, 8348–8355. [CrossRef]
69. Griggs, J.J.; Kulakova, E.; Sorbero, M.E.; Poniewierski, M.S.; Wolff, D.A.; Crawford, J.; Dale, D.C.; Lyman, G.H. Social and racial differences in selection of breast cancer adjuvant chemotherapy regimens. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2007, 25, 2522–2527. [CrossRef] [PubMed]
70. Field, K.M.; Kosmider, S.; Jefford, M.; Michael, M.; Jennens, R.; Green, M.; Gibbs, P. Chemotherapy dosing strategies in the obese, elderly, and thin patient: Results of a nationwide survey. J. Oncol. Pract. 2008, 4, 108–113. [CrossRef]
71. Vaz-Luis, I.; Keating, N.L.; Lin, N.U.; Lii, H.; Winer, E.P.; Freedman, R.A. Duration and toxicity of adjuvant trastuzumab in older patients with early-stage breast cancer: A population-based study. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2014, 32, 927–934. [CrossRef]
72. Di Capua, B.; Bellieni, A.; Fusco, D.; Gambacorta, M.A.; Tagliaferri, L.; Villani, E.R.; Bernabei, R.; Valentinii, V.; Colloca, G.F. Perspectives and limits of cancer treatment in an oldest old population. Aging Clin. Exp. Res. 2021, 1–7. [CrossRef]
73. Bellieni, A.; Fusco, D.; Sanchez, A.M.; Franceschini, G.; Di Capua, B.; Allocca, E.; Di Stasio, E.; Marazzi, F.; Tagliaferri, L.; Masetti, R.; et al. Different Impact of Definitions of Sarcopenia in Defining Frailty Status in a Population of Older Women with Early Breast Cancer. J. Pers. Med. 2021, 11, 243. [CrossRef]
74. Hurria, A.; Dale, W.; Mooney, M.; Rowland, J.H.; Ballman, K.V.; Cohen, H.J.; Muss, H.B.; Schilsky, R.L.; Ferrell, B.; Extermann, M.; et al. Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2014, 32, 2587–2594. [CrossRef] [PubMed]
75. Muss, H.B.; Berry, D.A.; Cirrincione, C.T.; Theodoulou, M.; Mauer, A.M.; Kornblith, A.B.; Partridge, A.H.; Dressler, L.G.; Cohen, H.J.; Becker, H.P.; et al. Adjuvant chemotherapy in older women with early-stage breast cancer. N. Engl. J. Med. 2009, 360, 2055–2065. [CrossRef] [PubMed]
76. Nayyar, A.; Strassle, P.D.; Iles, K.; Jameison, D.; Jadi, J.; McGuire, K.P.; Gallagher, K.K. Survival Outcomes of Early-Stage Hormone Receptor-Positive Breast Cancer in Elderly Women. Ann. Surg. Oncol. 2020, 27, 4853–4860. [CrossRef]
77. Riley, G.F.; Warren, J.L.; Harlan, L.C.; Smith, E.C.; Blackwell, S.A. Endocrine therapy use among elderly hormone receptor-positive breast cancer patients enrolled in Medicare Part D. Medicare Medicaid Res. Rev. 2011, 1. [CrossRef]
78. Biggers, A.; Shi, Y.; Charlson, J.; Smith, E.C.; Smallwood, A.J.; Nattinger, A.B.; Laud, P.W.; Neuner, J.M. Medicare D Subsidies and Racial Disparities in Persistence and Adherence with Hormonal Therapy. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2016, 34, 4398–4404. [CrossRef]
79. Bailur, J.K.; Pawelec, G.; Hatse, S.; Brouwers, B.; Smeets, A.; Neven, P.; Laenen, A.; Wildiers, H.; Shipp, C. Immune profiles of elderly breast cancer patients are altered by chemotherapy and relate to clinical frailty. Breast Cancer Res. 2017, 19, 20. [CrossRef]
80. Nappi, R.E.; Kroll, R.; Siddiqui, E.; Stoykova, B.; Rea, C.; Gemmen, E.; Schultz, N.M. Global cross-sectional survey of women with vasomotor symptoms associated with menopause: Prevalence and quality of life burden. Menopause 2021. [CrossRef]
81. Gradishar, W.J.; Moran, M.S.; Abraham, J.; Aft, R.; Agnese, D.; Allison, K.H.; Blair, S.L.; Burstein, H.J.; Dang, C.; Elias, A.D.; et al. NCCN Guidelines® Insights: Breast Cancer, Version 4.2021. J. Natl. Compr. Cancer Netw. 2021, 19, 484–493. [CrossRef] [PubMed]
82. George, C.N.; Canuas-Landro, V.; Theodoulou, E.; Muthana, M.; Wilson, C.; Ottewell, P. Oestrogen and zoledronic acid driven changes to the bone and immune environments: Potential mechanisms underlying the differential anti-tumour effects of zoledronic acid in pre- and post-menopausal conditions. J. Bone Oncol. 2020, 25, 100317. [CrossRef] [PubMed]