



## RESEARCH ARTICLE

## Frailty as a Prognosis Factor in Cancer for the Elderly

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### Abstract

**Introduction:** Frailty is a geriatric syndrome related to adverse health outcomes in the elderly, due to a decrease systems' functional reserve. Cancer is a common pathology in the elderly, and we need tools for identifying the response to treatment and prognosis of elderly cancer patients. This short revision aims to assess the significance of the detection of frailty in the elderly patient with a tumor as a possible prognostic factor in terms of mortality, and the impact of the 2013 Frailty Consensus in the research activity.

**Materials and methods:** A review of the literature from 2013 (when an International Consensus on frailty was published) to 2016 was made, choosing works that used some of the frail scales proposed by the consensus and had mortality results with a correct description of the statistic analysis.

**Results:** 15 papers were selected, finding an increased mortality risk in frail older people (OR from 2.07 to 12.5). The number of papers related to frailty in cancer patients increased from 1 in 2013 to 10 in 2015.

**Conclusions:** Frailty must be detected in old cancer patient as a potential prognosis factor that can help in choosing the better treatment. The impact of this entity in publications is growing since the International consensus of 2013, but further research must be made to establish a gold standard for the detection of the syndrome, and analyze all the consequences of frailty in the evolution and prognosis of cancer.

### Keywords

Frail elderly, Neoplasms, Mortality, Risk

### Introduction

Frailty is a syndrome related to adverse health events and an increased risk of mortality and morbidity [1]. As a result of an older population, we can find a higher number of frail patients. Frailty is more common in older people, and it is associated with sarcopenia (although they are different entities) [2] and cardiovascular risk [3]. Frail patients present disability more frequently than nonfrail people, and need more social attention [4].

Cancer is frequent among older patients. About the 60 per cent of the new diagnosis of cancer is set on people over 65-years-old, and the 30 per cent in patients that are 75 or older [5]. Elderly are more likely to present neoplasias due to loss of function of the different cell molecular structures. This is often reflected in cell atrophy, but also in the loss of the ability to keep the genome stable, producing mechanisms that contribute to uncontrolled cell proliferation both in molecular and tissue levels. In this way, we can understand cancer as an age-related illness [6], which shares the pathophysiological mechanisms of frailty in relation to the loss of molecular functions.

In 2013, a group of international experts remarked the importance of frailty as a predictor of outcomes, and a measurement of the "biological age" of the individuals. Frail individuals have a lower life expectancy. They recommended the use of well validated scales as FRAIL scale, the Groningen Frailty Indicator (GFI) or the Canadian Study on Health and Aging Frailty Index (CSHA), among others [7].

The presence of frailty can be a determining factor in the response of an elderly cancer patient to the various treatments and the associated morbidity, as well as in the survival rates. This short revision aims to assess the significance of the detection of frailty in the elderly patient with a tumor as a possible prognostic factor in terms of mortality. Moreover, the impact on publications of the recommendations made by the international experts on geriatrics in 2013 will be examined.

## Materials and Methods

A revision of the literature published from 2013 to May of 2016 about this subject has been made, in order to analyse the importance of frailty as a prognosis factor in cancer.

### Information sources

A Medline search strategy was developed, by using the search form "cancer" AND "frailty" AND "mortality", and applying special criteria for searching just the publications from 2013 to 2016, so the impact of the recommendations of the International Geriatrics Societies in 2013 can be analysed.

### Eligibility criteria

Publications needed to meet specific criteria for

being considerate. They should use some of the scales proposed by the international consensus in 2013 for measure frailty: Groningen Frailty Index (GPI), modified Frailty Index (mFI), Fried criteria, Frail scale, Canadian Study on Health and Aging Frailty Index (CSHA), Gerontopole Frailty Scale [7].

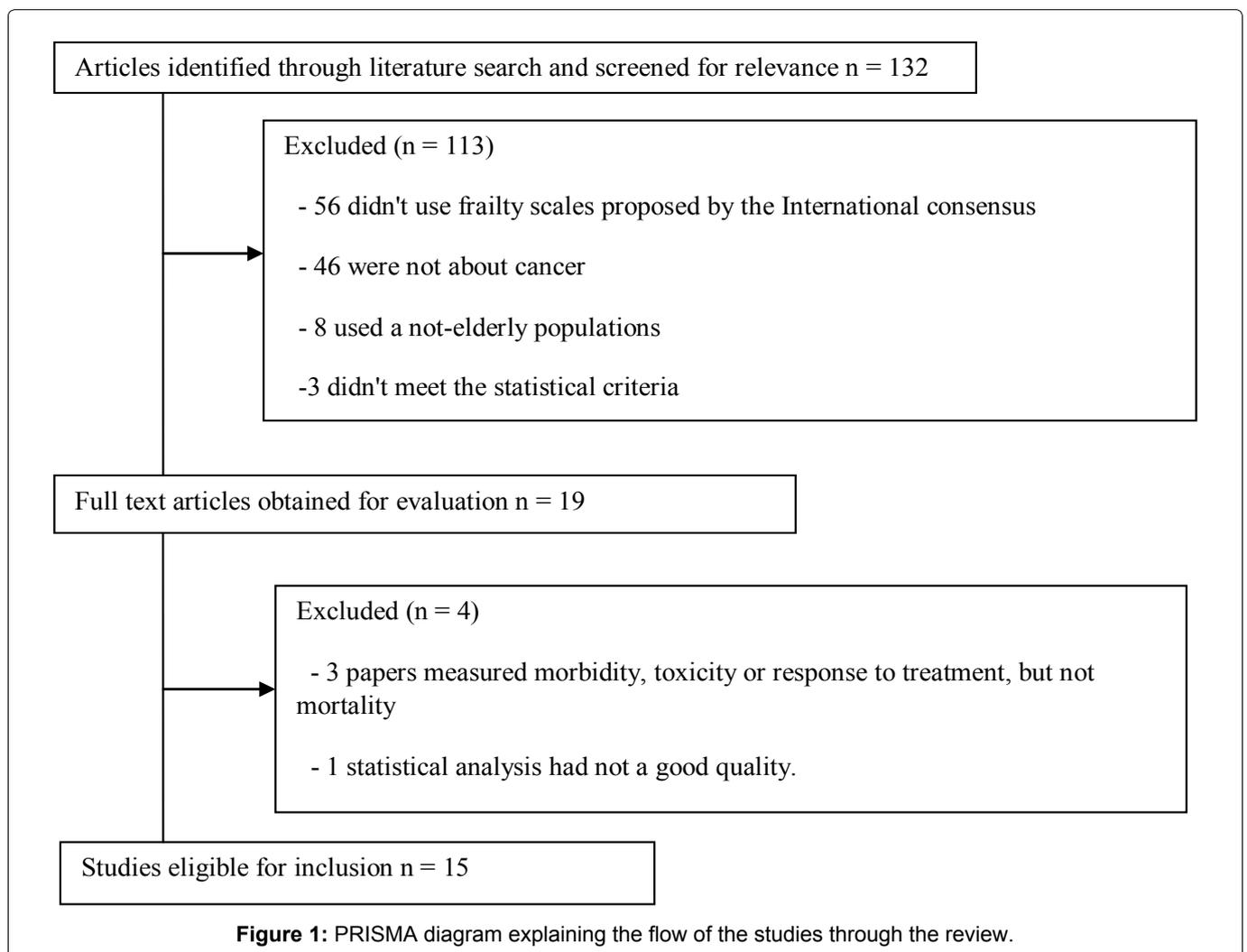
Articles must contain mortality results related to neoplasias in the elderly. Furthermore, statistics must be defined properly, giving and odds ratio (OR) or similar with a p value if possible. Confidence interval was not an essential criteria, but studies without it were remarked to signal the deficit.

Prospective and retrospective studies were included if they complied with the eligibility criteria.

### Study selection

The reading of the title and the abstract of all the results of the search was made, proceeding to read the complete articles specific on cancer on the elderly that complied the exposed criteria. The review was made by two independent investigators, resolving the conflicts by consensus.

The selected studies were classified depending on the publication year and the treatment applied to patients, as well as if they were general studies on cancer



or related to any specific neoplasia. Characteristics as if they were prospective or retrospective, the sample size and the odds or hazard ratio with p value and confidence intervals were extracted. The kind of treatment received by patients and the frailty scale employed were recorded.

## Outcomes

The principal outcome measured was mortality among frailty patients. Results on morbidity or response to treatment were analysed too.

Statistics: no statistic analysis could be made, due to the differences between the works in terms of sampling and objectives. A descriptive analyse was made, resuming the results of the publications.

## Results

Study selection: a PRISMA diagram explains the flow of the studies through the review (Figure 1). 232 articles were found, but just 19 papers examined frailty in on-

cology patients following one of the scales proposed by the International Consensus. Three of them measured toxicity, polypharmacy, morbidity or response to treatment, not mortality. Another one was discarded as in its result there was no odds ratio or similar parameter.

## Characteristics of the studies

Characteristics of the included studies are presented in Table 1 [8-22]. 5 studies had less than a hundred participants [10,15,18,20,22], 6 between a hundred and a thousand [11,12,14,19,21], and 5 more than this [8,9,13,16,17]. The population of three studies had any type of cancer [12,14,17], two urologic neoplasias [8,13], six digestive-related cancer [9,10,19-21], one was not specific but excluded skin cancer [11], another talked about lymphoma [18], one included neoplasias of the head, neck and skin [13] and two studied patients with gynaecological cancer (breast [22] or any other [16]).

## Frailty measurement

Four studies measured frailty thought the Modified

**Table 1:** Studies selected and its principal characteristics.

	Type of Study	Population	Treatment	Variable	Result	Year	Type of Neoplasia	Index
Chappidi, et al. [8]	Retrospective	2679	Surgery	Mortality (one month)	mFI > 3 OR 2.07 95%CI: 0.78-5.49 p > 0.01	2016	Urologic	Modified Frailty Index from the Canadian Study on Health and Aging Frailty Index
Buettner, et al. [9]	Prospective	1326	Surgery	Mortality	mFI score assessed at the time of initial surgery was not associated with 1-year mortality	2015	Digestive	Modified Frailty Index from the Canadian Study on Health and Aging Frailty Index and sarcopenia
Ugolini, et al. [10]	Prospective	46	Surgery	Mortality	TUGt OR 3.507, 95%CI: 1.35-9.11, p = 0.01 GFI was not associated with mortality	2015	Digestive	Timed up-and-go test and Groningen Frailty Index
Brown, et al. [11]	Prospective	416	Any kind of treatment	Mortality	Prefrail HR = 1.84 95%CI 1.28-2.65 p > 0.01 Frail HR 2.79, 95%CI: 1.34-5.81, p < 0.01	2015	Non-skin	Frailty Index
Aaldriks, et al. [12]	Prospective	520	Chemotherapy	Mortality	HR 1.47 95%CI 1.19-0.182 p < 0.001	2015	Any type of cancer	Groningen Frailty Index
Lascano, et al. [13]	Retrospective	41681	Surgery	Mortality (one month)	OR 5.95, 95%CI: 3.72-9.51, p < 0.01	2015	Urologic	Canadian Study on Health and Aging Frailty Index

Revening, et al. [14]	Prospective	393	Surgery	Mortality (one month)	Non frail OR 0.4 (not 95%CI) vs. frail OR 5.2 (not 95%CI) p = 0.07	2015	Any type of cancer	Modified Frailty Index from the Canadian Study on Health and Aging Frailty Index and sarcopenia
Bras, et al. [15]	Retrospective	90	Surgery	Mortality	GFI score didn't predict significantly death. p = 0.265	2015	Head, neck and skin	Groningen Frailty Index
Uppal, et al. [16]	Retrospective	6551	Any kind of treatment	Mortality and morbidity	OR mFI > 4 = 12.5 95%CI = 4.77-32.76 p > 0.01	2015	Gynecologic	Modified Frailty Index from the Canadian Study on Health and Aging Frailty Index
Handforth, et al. [17]	Retrospective (revisión)	2196	Any kind of treatment	Mortality	Prefrail HR 2.67, 95%CI 1.08-6.62; Frail HR 2.33, 95%CI 1.20-4.52	2015	Any	Various (phenotype, cumulative déficit, comprehensive geriatric assesment)
				Morbidity	4.86, 95% CI 2.19-10.78			
Aaldriks, et al. [18]	Prospective	90	Chemotherapy	Mortality	OR 2.55, 95%CI: 1.07-6.10; p = 0.04	2015	Lymphoma	Groningen Frailty Index
				Response to treatment	9.17, 95% CI: 1.51-55.8; p = 0.02			
Tegels, et al. [19]	Prospective	180	Surgery	Mortality	OR 4.0, 95%CI 1.1-14.1, p = 0.03	2014	Digestive (gastric)	Groningen Frailty Index
Dale, et al. [20]	Prospective	76	Surgery	Major complication or mortality	OR 4.06; p = 0.01	2014	Digestive (pancreatic)	Modified Frailty Index and Short Physical Performance Battery
				ICU admission	OR = 4.30; p = 0.01			
Aaldriks, et al. [21]	Prospective	143	Chemotherapy	Mortality	HR = 2.72 95% CI: 1.58-4.69; p < 0.001	2014	Digestive (colorectal)	Groningen Frailty Index
Aaldriks, et al. [22]	Prospective	55	Chemotherapy	Mortality	3.40 95% CI: 1.62-7.10; p = 0.001	2013	Breast	Groningen Frailty Index

Frailty Index from the Canadian Study on Health and Aging Frailty Index and sarcopenia [8,9,14,16], and another used this scale and the Short Physical performance Battery [20], The Groningen Frailty index (GFI) was used by six research groups [12,15,18,19,21,22], one used this index and the Timed up-and-go test too [10], and one else employed this tool combined with other measures [19]. The Canadian Study on Health and Aging Frailty Index was used in one publication [13], as well as the non-modified Frailty Index [11]. One of the studies used various frailty scales to identify frail and prefrail patients [17].

### Risk of mortality

Frailty was associated with a higher risk of mortality in all studies but three of them. The Groningen Frailty Index failed to alert from mortality in two studies [10,15], and the modified Frailty Index in one [19]. The increased mortality risk goes from de 2.07 [8] to 12.5 [16].

### Other results

Some of the works accepted measured other outcomes as ICU admission [20], or morbidity related to the

cancer process [16,17], as well as response to treatment [18]. In all cases, frailty was a predictor of a worse evolution of the neoplasia.

### Impact of frailty consensus

The number of articles about the studied subject increased significantly from 2013 to 2015, from one investigation [22] to ten [9-18] each year.

### Discussion

This revision has shows, as previous work, that frailty is clearly associated with higher mortality in old cancer patients [23]. Nevertheless, as there is no common standard for a frailty definition [4], studying the real impact of this entity among old cancer patients is quite complicated. In general, it is recommended to make a screening for frailty in older patients with oncological diseases, but the available frailty screening tools have not enough discriminative power to be useful in further assessment [24].

Frailty is a complex syndrome that must be suspected by geriatricians, family or general doctors [4], who usually knows better the patient, as it is a dynamic situation. It is important for oncologist, when the cancer diagnosis is made, to be assessed by other specialist on the patient way of live and the evolution of his health and functional abilities in the last years, in order to understand the possible implications of aging and frailty in the healing process. This complex procedure that includes physical, psychological, mental, functional and social evaluation of the elderly is called "geriatric assessment" [25].

Frailty represents an easy way of understanding the prognosis of a patient, as it is related with the functional reserve of the different organs and systems. A frail patient will not elaborate an appropriate answer to stress factors, so the homeostasis will be broken and disease, mortality or any other adverse health outcome will take place [1], as it has been demonstrated in this review.

This syndrome is related to sarcopenia and disability, although they are not synonyms. Understanding the frailty level of a patient is an easy way of evaluate the general status of the elderly within a few minutes [4]. The problem arrives when we have to choose one of the existing frailty definitions.

There are two approximations to frailty. In one hand, authors like Fried, et al. define frailty as a phenotype, so it can be found in patients who gather some symptoms and signs as slow gait speed, low grip strength, decreased aerobic capacity, fatigue and/or weight decrease [7]. It is necessary to know the parameters of the studied population, so we can compare the results of the physical examination of our patient with them. Furthermore, a dynamometer is needed to obtain all the parameters of the phenotype definition. Theses draw-

backs do not ease the application of the phenotype definition of frailty. In this revision, just two papers used phenotypic definitions of frailty [10,22].

On the other hand, authors like Rockwood have developed frailty scales from an addition of physical, mental, psychological and social deficits. Is the case of scales like the one of the Canadian Study on Health Aging group (CSHA), the modified Frailty Index (mFI) or the Groningen Frailty Index (GFI) [7]. One of the most important difficulties of these scales is that one of the deficits can explain the outcomes by itself, and these tools give the same prediction capacity to items as different as ischemic heart disease or widowhood in some cases. Nonetheless, most studies of this revision have used an accumulation of declines definition [9,11-19,21,22].

Three years ago, an International Consensus on frailty was proclaimed, trying to underline the importance of this entity and encouraging researches to examine the real impact of this syndrome in the different pathologies [7]. As a result, and as is showed in this paper, the number of publications has increased. Most of this publications use frailty within the addition of deficits definition.

There is a third way of defining frailty. The FRAIL scale mixes aspect from the phenotype and the addition of deficits definition. Through five questions (four about fatigue, aerobic capacity, strength and weight loose and one about number of a defined classification of illnesses) can determine if an individual meets the criteria for frailty, is not frail or can be classified in an intermediate state called "prefrailty" [26]. No works have been found that use the FRAIL scale as a prognosis tool for cancer patients.

Frailty has been related with and increased risk for mortality and morbidity derived from neoplasias and its treatment [8,10-12,14-22]. This result is consistent with studies in other pathologies [1], as cardiovascular diseases [3]. Frailty maximizes the cardiovascular risk through the generation of an increased trend to inflammation, and a decreased muscle mass that carries to insulin resistance. Inflammation provided by cancer can be added to the one derived from frailty, and produce a higher number of adverse health outcomes [6]. Nevertheless, the physiological influence of frailty and its metabolic ways must be defined in cancer patients.

Old patients have an immune system that does not react properly to infection. Cancer patients have a greater risk of infection due to the loss of immune response and to the suppression of it secondary to the treatments. Frailty is related to immunosenescence what means that frail people will respond worst to infection and its treatment if presented, because their immune system can no longer attack the microorganisms as well as it did before [27,28]. This can be part of the reason of the increased mortality and morbidity among

old frail cancer patients.

Only three works were not compatible with the increased mortality and morbidity associated with frailty. The study led by Bras' population included only patients with neck, head and skin neoplasias [15]. This neoplasias are not very common among elderly, and are infrequent in general population, so results are not quite representative of the elderly population and other risk factors might be associated with this type of cancer. Buettner, et al. designed an study that tried to describe the potential of sarcopenia in predicting risk of mortality in elderly cancer patients, adding this prediction power to frailty. They demonstrated that frail and sarcopenia individuals with sarcopenia suffer more complications and have a higher one-year mortality than frail non-sarcopenic people [9]. As sarcopenia and frailty are related, when we identify frail people with lower muscle mass we are selecting a group with higher risk of adverse outcomes, because they have two different syndromes that are related to mortality, morbidity and disability by themselves [2]. Ugolini, et al. didn't find connection between frailty (by using the Groningen frailty Index) and mortality [10], but they did with the Timed up-and-go test, which is considered an executive function test related to frailty [7].

## Conclusions

Frailty is a geriatric syndrome that should be taken into account when deciding the treatment in elderly cancer patients. As this entity is firmly related to increased mortality and morbidity, as well as poorer response to treatment, frailty must be checked in every old patient as a tool to decide the options of recovery, and consequently the best way to treat the neoplasia.

Although most cancer-related studies use the accumulation of deficits definition of frailty, it is possible that combining it with the phenotype definition increases the capacity of prediction of this syndrome, in terms of mortality, morbidity or response to treatment. Further research must be done in this field.

Since the publication of the Consensus on Frailty, many work on frailty has been developed. The importance of this syndrome is growing, and it is being subject of research in different fields, like cancer, due to its potential implications in the management of the patient because of the prognosis value it has in terms of life expectancy and response to treatment.

## References

- Chang SF, Lin PL (2015) Frail phenotype and mortality prediction: a systematic review and meta-analysis of prospective cohort studies. *Int J Nurs Stud* 52: 1362-1374.
- Reijnierse EM, Trappenburg MC, Blauw GJ, Verlaan S, de van der Schueren MA, et al. (2016) Common Ground? The Concordance of Sarcopenia and Frailty Definitions. *J Am Med Dir Assoc* 17: 371.e7-371.e12.
- Graciani A, García-Esquinas E, López-García E, Banegas JR, Rodríguez-Artalejo F (2016) Ideal Cardiovascular Health and Risk of Frailty in Older Adults. *Circ Cardiovasc Qual Outcomes* 9: 239-245.
- Acosta Benito MÁ (2014) Fragilidad en el anciano: del síndrome a la planificación sociosanitaria y legal [article in Spanish]. *Rev Esp Med Legal* 41: 45-88.
- Farré Mercadé MV, Benavent Boladeras R (2006) Cáncer. Neoplasias más frecuentes [text in Spanish]. In Spanish Society of Geriatrics and Gerontology. *Tratado de Geriatria para residentes*.
- Campisi J (2013) Aging, cellular senescence, and cancer. *Annu Rev Physiol* 75: 685-705.
- Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, et al. (2013) Frailty consensus: a call to action. *J Am Med Dir Assoc* 14: 392-397.
- Chappidi MR, Kates M, Patel HD, Tosoian JJ, Kaye DR, et al. (2016) Frailty as a marker of adverse outcomes in patients with bladder cancer undergoing radical cystectomy. *Urol Oncol* 34: 256.e1-256.e6.
- Buettner S, Wagner D, Kim Y, Margonis GA, Makary MA, et al. (2016) Inclusion of Sarcopenia Outperforms the Modified Frailty Index in Predicting 1-Year Mortality among 1,326 Patients Undergoing Gastrointestinal Surgery for a Malignant Indication. *J Am Coll Surg* 222: 397-407.
- Ugolini G, Pasini F, Ghignone F, Zattoni D, Bacchi Reggiani ML, et al. (2015) How to select elderly colorectal cancer patients for surgery: a pilot study in an Italian academic medical center. *Cancer Biol Med* 12: 302-307.
- Brown JC, Harhay MO, Harhay MN (2015) The Prognostic Importance of Frailty in Cancer Survivors. *J Am Geriatr Soc* 63: 2538-2543.
- Aaldriks AA, Maartense E, Nortier HJ, van der Geest LG, le Cessie S, et al. (2016) Prognostic factors for the feasibility of chemotherapy and the Geriatric Prognostic Index (GPI) as risk profile for mortality before chemotherapy in the elderly. *Acta Oncol* 55: 15-23.
- Lascano D, Pak JS, Kates M, Finkelstein JB, Silva M, et al. (2015) Validation of a frailty index in patients undergoing curative surgery for urologic malignancy and comparison with other risk stratification tools. *Urol Oncol* 33: 426.e1-426.e12.
- Revenig LM, Canter DJ, Kim S, Liu Y, Sweeney JF, et al. (2015) Report of a Simplified Frailty Score Predictive of Short-Term Postoperative Morbidity and Mortality. *J Am Coll Surg* 220: 904.e1-911.e1.
- Bras L, Peters TT, Wedman J, Plaat BE, Witjes MJ, et al. (2015) Predictive value of the Groningen Frailty Indicator for treatment outcomes in elderly patients after head and neck, or skin cancer surgery in a retrospective cohort. *Clin Otolaryngol* 40: 474-482.
- Uppal S, Igwe E, Rice LW, Spencer RJ, Rose SL (2015) Frailty index predicts severe complications in gynecologic oncology patients. *Gynecol Oncol* 137: 98-101.
- Handforth C, Clegg A, Young C, Simpkins S, Seymour MT, et al. (2015) The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Ann Oncol* 26: 1091-1101.
- Aaldriks AA, Giltay EJ, Nortier JW, van der Geest LG, Tanis BC, et al. (2015) Prognostic significance of geriatric assessment in combination with laboratory parameters in elderly patients with aggressive non-Hodgkin lymphoma. *Leuk Lymphoma* 56: 927-935.

19. Tegels JJ, de Maat MF, Hulsewé KW, Hoofwijk AG, Stoot JH (2014) Value of geriatric frailty and nutritional status assessment in predicting postoperative mortality in gastric cancer surgery. *J Gastrointest Surg* 18: 439-445.
20. Dale W, Hemmerich J, Kamm A, Posner MC, Matthews JB, et al. (2014) Geriatric assessment improves prediction of surgical outcomes in older adults undergoing pancreaticoduodenectomy: a prospective cohort study. *Ann Surg* 259: 960-965.
21. Aaldriks AA, van der Geest LG, Giltay EJ, le Cessie S, Portielje JE, et al. (2013) Frailty and malnutrition predictive of mortality risk in older patients with advanced colorectal cancer receiving chemotherapy. *J Geriatr Oncol* 4: 218-226.
22. Aaldriks AA, Giltay EJ, le Cessie S, van der Geest LG, Portielje JE, et al. (2013) Prognostic value of geriatric assessment in older patients with advanced breast cancer receiving chemotherapy. *Breast* 22: 753-760.
23. Denewet N, De Breucker S, Luce S, Kennes B, Higuete S, et al. (2016) Comprehensive geriatric assessment and comorbidities predict survival in geriatric oncology. *Acta Clin Belg* 71: 206-213.
24. Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, et al. (2012) Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. *Lancet Oncol* 13: e437-e444.
25. Korc-Grodzicki B, Holmes HM, Shahrokni A (2015) Geriatric assessment for oncologists. *Cancer Biol Med* 12: 261-274.
26. Morley JE, Malmstrom TK, Miller DK (2012) A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging* 16: 601-608.
27. Turner JE (2016) Is immunosenescence influenced by our lifetime "dose" of exercise? Turner JE. *Biogerontology* 17: 581-602.
28. Suh JD, Cho JH (2012) Trends in Head and Neck Cancer in South Korea Between 1999 and 2012. *Clin Exp Otorhinolaryngol* 9: 263-269.