Annals of Gastroenterological Surgery

WILEY

REVIEW ARTICLE OPEN ACCESS

Surgery for Older Cancer Patients: Cross-Organ Review and Good Practice Statement by the Japanese Geriatric Oncology Guideline Committee

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Received: 11 March 2025 | **Revised:** 2 May 2025 | **Accepted:** 19 May 2025

Funding: The preparation of these guidelines was funded by the Ministry of Health, Labour and Welfare (MHLW), Japan (21445722). We did not receive any financial support from other organizations or companies.

Keywords: cancer | older patients | surgery

ABSTRACT

Background: Although the number of older people is increasing, there is a lack of evidence and insufficient consensus regarding postoperative complications and survival in older cancer patients. In this study, we conducted a literature search and systematic review focusing on the outcomes after surgery for older cancer patients.

Methods: Literature focusing on surgical treatment for older cancer patients was extracted from Japanese clinical practice guidelines for gastric cancer, lung cancer, colorectal cancer, liver cancer, and gynecological cancers (uterine body, uterine cervix, ovary, and external genitalia and vagina). Outcomes were reviewed, and committee members determined the strength of evidence on a four-point scale (A to D), with A being the highest and D being the lowest.

Results: Older cancer patients tend to have a higher incidence of postoperative complications and postoperative syndromes, and their expected survival is generally shorter compared to non-older patients. When extensive surgeries such as para-aortic lymph node dissection and/or resection with other organs are performed for older cancer patients, the postoperative mortality rates tend to increase compared to non-older patients.

Conclusion: Surgical treatments for older cancer patients tend to result in higher morbidity even when the patients are in good health status. Nevertheless, there is still a possibility that a certain fraction of the patients achieve treatment outcomes comparable to those of non-older patients. Therefore, surgical indication and procedure for older cancer patients should be carefully determined based on surgical invasiveness and patient tolerability.

1 | Introduction

The proportion of older people in the general population is increasing in Japan. According to a Cabinet Office report, the average life expectancies of women and men as of 2020 were 87.7 and 81.6 years, respectively [1]. Older adults develop cancer more often than the younger population; 73% of patients newly diagnosed with cancer and 87% who die of cancer are 65 years old or older [2, 3].

We need to develop standardized cancer treatment for older patients, especially for vulnerable patients. In general, after determining the clinical stage of cancer, the indication for various treatment strategies in patients with cancer is decided according to the evidence established by prospective clinical trials [4]. However, most of the pivotal clinical trials mainly include patients aged < 75 years [5], because the inclusion of older patients with higher incidences of comorbidities and impaired cognitive function may obscure the trial results [6]. Even if older patients were included in some of those trials, they would likely be highly selected patients with good general conditions. Thus, discreet consideration on a case-to-case basis has been deemed necessary to decide whether an older patient with cancer should be indicated for invasive procedures such as major surgery. However, the information regarding the incidence of postoperative complications and survival outcomes for older patients with cancer has not been sufficiently accumulated and analyzed.

Therefore, in this study, we conducted a literature search and systematic review to develop Japanese Geriatric Oncology Guidelines, focusing on the outcomes after surgery for older patients with cancer.

2 | Methods

2.1 | Literature Search Strategy and Study Selection

Literature focusing on surgical treatment for older cancer patients was extracted from the Japanese clinical practice guidelines for gastric cancer, lung cancer, colorectal cancer, gynecological cancers (uterine body, uterine cervix, ovary, and external genitalia and vagina), and liver cancer. The guidelines for breast cancer were excluded due to some differences in the relevance of surgical treatments when compared with other solid cancers. Three investigators (C.T., D.I., and K.N.) independently searched the reports and participated in the trial selection process. Study quality was also formally assessed for all included studies independently by the three investigators and two reviewers (K.T. and H.I.). In addition, other important papers regarding older cancer patients were identified through a manual literature search and were included in the analyses. In retrospective observational studies, we selected articles that conducted multivariate analysis.

2.2 | Process of Guideline Development

The expert panel of the Japanese Geriatric Oncology Guideline Committee consisted of oncologists, medical doctors, surgeons, geriatricians, radiologists, psychiatrists, pharmacists, nurses, and representatives from patient advocacy groups. Their positions are disclosed in Table S1, and their conflicts of interest were strictly controlled according to the regulations of the Japanese Association of Supportive Care in Cancer. Initially, they developed a clinical question (CQ) and collected evidence through a literature search. Then, they determined the strength of evidence based on the outcomes using a four-point scale (A to D), with A being the highest and D being the lowest. The response to this clinical question was presented as good practice statements (GPS) based on a comprehensive evaluation obtained through a literature search.

2.3 | Outcomes

In this review, we will focus on the following CQ: "Should curative surgery be recommended for older cancer patients?" We selected postoperative complication, postoperative syndrome postoperative mortality, and survival benefit as the outcome measures for assessing the CQ.

3 | Results

3.1 | Study Selections

Eight hundred thirty-three articles (lung 218, stomach 123, uterine body 113, liver 97, colon and rectum 93, uterine cervix 79, ovary 59, and external genitalia and vagina 51) focusing on surgical treatment were extracted from the Japanese treatment guidelines, and an abstract and full-text review were conducted (Figure 1). Among them, 815 articles were excluded after the abstract and full-length screening (716 and 99, respectively), and 22 trials focusing on older cancer patients that were suitable to respond to the CQ were selected. There was heterogeneity in patient characteristics such as cancer types and conditions among the trials.

3.2 | Clinical Question and Answer

CQ: Should curative surgery be recommended for older cancer patients?

GPS: Curative surgery indicated for non-older patients should also be considered for older patients. Age does not always limit the indication for the surgical risk. However, the following outcomes for older patients were revealed compared to non-older patients,

1. The incidence of postoperative complications and postoperative syndrome rates tended to be higher.
2. The postoperative mortality rates were varied and depended on the magnitude of the surgical procedure.
3. Overall survival rates tended to be lower.

Therefore, for older patients with cancer, it is mandatory to decide on the indication for surgery comprehensively on a case-by-case basis, taking into consideration preoperative body function and surgical invasiveness. It is desirable that the final decision-making of whether or not to undergo surgery be made by the patient after sharing various issues related to the indication for surgery with the patient and the family.

3.3 | Cross-Organ Literature Review for Each Outcome

3.3.1 | Postoperative Complications and Postoperative Syndrome (Evidence Level C)

In studies evaluating the incidence of postoperative complications for (Tables 1 and 2) older cancer patients undergoing surgical treatment through post hoc analysis of retrospective observational studies and randomized controlled trials (RCTs), seven articles were identified (Table 1). A post hoc analysis of a RCT comparing open surgery to laparoscopic surgery for distal gastrectomy in advanced gastric cancer revealed that 60 years or older was an independent risk factor for overall postoperative complications (odds ratio [OR] 2.362 [95% CI: 1.236–4.512]; $p = 0.009$) [7]. Similarly, another post hoc analysis of a randomized trial comparing open surgery and laparoscopic surgery for distal gastrectomy in advanced gastric cancer for aged 20–80 years revealed that 60 years or older is an independent risk factor for overall postoperative complications (OR 1.562 [95% CI: 1.087–2.243]; $p = 0.016$) [8]. Age 60 years or older was identified as an independent risk factor for Clavien-Dindo classification III or higher postoperative complications in a retrospective analysis compared among open, laparoscopic, and robot-assisted gastrectomy for gastric cancer (hazard ratio [HR]

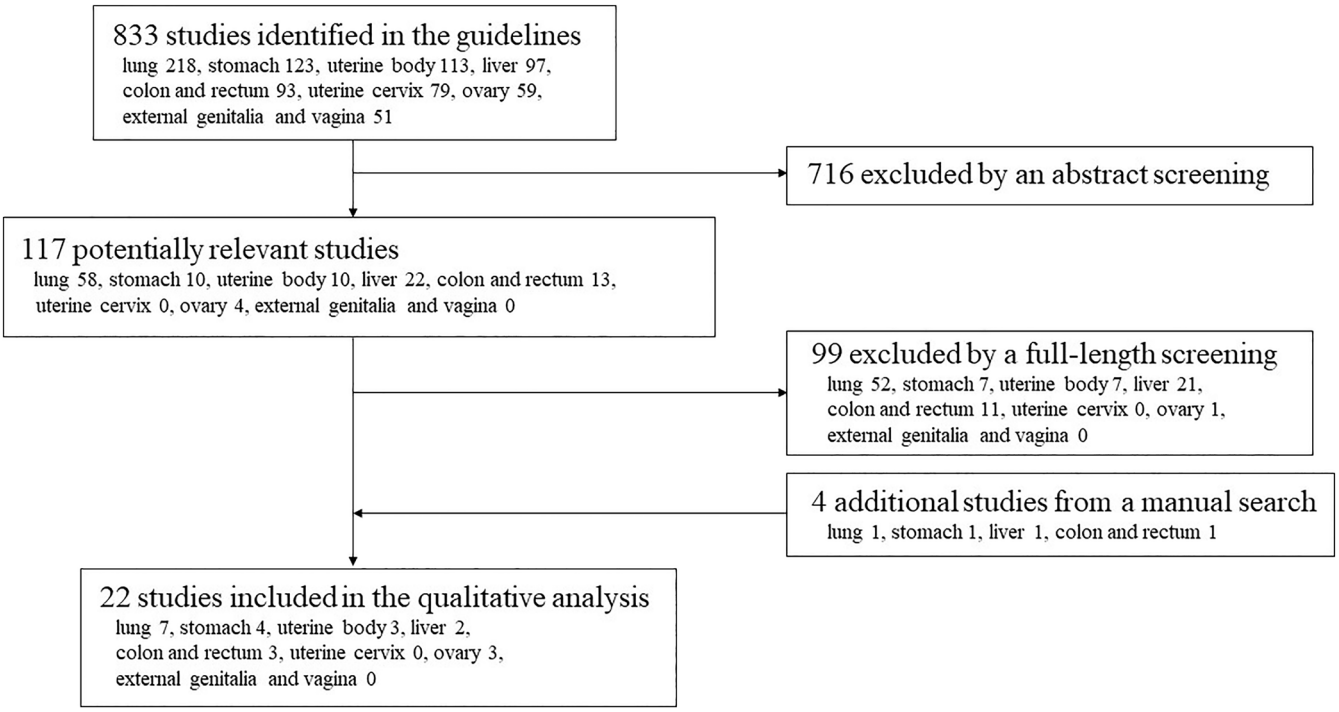

FIGURE 1 | Flowchart of study selection.

TABLE 1 | Postoperative complications.

Study	Cancer type	Surgical procedure	Age (years)	Outcomes	*p*
Wang [7]	Advanced gastric cancer	Distal gastrectomy	≥60	OR 2.362 (1.236–4.512)	0.009
Lee [8]	Advanced gastric cancer	Distal gastrectomy	≥60	OR 1.562 (1.087–2.243)	0.016
Yang [9]	Gastric cancer	Gastrectomy	≥60	HR 2.223 (1.024–4.824)	0.043
Altorki [10]	Non-small cell lung cancer T1aN0	Lobectomy/sublobar resection	≥60 Each 10-year	OR 1.308 (1.001–1.709)	0.049
Suzuki [11]	Non-small cell lung cancer tumor size ≤2 cm	Lobectomy/ segmentectomy	>75	25.8% versus 29.6% OR 1.25 (0.84–1.87)	NA 0.28
Lim [12]	Advanced ovarian cancer	Resection	≥65	22.9% versus 31.3%	0.355
Tamini [13]	Rectal cancer	Radical surgery	≥75	23.8% versus 33.8%	0.162

Abbreviations: HR, hazard ratio; OR, odds ratio.

TABLE 2 | Postoperative syndrome.

Study	Cancer type	Surgical procedure	Age (year)	Outcomes	*p*
Yamada [14]	Low rectal cancer	Intersphincteric resection	NA	[Fecal incontinence] Kirwan grade 3–4; OR 0.93	0.013
Saito [15]	Rectal cancer Stage II, III	Total mesorectal excision versus total mesorectal excision with lateral lymph node dissection	≤75	[Sexual dysfunction] International Index of Erectile Function ≤55 versus ≥56 Median [IQR]; 4 [1–11] versus 8 [1–14]	0.02

Abbreviation: OR, odds ratio.

2.223 [95% CI: 1.024–4.824]; $p=0.043$) [9]. Moreover, a post hoc analysis of a randomized trial comparing lobectomy with sublobar resection for T1aN0 peripheral non-small cell lung cancer showed each 10-year increase in age is a significant risk factor of CTCAE v4.0 grade 3 or higher postoperative complications (age [10 years unit]: OR 1.308 [95% CI: 1.001–1.709]; $p=0.049$) [10], whereas in a randomized trial comparing lobectomy to segmentectomy for non-small cell lung cancer with tumor size ≤2 cm, there were no significant differences in the incidence of CTCAE v4.0 grade 2 or higher early postoperative complications between aged 76 years or older and 75 years or younger (OR 1.25 [95% CI: 0.84–1.87]; $p=0.28$) [11]. In a single-center retrospective observational study evaluating short-term and long-term outcomes of cytoreductive surgery for advanced ovarian cancer between patients younger than 64 and those 65 and older, older patients showed a higher incidence of overall postoperative complications within 30 days (31.3%) compared to non-older patients (22.9%), though there were no significant differences between the two groups ($p=0.355$) [12]. Furthermore, a prospective study evaluating short-term and long-term outcomes of radical surgery for rectal cancer in patients aged 75 years and older compared to those under 75 showed no significant difference in the primary endpoint of overall complication rates (33.8% vs. 23.8%, respectively; $p=0.162$) [13].

Regarding the postoperative syndrome, two articles were identified evaluating the risk factors for fecal incontinence and sexual dysfunction following radical surgery for rectal cancer (Table 2). A study investigating long-term outcomes in patients receiving intersphincteric resection for lower rectal cancer showed that age was an independent risk factor for grade 3–4 fecal incontinence according to Kirwan classification (OR 0.93; $p=0.013$) [14]. A study focusing on sexual dysfunction following curative resection with lateral lymph node dissection for lower rectal cancer in 701 patients under 75 years old revealed that age over 56 was an independent risk factor for erectile dysfunction according to the International Index of Erectile Function (IIEF-5) questionnaire (median [IQR], compared to preoperative) (4 [1–11] vs. 8 [1–14]; $p=0.02$) [15].

In summary, postoperative complications and postoperative syndrome rates tended to be higher in older patients across various types of cancer compared to non-older patients. Unfortunately, however, this conclusion was obtained from studies that were diverse in terms of the definition of older patients, the method of evaluation, and the type and severity of postoperative complications and postoperative syndrome. Therefore, this evidence level of the clinical question was determined as C.

3.3.2 | Postoperative Mortality (Evidence Level D)

In studies evaluating postoperative mortality rates through post hoc analysis of RCTs and prospective or retrospective observational studies, 4 articles were identified (Table 3). There was no significant difference in 90-day postoperative mortality between patients with rectal cancer aged 75 years and older and those under 75 (2.5% vs. 1.2%, respectively; $p=0.560$) [13]. On the other hand, in a post hoc analysis of a randomized trial comparing lobectomy to sublobar resection for patients with peripheral early-stage non-small cell lung cancer, no significant differences in 30-day/90-day postoperative mortality rates were detected between older and non-older patients [10]. A large cohort study for stage I gastric cancer reported a postoperative 30-day mortality rate of <0.7% in all age groups. However, postoperative 60-day and 90-day mortality rates were higher in patients aged 75 years and older compared to those under 75 (1.2%–5.1% and 0.9%–2.3%, respectively) [16]. The 30-day mortality rate in patients aged 70–79 years and 80 and older was higher compared to those aged 20–69 years in cytoreductive surgery, involving pelvic and para-aortic lymph node dissection and/or resection with other organs such as the small intestine and colon and/or colostomy for advanced ovarian cancer (6.6%, 9.8%, and 1.5%, respectively) [17].

In summary, some reports detected significant differences in postoperative mortality rates between older cancer patients and non-older patients receiving curative surgery, while other reports did not. This is because the postoperative mortality rates vary depending on the surgical procedure and invasiveness, along with the influence of age in older patients compared to non-older patients. Thus, definitive conclusions applicable to all cancer types cannot be drawn, and the evidence level of this clinical question was determined as D.

3.3.3 | Overall Survival (Evidence Level C)

There were 16 trials evaluating survival outcomes in post hoc analyses of RCTs and prospective or retrospective observational studies. Tables 4 and 5 showed the outcomes related to survival effects.

An analysis of 8797 cases of early-stage non-small cell lung cancer (T1a) treated by lung resection using the Surveillance Epidemiology and End Results (SEER) database in the U.S. showed that people who are aged 70 years and older is an independent risk factor for death [18]. A study of 854 patients who

TABLE 3 | Postoperative mortality.

Study	Cancer type	Surgical procedure	Age (year)	Outcomes	*p*
Tamini [13]	Rectal cancer	Radical surgery	≥75	90-day; 1.2% versus 2.5%	0.560
Altorki [10]	Non-small cell lung cancer T1aN0	Lobectomy/ sublobar resection	≥60 Each 10-year	Lobectomy 30-day; 1.1% versus 0.7% versus 0.9% versus 5.9% 90-day; 1.1% versus 1.4% versus 1.8% versus 5.9%	Not significant
Nunobe [16]	Gastric cancer Stage I	Gastrectomy	≥75	30-day; 0.1% versus 0.5%–0.7% 60-day; 0.3% versus 0.9%–2.3% 90-day; 0.3% versus 1.2%–5.1%	NA
CG Gerestein [17]	Advanced epithelial ovarian cancer	Cytoreductive surgery	20–69 years versus 70–79 years versus ≥80	30-day; 1.5% versus 6.6% versus 9.8%	NA

received lung resection for non-small cell lung cancer showed that a 10-year increment in age was an independent risk factor for death (OS-HR 1.36 [95% CI: 1.24–1.48]; $p < 0.001$) [19]. In Japan, a study using the Japanese Lung Cancer Registry for 13 010 patients with non-small cell lung cancer showed 5-year survival rates for ages under 50, 50–69, and 70 or older were 69.9%, 66.0%, and 54.9%, respectively ($p = 0.0000$), and aged 70 years or older was an independent risk factor for death [20]. Another study for 215 patients with locally advanced (T4) non-small cell lung cancer also identified that people who are aged 70 years or older were an independent risk factor for death (OS-HR 1.516 [95% CI: 1.061–2.167]; $p = 0.022$) [21]. A large cohort study using nationwide gastric cancer registration data in the Japan Gastric Cancer Association revealed that OS in the patients under 75 years for stage I gastric cancer was also higher compared to those aged 75 years and older (1-year: 98.7% vs. 85.2%–96.0%, 3-year: 95.9% vs. 65.7%–88.6%, 5-year: 93.1% vs. 47.0%–81.1%, respectively) [16]. On the contrary, a 10-year survival analysis for 369 patients (including 120 cases aged 70 years or older) who survived 5 years after surgery for stages I–IIIa non-small cell lung cancer revealed that age was not an independent risk factor for death ($p = 0.70$) [22]. In a prospective observational study for cases undergoing curative resection for rectal cancer in all stages, 1-, 3-, and 5-year survival rates in the aged 75 years and older group declined compared to those under 75 (1-year: 92.5% vs. 96.2%, 3-year: 64.3% vs. 88.4%, 5-year: 50.6% vs. 75.9%, respectively) [13]. A post hoc analysis of a RCT examining the impact of surgical procedures in early-stage endometrial cancer showed that death risks in patients aged 65 years and older were significantly increased compared to those under 65 years old [23, 24]. In a retrospective observational study of 1385 patients with uterine clear cell carcinoma undergoing curative surgery, aged 65 years and older were an independent risk factor for mortality with OS-HR 2.3 [95% CI: 1.92–2.81, $p < 0.001$] for all stages and OS-HR 3.5 [95% CI: 2.6–4.7; $p < 0.001$] for stages I and II cancer [25]. In a retrospective observational study of patients undergoing tumor reduction surgery for advanced ovarian cancer, those aged 65 years and older were an independent risk factor for death compared to those under 65 ($p = 0.016$). Although survival after surgery undergoing surgical debulking for ovarian cancer tended to be shortened with aging (median: 65–69 years vs. 70–74 years vs. 75–79 years vs. 80 years and older = 3.4 years vs. 2.7 years vs. 2.0 years vs. 1.6 years, $p < 0.0001$), no significant differences in OS were detected among patients who underwent complete resection between the groups aged 65–69, 70–74, 75–79, and ≥80 years (median 5.9 years vs. 7.9 years vs. 5.4 years vs. 5.0 years) [26].

The postoperative death caused by other diseases in older cancer patients increases compared to non-older patients. Therefore, some trials reported not only OS but also tumor-specific survival, excluding events such as death from other diseases. Four articles evaluating tumor-specific survival were identified (Table 5). In the prospective observational study of rectal cancer, although the tumor-specific survival rates (TSS) in those aged under 75 were higher compared to those 75 and older, the differences were not statistically significant (1-year: 96.2% vs. 89.9%, 3-year: 89.6% vs. 77.3%, 5-year: 79.9% vs. 72.5%, respectively, $p = 0.117$) [13]. In a large cohort study of stage I gastric cancer, disease-specific survival (DSS) rates were over 90% in both those under 75 and those aged 75 years and older groups (1-year: 99.8% vs. 97.9%–99.4%, 3-year: 98.9% vs. 93.7%–97.8%, 5-year: 98.2% vs. 91.4%–96.5%) [16]. A prospective observational study comparing anatomical resection with nonanatomical resection for 1298 patients with solitary ≤5 cm hepatocellular carcinoma (HCC) revealed that the age ≥65 was not a significant risk factor for mortality (DSS-HR 1.00 [95% CI: 0.57–1.77], $p = 0.995$) [27]. On the contrary, a study of 223 patients with hepatitis C virus-related HCC treated with liver resection showed that the age ≥65 was an independent risk factor for recurrence compared to those under 65 (Relative Risk 1.63 [95% CI 1.12–2.37], $p = 0.010$) [28].

In summary, while many reports indicated that OS after curative surgery in the older cancer group was lower compared to the non-older group, some studies showed that age was not a risk

TABLE 4 | Overall survival.

Study	Cancer type	Surgical procedure	Age (year)	Outcomes	*p*
Yendamuri [18]	Non-small cell lung cancer T1a	Sublobar and lobar resections	≥ 70	50–69; HR 0.55 (0.43–0.70) < 50; HR 0.25 (0.10–0.60)	NA
Ferguson [19]	Non-small cell lung cancer All stages	Major lung resection	NA	10-year increment HR 1.36 (1.24–1.48)	< 0.001
Asamura [20]	Non-small cell lung cancer All stages	Pulmonary resections	≥ 70	< 50 years versus 50–69 versus ≥ 70 69.9% versus 66.0% versus 54.9%	0.0000
Watanabe [21]	Non-small cell lung cancer T4NX	Resection	≥ 70	HR 1.516 (1.061–2.167)	0.022
Martini [22]	Non-small cell lung cancer Stage I–IIIa	Resection	≥ 70	NA	0.70
Nunobe [16]	Gastric cancer Stage I	Gastrectomy	≥ 75	< 75 versus ≥ 75 1 year; 98.7% versus 85.2%–96.0% 3 years; 95.9% versus 65.7%–88.6% 5 years; 93.1% versus 47.0%–81.1%	NA
Tamini [13]	Rectal cancer	Radical surgery	≥ 75	< 75 versus ≥ 75 1 year; 96.2% versus 92.5% 3 year; 88.4% versus 64.3% 5 year; 75.9% versus 50.6%	0.001
Signorelli [23]	Endometrial cancer Stage I	Hysterectomy	≥ 65	HR 4.20 (2.34–7.53) [DFS] HR 2.00 (1.18–3.37)	0.004 0.0008
Benedetti Panici [24]	Endometrial carcinoma early-stage	Hysterectomy pelvic lymphadenectomy versus no lymphadenectomy	≥ 65	HR 2.85 (1.65–4.92) [DFS] HR 1.49 (0.93–2.38)	< 0.001 0.09
Mahdi [25]	Uterine clear cell carcinoma	Surgically treated	≥ 65	HR 2.3 (1.92–2.81) Stage I–II: HR 3.5 (2.6–4.7)	< 0.001 < 0.001
Lim [12]	Advanced epithelial ovarian cancer	Surgically treated	≥ 65	Median; ≥ 65 versus < 65 57.8 M versus not reached	0.016
Langstraat [26]	Ovarian cancer Stage IIIC, IV	Surgical debulking	≥ 65	Median; 65–69 versus 70–74 versus 75–79 versus ≥ 80 All; 3.4 years versus 2.7 years versus 2.0 years versus 1.6 years R0; 5.9 years versus 7.9 years versus 5.4 years versus 5.0 years	< 0.0001 0.5516

Abbreviations: DFS, disease-free survival; HR, hazard ratio; OR, odds ratio; OS, overall survival.

TABLE 5 | Tumor-specific survival.

Study	Cancer type	Surgical procedure	Age (year)	Outcomes	*p*
Tamini [13]	Rectal cancer	Radical surgery	≥ 75	[TSS] < 75 versus ≥ 75 1 year; 96.2% versus 89.9% 3 years; 89.6% versus 77.3% 5 years; 79.9% versus 72.5%	0.117
Nunobe [16]	Gastric cancer Stage I	Gastrectomy	≥ 75	[DSS] < 75 versus ≥ 75 1 year; 99.8% versus 97.9%–99.4% 3 years; 98.9% versus 93.7%–97.8% 5 years;98.2% versus 91.4%–96.5%	NA
Shindoh [27]	solitary HCC measuring ≤ 5.0 cm	Anatomic resection versus nonanatomic resection	≥ 65	[DSS] HR 1.00 (0.57–1.77)	0.995
Kubo [28]	Hepatitis C virus-related hepatocellular carcinoma	Resection	≥ 65	[TFS] HR 1.63 (1.12–2.37)	0.010

Abbreviations: DSS, disease-specific survival; TFS, tumor-free survival; TSS, tumor-specific survival.

factor for OS. Moreover, several studies have shown that age has a relatively small influence on cancer-specific survival after a potentially curative resection.

4 | Discussion

Although there are many clinical reports on surgical treatment for older cancer patients, most of these reports are retrospective case studies, and large-scale prospective observation reports are rarely found. According to the literature review we conducted, it has been revealed that surgical treatment for older patients is associated with increased postoperative complications and postoperative syndrome, an increased mortality rate in highly invasive surgery, and lower overall survival rates.

When evaluating the effectiveness of surgical treatment for older cancer patients, the most desirable approach would be to conduct a RCT with a control group of nonsurgical observation or alternative treatment. However, RCTs that involve an alternative of not providing any cancer treatment are often ethically challenging. Additionally, there are often no alternative treatments that can replace surgical treatment in cancer treatment. Therefore, the evidence for surgical treatment for older cancer patients is mostly indirect. Moreover, although surgical procedures are commonly performed in older patients, sufficient literature reviews have not been previously performed. Comprehensive reviews on surgical treatment for older patients are expected to provide a necessary message for clinical practice. Thus, we conducted a cross-organ review and presented answers to the clinical questions in the form of GPS in which the statement was provided but not determine any recommendations.

To evaluate the significance of surgical treatment for older cancer patients, a comprehensive literature search was independently performed using the PubMed database, supported by the Japan Medical Library Association (Tokyo, Japan). As a result of this literature search, over 100000 clinical research reports were extracted (Table S2). However, only a few of the clinical research results retrieved could be directly extrapolated to the clinical practice in Japan because of the differences in the standard of care between different countries and regions. Therefore, in this review, we extracted literature focusing on surgical treatments for older cancer patients exclusively from the major cancer treatment guidelines in Japan so that we can produce statements that more or less reflect our current clinical practice, and summarized the evidence obtained from these studies. We selected the treatment guidelines for organ-specific surgeries that affect major thoracic and abdominal organs. Cancers with different levels of invasiveness and curability compared to other types of cancers (e.g., breast cancer, pancreatic cancer) were excluded from this review. In reality, the Breast Cancer Treatment Guidelines for the 2018 edition clarifies that "surgical treatment is the standard of care for older patients with breast cancer if they are sufficiently healthy to tolerate surgery" [29].

In general, surgical treatment in older patients is performed as safely as in non-older patients without a significant increase in postoperative mortality, although the incidence of postoperative complications and postoperative syndrome may be higher. However, when more intense surgery such as para-aortic lymph node dissection and/or resection with other organs is required, the postoperative mortality would likely increase among older patients. Therefore, it is important that preoperative functional assessment must be performed and interpreted meticulously for patient selection, especially when considering major surgery. As

an example, it has been written in the Clinical Practice Guidelines for Hepatocellular Carcinoma 2021that "It seems rational to say that age does not always limit the indications for hepatectomy and that hepatectomy deserves consideration also in elderly patients. However, it has been reported that the post-hepatectomy complications and the capability of patients to carry out daily living without assistance are affected by the aging-related reduction of activity of daily living (ADL) and physical/social/psychomental decline as well as by the so-called performance status, sarcopenia, and frailty, suggesting that comprehensive evaluation of functions during senility is essential when judging the indication of elderly patients for hepatectomy" [30].

The shortened OS after curative surgery among older patients may be attributable to both the invasiveness of the procedure and the inherently shorter life expectancy. Some studies attempt to minimize the impact of the short life expectancy by using outcome measures such as tumor-specific survival. However, the relevance of aging-related factors such as preoperative comorbidities and/or cognitive function could be overlooked in the studies that examine tumor-specific survival. All in all, because of the variability in target organs and evaluation methods, it is difficult to draw a definitive conclusion about the survival benefit of oncological surgery in older patients in general. However, it is important to bear in mind that overall expected prognoses in older cancer patients are often worse compared to non-older patients. In addition, older patients, especially those with frailty, are liable to suffer from prolonged surgical hospital stays that would both adversely affect the ADL and increase the medical cost [31, 32]. From the viewpoint of sustainability of the healthcare system within a rapidly aging population, medical professionals in Japan will be obliged in the future to consider more seriously the issue of cost-effectiveness.

The limitations of the present study are as follows: First, this review is different from a typical systematic review in that, instead of scrutinizing the results of global clinical trials extracted from commonly used literature review systems such as PubMed, we focused on extracting papers that are referred to in the major cancer treatment guidelines in Japan. Second, this review only included guidelines published before October 2021. However, to the authors' knowledge, there have been no clinical trial results after that date which could result in a paradigm shift in the surgical treatment of older cancer patients. Finally, due to the difficulty in analyzing cost-effectiveness under the national health insurance system in Japan, the impact of treatment costs on older patients with cancer was not evaluated in this guideline.

5 | Conclusion

For older cancer patients, surgical indications and procedures should be carefully determined based on surgical invasiveness and patient tolerability. Moreover, it is important to consider that life expectancy in older cancer patients is generally shorter compared to non-older patients.

Author Contributions

Chie Tanaka: conceptualization, methodology, investigation, writing – original draft, writing – review and editing, data curation, project administration, visualization, funding acquisition, supervision, formal analysis. **Takashi Ofuchi:** writing – review and editing, writing – original draft, conceptualization, methodology. **Kiichiro Ninomiya:** conceptualization, investigation, methodology. **Daisuke Inoue:** investigation, conceptualization, methodology. **Ken Sugimoto:** conceptualization, investigation, methodology. **Keiko Murofushi:** conceptualization, investigation, methodology. **Toru Okuyama:** investigation, conceptualization, methodology. **Shigeaki Watanuki:** investigation, conceptualization, methodology. **Chiyo Imamura:** conceptualization, investigation, methodology. **Daisuke Sakai:** conceptualization, investigation, methodology. **Naomi Sakurai:** conceptualization, methodology, investigation. **Kiyotaka Watanabe:** conceptualization, investigation, methodology. **Kazuo Tamura:** conceptualization, investigation, methodology. **Toshiaki Saeki:** conceptualization, investigation, methodology. **Hiroshi Ishiguro:** conceptualization, investigation, supervision, methodology.

Disclosure

The authors have nothing to report.

Conflicts of Interest

The authors whose names are listed immediately below report the following details of affiliation or involvement in an organization or entity with a financial or nonfinancial interest in the subject matter or materials discussed in this manuscript. Ninomiya K reports honoraria outside the current work from AstraZeneca, MSD, Bristol-Myers Squibb, Boehringer Ingelheim, Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, Ono Pharmaceutical, Nippon Kayaku, Kyowa Kirin, Novartis, Takeda Pharmaceutical, and Pfizer. Dr. Tanaka is a current editorial member.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.