Refusal of medical treatment by older adults with cancer: a systematic review

Laiane Moraes Dias[1,2], Mirella Rebello Bezerra[1,3], Williams Fernandes Barra[2], Francisca Rego[1]

[1]Faculty of Medicine of the University of Porto, Porto, Portugal; [2]João de Barros Barreto University Hospital, Federal University of Pará, Belém-Pará, Brazil; [3]IMIP, Instituto de Medicina Integral Professor Fernando Figueira, Recife, Brazil

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Correspondence to: Laiane Moraes Dias. Dom Romualdo de Seixas, 1476, Room 2207, 66055-200, Belém-Pará, Brazil. Email: laianemoraes@hotmail.com.

Abstract: The literature about the factors associated with cancer treatment refusal, especially by the older patients is scarce. Therefore, this study aimed to identify predictive factors associated with treatment refusal by older patients with cancer. A systematic review was conducted using three databases, Medline, Web of Science, and Scopus with the key concepts, "refusal treatment" and "cancer" and "decision making" and "elderly" or "aged". The search took place in July 2020 and it included articles published in the last 5 years. Of the 211 articles found, 22 were included in the review. Most studies have focused on head and neck and breast cancer treatment decisions and used a quantitative design. The majority of studies evaluated refusal of surgery interventions. Important factors associated with refusal cancer treatment include gender, marital status, race, having government insurance, advanced cancer, poor performance status (cancer stage III or IV) and Charlson Comorbidity Index ≥2. Thus, there are socio-demographic and clinical variables associated with treatment refusal. More studies with the elderly are needed. Understanding these factors may be useful to recognize situations where active education and support can help elderly patients accept optimal care.

Keywords: Cancer; elderly; decision-making; treatment refusal

Introduction

Cancer is a global health problem of great magnitude, particularly in older patients. A considerable number of older adults are diagnosed with this disease. For older adults, an increase of 67% in cancer incidence is anticipated, compared with younger adults (11% increase). Also, 60% of the mortality cases due to cancer are estimated to occur in people aged 70 and older (1-3).

To date, the perspective of older patients with cancer regarding oncology treatment is an unexplored field. A review about decision-making on cancer treatment showed that research is still poor regarding treatment decision in older adults (4). Refusal therapy and underuse of treatment are more common in older adults, and they are associated with worst outcomes such as higher rates of cancer recurrence and worst survival, even knowing that cancer-directed treatments have evolved and that more "elderly-friendly" treatments have been developed (3). Furthermore, the heterogeneity of this population's health and functional status may interfere in treatment preferences and must be taken into account (3-5).

Many studies have explored the actual role in the decision-making process; however, most were conducted years ago and with a relatively young population. With advances in cancer treatment and more available options for the elderly population, older adults may have different views than those included in previous studies (5).

One of the principles of good care is respect and receptivity to patients' wishes and values; thus, it is

important to understand patients' perspectives about cancer treatment. Most studies have focused on the decision-making processes related to the choice between cancer-directed therapies and palliative care (5,6). However, little is known about the factors associated with treatment refusal in oncology. Some preliminary data suggest that therapeutic refusal is partially based on balancing the pros and cons of treatment (6).

Thus, the aim of this review was to identify the factors associated with treatment refusal by older adults with cancer. We expect that this systematic review provides knowledge regarding the clinical and sociodemographic characteristics associated with therapeutic refusal in this population.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-20-2439).

Methods

Search strategy

We conducted a systematic review starting with the search in three databases in July 2020, namely Medline (PubMed), Web of Knowledge (ISI) and Scopus, using the key concepts: "refusal treatment" and "cancer treatment" and "decision making" and "elderly" or "aged".

Inclusion criteria

Studies that included the factors or reasons for refusing cancer therapy in the elderly (65 years or older), not necessarily exclusively to the elderly as long as there are reported results on a subgroup analysis of older adults. We consider 'therapeutic refusal' any cancer treatment, such as surgery, chemotherapy, radiotherapy, as well as curative or palliative treatment.

We included studies written in English, French, Portuguese and Spanish languages. Empirical articles, quantitative and qualitative studies were also included. Given that a similar review was conducted in 2015, we considered studies from 2015 until July 2020 for updated scientific and research developments in this area.

Exclusion criteria

Editorials, letters to the editor, reviews, comments and narrative case reports were excluded. Studies on other

related topics, such as transition of care and no indication of active treatment for advanced disease, were also excluded. We considered only those studied related to a patient's refusal of therapy.

Quality assessment of studies and data extraction

Study quality and eligibility were individually assessed by the two researchers (LD, MRB). The extraction of data was done manually without extraction software. There was a critical review of the results by the researchers (LD, MRB) and coordinators (WFB, FR). In case of different opinions regarding articles' relevance, a consensus was reached by the authors. Data systematization was evaluated by the periodical (title, volume, number and year), study location country, objectives (article or search), method (type of research, sample, participants), results, and mention of treatment refusal. Final assessment of the quality and level of evidence and the recommendation force of the articles, when absent in the original articles, were conducted by the authors, according to the criteria of the Strength of Recommendation Taxonomy scale by the American Family Physician (7) (Table S1).

Results

Through the search strategy, 221 studies were initially identified: 67 in PubMed, 58 in ISI, and 87 in Scopus. Ten studies were found in other databases because they were found in the articles' references and met the eligibility criteria for this study.

The PRISMA (Preferred Reporting Items For Systematic Reviews and Meta-Analyses) flow diagram ame (8) is shown in *Figure 1*. Screening covered the stages of analysis by titles and summary. Based on the title and abstract, 139 articles (screening) were excluded. In addition, 45 duplicate articles were excluded. A total of 37 full-text articles were analyzed, of which 14 were excluded as they did not respect the study criteria. A total of 22 articles met the inclusion criteria and were included in this review (*Table 1*).

Characteristics of the studies and quality assessment

The included studies' characteristics are shown in *Table 1* and information about the quality assessment is described in Table S1. Nineteen studies used a retrospective, cross-sectional analytical design, and at least thirteen had controlled data and were compared with a case
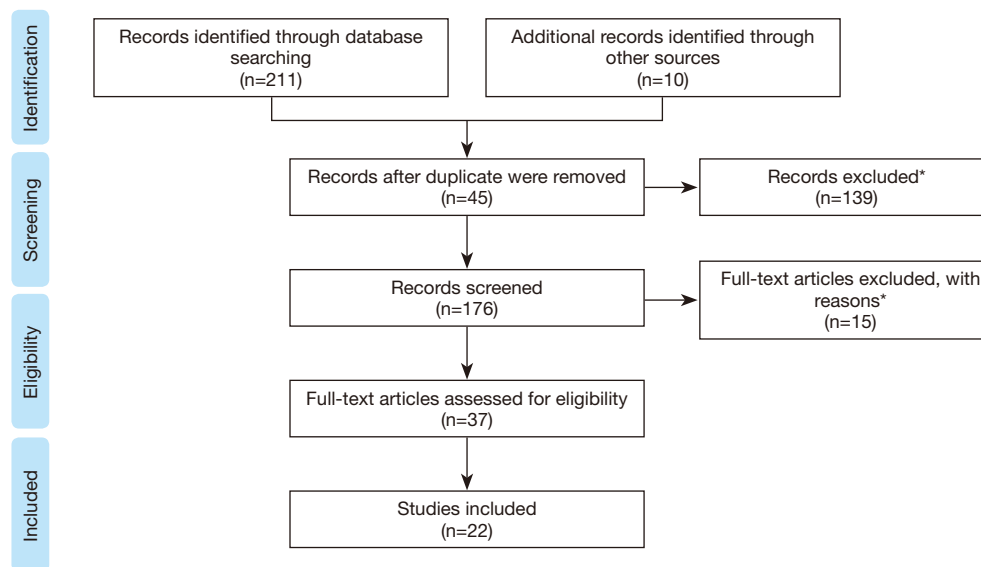
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Figure 1 PRISMA flow diagram showing the literature method search. n: number of articles. Records excluded*: they did not specify the factors/reasons of refusal treatment; or did not provide data specifically in older adults; some of them were a review/editorial/expert opinion paper.

Table 1 Study characteristics and factors associated with refusal treatment

Study	First author & year published	Title	Type of analysis	Type of cancer/ treatment	Factors associated with treatment refusal
P1 (9)	Restrepo DJ, 2019 USA	Characteristics of breast cancer patients who refuse surgery	Retrospective cross-sectional study	Breast/surgery	Non-White race, government insurance and uninsured patients (P<0.001)
P2 (10)	Coffman A, 2019 USA	Correlates of refusal of surgery for the treatment of non-metastatic pancreatic adenocarcinoma	Observational retrospective	Non-metastatic pancreatic adeno-carcinoma/ surgery	Old age, female, black race, treatment at a non-academic institution/non-metro facility, government insurance, Charlson comorbidity index of ≥2 (P≤0.01), and advanced disease (T3-T4 stage; tumor size >20 cm (P≤0.01)
P3 (11)	Crippen MM, 2018 USA	Refusal of cancer-directed surgery in head and neck squamous cell carcinoma patients	Retrospective review	HNC** , any stage/surgery	Elderly (>75 years) and stage III or IV at diagnosis; Black race; non-married and have Medicaid insurance; primary site: larynx or base of tongue
P4 (12)	Rahouma M, 2018 USA	Consequences of refusing surgery for esophageal cancer: A national cancer database analysis	Retrospective study, cross-sectional N=18,459	Esophageal T2-T4 M0/surgery	Old age, female, non-white race, squamous histology, early diagnosis, no insurance, treatment at non-academic centers, lower income, and clinical stage I/II (P<0.001). Median survival was better for patients who went surgery vs. patients who declined surgery (32 vs. 21 months, P<0.001)
P5 (13)	Tohme S, 2018 USA	Race and health disparities in patient refusal of surgery for early-stage pancreatic cancer: an NCDB Cohort Study	Cohort retrospective study	Early-stage pancreatic cancer (T1/ T2N0M0) surgery	Old age; female; African American on Medicare/ Medicaid; Charlson score ≥2; patients; treatment at non-academic centers; Significant worst survival for patients who declined surgery compared with who received surgery [median survival 6.8 vs. 24 months]

Table 1 (continued)

Table 1 *(continued)*

Study	First author & year published	Title	Type of analysis	Type of cancer/ treatment	Factors associated with treatment refusal
P6 (14)	Cheraghlou S, 2018 USA	Untreated oral cavity cancer: long-term survival and factors associated with treatment refusal	Retrospective descriptive	HNC**-any stage/surgery	Elderly; no insurance or have government insurance, advanced disease (P<0.001)
P7 (15)	Chiang TY, 2015 Taiwan	Factors related to treatment refusal in Taiwanese cancer patients	Retrospective descriptive	Miscellaneous/ any treatment	Elderly, poor physical condition (P<0.001), concerns about adverse effects (P<0.001), changes in medical status (P<0.001), poor performance (P<0.001), timing of case manager contact (P=0.026), methods of patient contact by case manager (P<0.001), poor social support and lost contact
P8 (16)	Gaitanidis, 2018 Greece	Refusal of cancer-directed surgery by breast cancer patients: Risk factors and survival outcomes	Retrospective study	Breast cancer— any stage/ surgery	Elderly (age >70), ethnicity, unmarried status, advanced tumor and lack of insurance. Refusal treatment was associated with a higher risk of mortality (increase of 2.42 compared with those who received treatment) (P<0.001)
P9 (17)	Massa ST, 2017 USA	Survival after refusal of surgical treatment for locally advanced laryngeal cancer	Retrospective study	Laryngeal cancer (T1–T4M0)/ surgery	Unmarried, Black race, T3 tumors. Decreased 5-year survival compared with those who went to surgery (50.0% *vs.* 60.1%)
P10 (18)	Suh WN, 2017 South Korea	Risk factors associated with treatment refusal in lung cancer	Retrospective study	Lung cancer— any stage/any anti-cancer treatment	Elderly, low educational status, low weight, and ECOG 3–4. *P<0.05
P11 (19)	Gilbar P, 2017 Australia	Why adjuvant chemotherapy for stage III colon cancer was not given: Reasons for non-recommendation by clinicians or patient refusal	Retrospective study	Colon cancer stage III/ chemotherapy	Reasons for refusal were not detailed in most patients' charts (63.6%).
P12 (20)	Chen SJ, 2015 Taiwan	Characteristics of the delayed or refusal therapy in breast cancer patients: a longitudinal population-based study in Taiwan	Cohort retrospective	Breast any stage/any anticancer treatment	Elderly, higher Charlson score, advanced tumor stage, other catastrophic illness or injury, and the level of diagnostic hospitals. *P<0.05
P13 (21)	Chiang TY, 2018 Taiwan	Colorectal cancer in Taiwan: A case-control retrospective analysis of the impact of a case management program on refusal and discontinuation of treatment	A case-control longitudinal, retrospective	Colorectal cancer—any stage Any anti-cancer treatment	Elderly*, concerns about adverse effects*, poor performance status*, changes in medical condition*, the methods and frequency by which case managers contact patients*; *P<0.001
P14 (22)	Stavas MJ, 2015 USA	The refusal of palliative radiation in metastatic non-small cell lung cancer and its prognostic implications	Retrospective database study	Metastatic non-small cell lung cancer/radiation therapy	Elderly*, non-Black/non-White*, unmarried* and female*; *(P<0.001 in all cases)

Table 1 *(continued)*

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Table 1 (continued)

Study	First author & year published	Title	Type of analysis	Type of cancer/treatment	Factors associated with treatment refusal
P15 (23)	Lu PW, 2020 USA	Sociodemo-graphic predictors of surgery refusal in patients with stage I–III colon cancer	Retrospective database study	Stage I-III colon cancer/curative surgery for colon cancer	Older age*, Black race*, higher Charlson score*, have government insurance* or lack of insurance*; *P<0.001. A significant difference in survival of 5-year was found for patients who refused surgery *vs.* those who undertook surgery (P<0.001)
S1 (24)*	Wan J *et al.*, 2018 China	Management and survival analysis of elderly patients with a cancer in the digestive system who refused to receive anti-cancer treatments	Retrospective observational study N=57	Digestive system cancer, any stage/any active therapy	Advanced or late stage at the time of diagnosis and impairment of multiple organs. The average number of malfunctioning organs was 3.68 per patient
S2 (25)	Dronkers EAC, 2015 the Netherlands	Noncompliance with guidelines in head and neck cancer treatment; associated factors for both patient and physician	Retrospective observational study N=829	HNC**, any stage/any active treatment	Elderly, non-married, female, high tumor stage, and severe comorbidity (P<0.001). Refusal treatment was associated with lower overall 3-year survival (34% *vs.* 70%)
S3 (26)	Parhar HS, 2018 Canada	Patient Choice of Nonsurgical Treatment Contributes to Disparities in Head and Neck Squamous Cell Carcinoma	Retrospective nationwide analysis (cross-sectional) N=58,816	HNC** (squamous cell carcinoma) any stage/surgery	Age (67.1±12.6 *vs.* 63.6±13.1, P<0.01), non-white; unmarried, advanced stage tumor, and having a primary site in the hypopharynx or larynx (P<0.001)
S4 (27)	Wallace SK, 2016 USA	Refusal of Recommended Chemotherapy for Ovarian Cancer: Risk Factors and Outcomes; a National Cancer Data Base Study	Cohort retrospective N=147,713 (2,707 refused treatment)	Ovarian—any stage/chemotherapy	Older age (>70), comorbidities (≥2 *vs.* 0; OR, 1.8), have no insurance (OR, 1.4–2.9), later year of diagnosis (OR, 1.3), Higher Stage (I *vs.* IV; OR, 2.2), P<0.005
S5 (28)*	Sowerbutts, 2015 UK	Why are older women not having surgery for breast cancer?	Qualitative case study N=28	Breast—any T/surgery	These patients rejected surgery as they were not interested in maximizing their survival, referring to their age or concerns about impact of treatment on their functional level
I1 (29)	Rapp J, 2019 USA	Disparities in surgery for early-stage cancer: the impact of refusal	Observational cross-sectional N=498,927	Surgery	Increasing age*, non-Hispanic Black race/ethnicity*, uninsured*, unmarried*, and stage disease*. *P<0,001. Patients who refused surgery were more likely to experience mortality in comparison to those who received surgery
I2 (30)	Islam KM, 2015 USA	Prostate cancer patients' refusal of cancer-directed surgery: a statewide analysis	Retrospective cross-sectional N=14.876	Surgery	Early-stage prostate cancer (P<0.0001), older age (P<0.0001), Black race (P=0.024), unmarried (P=0.0003), have Medicaid/Medicare (P<0.0001)

*Studies with elderly patients with cancer exclusively; **head and neck cancer (HNC).

group (patients who refused treatment) and case control (patients who received treatment). Thirteen studies (9-14,16,20,22,23,26,27,30) were non-randomized but with a large sample size, with data collected from National Database, thus representing a nationwide population. Almost all of the studies used retrospective chart reviews and/or an administrative database. There was just one study with a qualitative design (28), with a sample size of 28 patients. The sample size for quantitative studies ranged from 58 to 498,927 patients (24,29). Study quality ranged from poor to moderate for most studies (level 2 and 3 evidence; Appendix A. The majority of studies focused on head and neck (11,14,17,25,26), breast (9,16,20,28), and colorectal cancers (19,21,23). There were two studies on lung cancer (18,22) and two on pancreatic cancer (10,13). Three studies included different types of cancer (miscellaneous) (15,24,29). Most of the studies were from the United States (9-14,17,22,23,27,29,30). There were five Asian (15,18,20,21,24) and three European studies (16,25,28) There were no studies from Latin America.

Predictive factors associated with refusal treatment in the elderly

Socio-demographic factors
Only two studies included elderly patients exclusively (24,28): one included only elderly women with breast cancer and the other one included elderly people with digestive cancer. The vast majority of studies (10-16,18,20,22,23,26,27,29) showed that being elderly was an important refusal factor. The factors associated with treatment refusal were mostly unmarried status (11,16,17,22,25-27,29,30) female gender (10,12-14,22,25), non-white race (9-13,16,17,23,26,29,30) having government insurance (9-11,13,14,23,30), or not having insurance (9,14,16,23,27,29).

Types of intervention
The majority of studies evaluated refusal of surgery interventions (9-14,16,17,23,26,28-30). Two studies evaluated refusal of chemotherapy (19,27). One article included palliative treatment (radiotherapy) exclusively, and showed that older patients with non-small cell lung cancer (NSCLC) with metastases were more likely to refuse radiation therapy (22).

Clinical characteristics
Most studies showed that clinical status was a predictive

factor associated with treatment refusal. Cancer stage III or IV (10,11,14,16,17,24-27) was more associated with refusal treatment, as well as poor performance status (Eastern Cooperative Oncology Group 3 or 4) and Charlson comorbidity score >2 (10,13,15,18,20,21,23-25,27).

Discussion

Although there have been few studies on the treatment refusal of the older patient with cancer, the majority of studies analyzed described old age as one of the strongest predictive factors associated with therapy refusal. A national cohort study of lung cancer in Taiwan described that the rate of treatment refusal increased proportionally for each 10-year age increase, and among patients aged 75 and older was increased 2.6 times compared to those aged 44 or under (18,31). Administration of chemotherapy decreased with age and increasing number of comorbidities. Walter *et al.* (32) showed in a sample of patients with stage III colon cancer in Germany that old age was the strongest predictor of non-administration of chemotherapy, irrespective of comorbidity and other potential determinants. Evidence suggests that the increase in patient refusal rate corroborates with the still apparent issue of undertreatment in healthy older patients (3).

The factors associated with treatment refusal found in this review were unmarried status (11,16,17,25-27,29,30) non-white race (9-13,16,17,23,26,29,30) female gender (10,12-14,22,25), having government insurance (9-11,13,14,23,30) or having no insurance (9,14,16,23,27,29) and Charlson comorbidity index >2 (10,13,15,18,20,21,23,24,27). These results are aligned with the factors shown recently by Rapp *et al.* (29), although this British study only included patients who were recommended for surgery for early-stage disease (primary stage I and II lung, breast, prostate and colon cancers). However, the reasons behind these clinical-demographic factors were not well established in these studies, as the vast majority were descriptive studies (9-14,16,17,22,23,27,29,30).

Regarding the demographic factors, Chiang *et al.* (21), Suh *et al.* (18), and Chiang *et al.* (15) also showed that patients older than 70 years old, widowed or unemployed were more likely to refuse treatment. Poor social support and lower income were also described as factors related with treatment refusal (12,13,28). Furthermore, non-white race and female gender appeared to be strong predictive factors of therapy refusal (9,10,12-14,22,25,28). Despite the absence of a clear explanation in literature, we speculate that regional and cultural characteristics may influence the

decision-making treatment. A relationship between race, age and unmarried status and patient refusal of surgery for lung cancer was found in a US study, suggesting cultural differences in decision-making regarding treatment (33). The patient's cultural background and socioeconomic status can impact the desire to overcome cancer in a particular country or region. Low educational and economic status was considered a significant variable in treatment refusal, maybe due to difficulty in accessing health services or lack of knowledge about disease (18). Patients perceive and experience illness, care, and death according to their culture, values, beliefs, life experiences and meaning of life (34). Thus, it is argued that spirituality, culture, the socioeconomic status and policies of access to healthcare may influence patients' healthcare decision-making (35). In this review, the five Asian studies (15,18,20,21,24) did not described the female gender as a predictive factor, which was mostly described by American studies. We did not find studies that included Latin American elderly patients.

The clinical factors associated with refusal treatment reported in the majority of the studies were mainly advanced disease stage (III or IV) (10,11,14,16,17,24-27) Charlson score greater than two (10,13,15,18,20,21,23-25,27), and poor performance status (ECOG 3 or 4) (15,18,21,23,25). This may be related to the desire not to undergo treatments without a curative proposal considering advanced disease (22,25). Only one systematic review was found about factors associated with acceptance and refusal of cancer treatment in the elderly. The results showed that the physician's recommendation, trusting and having good communication with the physician, and expectations about side effects were predictive factors of therapy refusal, with the latter representing the main factor related to treatment refusal that was also found in the current review (3,21,28,29).

The majority of studies in this review did not examine the particular reasons for older adults to decline treatment (9,10,12-14,16-18,20,21,25,27). Thus, it is unclear if other factors were not reported because they were not important or because they were not been studied. Relevant characteristics of geriatric health, such as cognitive and sensory impairment, were not described in these articles, but were found in the previous systematic review (3). So, it is important that multicenter studies with a larger sample size and of higher methodological quality are conducted, considering the clinical characteristics and aspects of patients, such as their culture, values, beliefs. As well as qualitative studies to better understand the reasons for therapeutic refusal (3,24).

A 2015 qualitative study in the United Kingdom (28), including only elderly women with breast cancer who refused surgery, reported that these patients declined surgery either because they wanted to avoid treatments that could impact their current functional level or because of their age perception. These patients, who tended to be older, mentioned their age as a representation of various reasons, including having a limited life span, not wishing to prolong their life due to comorbidities or lack of desire. In this review, there is only one qualitative study that evaluated the psychological and existential aspects of treatment refusal. Juang *et al.* suggested that one of the reasons for treatment refusal is that older patients may have lack of knowledge about their medical conditions; thus, they may feel uncertain about the disease, which can lead to depression and affect patients' adherence to treatment (36).

Compared to the latest systematic review on the topic (3), we found some differences. In that review, most studies used a qualitative design based on breast and prostate cancer treatment decisions, and described as important factors associated with therapeutic refusal the concerns with the discomfort of the treatments, fear of side effects and transportation barriers. In this study, most studies used a retrospective and descriptive design and focused on breast, colorectal, and head and neck cancers. The differences related to the predictive factors between the two reviews could be influenced by the nature of the studies' design. The qualitative and prospective design prevalent in the first review (3) favors the discussion of psychological aspects such as fear of adverse effects.

It is important to consider that not all studies in this review involved only curative treatment. One study had a palliative proposal for non-small cell lung cancer, which also showed some factors of refusal described in this review such as elderly, unmarried, and female patients. Stavas (22) and Aizer *et al.* (37) compared refusal characteristics of patients undergoing curative and palliative care and they found that older and unmarried patients were more likely to decline palliative and curative radiation, demonstrating that these are stable predictors of refusal, independent of treatment indication. Regarding gender, women were more likely to refuse palliative radiotherapy (RT) and men were more prone to refuse definitive RT (22). Unfortunately, the database used in most studies in this review [the Surveillance Epidemiology and End Results (SEER) and National Cancer Database] (9-14,16,17,22,23,27,29-31) did not give further information to detail these differences. Thus, further investigation into the demographic factors

related with treatment refusal should be conducted.

Regarding the type of treatment (10-18,20,21,23-26,28-30), the majority of studies evaluated the refusal of surgery interventions, which may be associated with the nature of the cancer. Most of the studies included head and neck, breast, and digestive system early-stage cancer treatment, where surgery has a well-established role in treatment (10-14,16,17,26,28-30). Seven studies (12,13,16,17,23,25,29) described an overall lower survival rate of patients who refused treatment compared with those who received standard treatment, most of them regarding surgery intervention. Lu *et al.* (23) showed that old age was a predictive factor of refusing surgery in patients with stage I-III colon cancer. The previous study has also described that elderly patients were more likely to decline surgery for other neoplasms when compared to younger patients, even though they were suitable surgical candidates. About the reasons for declining surgery, Rothman *et al.* (38) described that most older patients with advanced illness refused a surgical/medical procedure and the main reason was the fear of side effects.

It is know that the integration of palliative care improves several outcomes, such as quality of life and symptom burden and less use of medical resources (39). The American Society of Clinical Oncology has recommended that palliative care should be offered since cancer diagnosis, together with traditional oncologic care. Although the benefits of early palliative care are already well established scientifically, there are challenges to its implementation, such as the current health care policies, limited resources, and the different clinical practice settings, which consequently lead to palliative care referrals occuring late in the illness process (40). Although all patients with metastatic disease or poor performance status would benefit from palliative care, identifying those individuals who refuse treatment is also a good indication for referral (22,39).

Further research is needed to understand why these disparities exist for treatment refusal, especially in patients with early-stage cancer. Most studies are retrospective, which makes it difficult to analyze the reasons behind treatment decision-making. Some possible explanations include the lack of healthcare literacy and mistrust of individual medical providers and of the overall healthcare system described by minority patients. The two articles (24,28) that exclusively enrolled older patients showed that in particular, patients 80 years and older may be more likely to refuse surgical intervention due to fear of decreased quality of life, as they may be affected by other conditions

that lead to frailty, while the unmarried patients might be more likely to decline treatment because of a perception of a poor social support, which also was observed in prior studies (29,41).

This review has some limitations. The methodological quality of the included studies limited some of the findings. The retrospective and descriptive nature of most of the studies made it difficult to clarify the reasons behind treatment refusal. No meta-analysis was conducted, as the studies were too heterogeneous regarding the population studied and data collected. The strengths of this study were the nature of the systematic review that included both quantitative and qualitative studies, most of which were from large nationwide and multicentric databases (9-14,16,20,22,23,26,30,31) and up-to-date about an issue that is still scarce in the literature.

Conclusions

This study reviewed the factors associated with treatment refusal in older patients with cancer. Predictive factors of refusal treatment included female gender, unmarried status, non-white race, having government insurance or not having insurance, higher disease stage, and poor performance status (9-18,20-27,30). Understanding these factors is important in clinical practice to improve treatment adherence, reduce errors, improve results and provide optimal care, considering the best interests and values of patients (3,6,10). Thus, acknowledging patients' specific demographic and clinical characteristics may help to predict patients' attitudes towards decision-making in health and allow to elaborate an adequate care plan, also considering patients' culture and personal values and beliefs. Additional studies are needed with elderly patients to evaluate decision-making, particularly regarding the psychological and existential aspects, and incorporating both health literacy and comorbidity.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table S1

Study	First author & year publi-shed	Factors that decrease the risk of bias	Factors that increase the risk of bias	SORT
P1[10]	Restrepo DJ, 2019, USA	- A nationwide cohort,large and quality-controlled data identified from the National Cancer Data Base (NCDB). Data from 2004–2015 - Large sample size – N= 2,445,870 - Well-established inclusion and exclusion criteria and methods - Demographic, socioeconomic, and tumor-specific predictors were compared between patients who refused breast cancer surgery versus those who agreed to surgery, using bivariate and multivariate models.	- Retrospective study - Non-randomized study - Data extraction from NCDB, which does not contain detailed information regarding the specifics or extent of nonsurgical treatment, and all reasons underlying patient treatment refusal	2
P2[11]	Coffman A, 2019, USA	- A nationwide cohort, a large and quality-controlled data identified from the NCDB (from 2004 to 2013). - Large sample-48902 (1795 refused treatment) -Well-established inclusion and exclusion criteria, outcomes - Univariate and multivariate logistic regression modeling was used to identify predictive factors of refusing surgery	- Retrospective analyzes - Selection bias that is inherent with all retrospective reviews. It is possible that the cohort of patients who refused surgery were less healthy or able to tolerate surgery in ways that could not be captured by the NCDB data.	2
P3[12]	Crippen MM, 2018, USA	- A cohort with a large,quality-controlled data identified from Surveillance, Epidemiology and End Results (SEER) database from 1989 to 2014 - N=598,270 were compared to patients who refused recommended surgery (N=53,582) - Groups were compared for patient social demographics and clinical characteristics. Binary logistic regression was performed to determine independent predictors of surgery refusal.	- Retrospective review - Data extraction from SEER, which does not contain detailed information regarding the specifics or extent of nonsurgical treatment. - It does not differentiate between those refusing surgery in favor of nonsurgical management versus those refusing all type of treatment.	2
P4[13]	Rahouma M, 2018, USA.	- The NCDB (data from 2004 to 2014) - N=18,459 (708 - 3.8% refused surgery) - Sample and inclusion criteria were well defined -Comparisons between the entire cohort and between propensity-matched groups were performed using analysis of variance and X^2 tests Logistic regression to identify predictors of refusing surgery	- Retrospective, cross-sectional - The database does not contain details about the extent and type of clinical staging	2
P5[14]	Tohme S, 2018, USA	- A cohort with a large and quality-controlled data - NCDB (2003- 2012) - N=26,358 - Multivariate models to identify factors predicting failure to undergo surgery and assess the impact on survival.	- Retrospective cohort review - The NCDB does not include the granularity to determine exactly why patients refused surgery and who was the primary provider directing their health choices.	2
P6[15]	Cheragh-lou S, 2018, USA	- A nationwide research with a large sample – NCDB - N=36251 (N=356 refused treatment) - A comparative study - Well-established objectives, criteria and methods Multivariate Cox regression as well as univariate Kaplan–Meier analyses were conducted.	- Retrospective review -Lack of some relevant information in database, such as about social factors - Unable to access data about the reasons behind patient treatment refusal	2
P7[16]	Chiang TY, 2015,Tai-wan	The study analyzed data from a case management system from 2010 to 2012 in Taiwan N= 14974 (N=253 patients- refused treatment) - Using the PRECEDE Model as a framework and logistic regression analysis to identify independent variables associated with refusal of therapy in cancer patients. A multivariate logistic regression model was also applied.	- Retrospective design - Data extracted from a databases/records from just one medical center in Taiwan	3
P8[17]	Gaitanidis, 2018, Greece	- A nationwide search of SEER database for patients with breast cancer diagnosed (2004-2013). - Sample size: N=528,311 (3389 who refused treatment) - Well-established inclusion and exclusion criteria	- Retrospective design. Such databases may often be associated with miscoding and missing information. - In addition, there was no information concerning the use of chemotherapy and whether its use was also dismissed by patients.	2
P9[18]	Massa ST, 2017, USA	- A cohort with a large, quality-controlled data identified from SEER (2004-2013) - N=5786 (138 patients who refused treatment) - They used a multivariate logistic regression model (comparative study)	- Retrospective observational nature - Data extraction from records/ databases - Lack of potentially relevant details. These details include some tumor information.	2
P10[19]	Suh WN, 2017, South Korea	- A cohort retrospective review of patient records (2010- 2014) -N=617 patients (149 who refused treatment [non-treatment group] were compared with 468 who received anti-cancer treatment [treatment group]) - A comparative study – controlled data	- Retrospective review - A non-randomized observational study - Data from one institution and selection bias in dividing the patients into two groups were also limitations.	3
P11[20]	Gilbar P, 2017, Austra-lia	Cohort selected (2010- 2014) Well-defined inclusion criteria and methodology.	-A retrospective observational from a single institution - Sample size-N=109 (12 refused treatment) - Lack of some important information about sociodemographic factors on database	3
P12[21]	Chen SJ, 2015, Taiwan	- A large cohort retrospective from Taiwan Cancer Registry Database (a national cohort) - N=35,095 - Well-defined inclusion criteria and methodology - univariate and multivariate analyses were used to identify predictors for refusal	- Retrospective analysis on secondary databases. - Some relevant factors such as patient occupation and family care and support were not able to be incorporated.	2
P13[22]	Chiang TY, 2018, Taiwan	- A case-control study, longitudinal database and secondary analysis of population-based data (2009- 2012) - Logistic regression was used to reveal the factors related to refusing treatment. -N=408 (68 case-group X 340 control-group)	- The study consisted of a secondary analysis of data and subjective measurement could not be evaluated. - A non-randomized observational study - Among case management benchmarks, this study measured the rates of refusing treatment and discontinuing treatment	3
P14[23]	Stavas MJ, 2015, USA	- A cohort with a large, robust, quality-controlled data identified from SEER database (1988 – 2010) - N=285,641 (N=3,795 refused treatment) - A comparative study -Well-defined methodology - univariate and multivariate analyses were used to identify predictors for refusal	-Retrospective observational nature -A non-randomized observational study -Lack of important details about performance status, previous treatment in some records/ databases	2
P15[24]	Lu PW, 2020 USA	- A large cohort- NCDB (2004-2015) - N=151,020 (N=1,071 refused surgery) - Well-defined inclusion criteria - Patients who underwent surgery were compared to those who refused surgery. -Multivariable analysis to identify factors associated with surgery refusal.	- Retrospective observational design - A non-randomized observational study - Some incomplete information in database- some factors that can influence patients' decision making when considering surgery that is not captured by the NCDB	2
S1[25]	Wan J et al. 2018. China	- Several authors - Cohort selection between 2007 and 2015 - Well-defined inclusion and exclusion criteria - Well-defined methodology and outcomes	- Sample size (N=57) - Retrospective observational design - Data records from just one center (China) - Lack of some relevant information about patients' characteristics in records	3
S2[26]	Dronkers EAC, 2015. Nether-lands	- Sample Size (N=829) - Cohort selection between 2010 and 2012. Well-defined inclusion and exclusion criteria - Well-defined methodology - Multivariate analysis using logistic regression methods to determine predictive factors associated with nonstandard treatment	-Retrospective observational design - Based on medical records - Data from just one center	2
S3[27]	Parhar HS, 2018, Canada	- Sample size (N= 58,816 candidates for surgery and 1,550 refused surgery) - Cohort selection from 2014 to 2014. - Well-defined methodology - Multivariable logistic regression was used to identify demographic and clinical factors associated with patient choice of nonsurgical treatment	- Retrospective observational design (cross-sectional) - Incomplete data from records - Data from just one country (Canada)	3
S4[28]	Wallace SK, 2016, USA	- a large cohort -NCDB (1998- 2011) - N=147,713 (2.707 refused chemotherapy) - Well-defined inclusion and exclusion criteria - Well-defined methodology - Multivariable logistic regression was used to identify demographic and clinical factors associated with patient choice of nonsurgical treatment - A comparative study	- Retrospective study - Non-randomized observational study - The relative proportion of unavailable data, which is a limitation of the ongoing nature of the NCDB data collection process - Data from just one country	2
S5[9]	Sowerbutts, 2015, UK	- A qualitative nested component of a larger quantitative project - Well-defined inclusion and exclusion criteria - Well-defined methodology - Transcripts were analyzed using the Framework method.	-Sample size (N=28) - A case-study - The overall sample for the most part was comprised of patients who underwent surgery but also contained a larger proportion of patients being treated with hormone therapy, who left the decision up to the surgeon - Does participation of relatives in the interview influence the decision treatment? - selection bias	3
I1[30]	Rapp, 2019, USA	- Intentional sampling - Sample size (N= 498,927, of whom 5,757 refused surgeries) - Multicentric - Several researchers - Well-characterized disease diagnosis - Well-defined inclusion and exclusion criteria - The Multivariable logistic regression models were used to assess association between sociodemographic variables and surgery refusal.	- Cross-sectional, retrospective study - Several types of cancer (heterogeneous population) - Limitations inherent in this retrospective analysis, i.e., unmeasured confounding, the study was limited by the inability to adjust for comorbidities given the lack of such information in database cancer registries.	2
I2[31]	Islam KM, 2015, USA	- Sample size (N=14,786), intentional sampling - Well-defined inclusion and exclusion criteria - The data used in the analyses were a subset of the Nebraska Cancer Registry (NCR) data, including all prostate cancer incidences recorded by the cancer registry (1995- 2012) - Well-defined methodology	- Retrospective, cross-sectional design - Analysis of medical records from an oncological center database - Sample from just a single center - Incomplete information about some socioeconomic factors in records	3

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