Sphincter-saving proctectomy for rectal cancer in the elderly

Ann. Ital. Chir., 2016 87: 257-262
pii: S0003469X16024726
www.annitalchir.com

Michele Ammendola*/**, Raffaele De Luca**, Giuseppe Sammarco*, Rosario Sacco*, Severino Montemurro**

**Department of Medical and Surgery Sciences, Clinical Surgery Unit, University of Catanzaro "Magna Graecia" Medical School, Catanzaro, Italy*
***Surgery Unit, National Cancer Institute, Research Centre, "Giovanni Paolo II", Bari, Italy*

Sphincter-saving protectomy for rectal cancer in the elderly

AIM: *Rectal cancer shows a high incidence in older patients, however, only few reports focused exclusively on rectal cancer with the exclusion of the surgery of the colon. This retrospective study aims to compare short-term and long-term outcomes for rectal cancer in patients more than 75 years old with that observed in younger patients.*
MATERIAL OF STUDY: *Four hundred consecutive patients operated on for primary rectal adenocarcinoma were collected in a prospective institutional database and divided into two groups: group 1 (≥ 75 years, n =98); group 2 (<75 years, n= 302). Sphincter-saving restaurative proctectomy was the only procedure considered. Main clinical and pathological data, morbidity, clinical anastomotic leakage, reoperation rate, 30-day mortality, overall survival, and cancer-related survival were assessed and compa*red.
RESULTS: *In our experience, advanced age itself is not a contraindication for surgical sphincter-saving proctetomy in rectal cancer patients, although it is associated with higher morbidity and mortality. Overall survival is lower in patients over 75 age, but cancer-related survival is not different between the two groups.*
CONCLUSIONS: *In our experience, advanced age itself is not a contraindication for surgical sphincter-saving proctetomy in rectal cancer patients, although it is associated with higher morbidity and mortality. Overall survival is lower in patients over 75 age, but cancer-related survival is not different between the two groups.*

KEY WORDS: Outcomes, Rectal Cancer, Elderly, Sphincter-saving, Surgery

Introduction

Elderly people represent almost all patients diagnosed with and treated for rectal cancer. Surgical management and treatment decisions for this disease are becoming increasingly complex, but only few data are in literature with older patients. Incidence of rectal cancer increases with age, with an age specific incidence of 135 new cases per 100 000 people per year between 80 and 84 years of age [1-2]. Surgical resection of the primary tumour site and its lymph node tributaries, when technically possible, is the unique treatment which avoids complications that compromise the quality of life, such as obstruction or bleeding. For these reasons, surgery is a necessary curative therapy for patients with rectal cancer but there are many points of view about the optimum surgical management of elderly patients who are a heterogeneous group, ranging from fit to frail people. The percentage of patients that need surgery decreases with age and the curative surgery rate is substantially lower in older patients. Elderly people need more emergency surgery than do younger patients [3-6]. Usually, non restorative procedures are performed, such as Hartmann' s procedure, abdomino-perineal resection or local excision [7,8]. Transanal Endoscopic Microsurgery (TEM), is also useful for elderly and unfit patients [9-12].

Pervenuto in Redazione Settembre 2015. Accettato per la pubblicazione Novembre 2015.
Correspondence to: Michele Ammendola MD, Department of Medical and Surgical Sciences, Clinical Surgery Unit, University of Catanzaro "Magna Graecia" Medical School, Viale Europa, loc. Germaneto, Catanzaro, Italy (e-mail: michele.ammendola@libero.it)

Generally, elderly patients are recruited to clinical trials less often than younger patients, neoadjuvant radiotherapy or chemoradiotherapy is less used and in most colorectal cancer guidelines, routine screening is not offered to patients older than 75 years [13-16].
The resection of rectal cancer is one of the physiologic status and high rate of complications and its risks and benefits in the elderly have not been clearly defined. In literature, no data shows surgical sphincter-saving proctectomy outcomes for rectal cancer in the elderly.
Our retrospective study aims to compare short-term and long-term outcomes for rectal cancer in patients more than 75 years old with that observed in younger patients.

Methods

Study Populations

A series of 400 rectal cancer patients observed at National Cancer Centre "G. Paolo II" and at University of "Magna Graecia" were collected in a prospective institutional database and divided into two groups: group 1 (≥ 75 years, n =98); group 2 (<75 years, n=302). In the global series, there were 400 primary rectal adenocarcinomas with stage $T_{1-4}N_{0-2}M_{0-1}$ (according to the American Joint on Committee on Cancer 7th Edition, TNM Staging for Colo-Rectal Cancer) [17-19]. Helical computed tomography of the thorax, abdomen and pelvis revealed that patients had distant metastases. Before surgery, each patient was classified by the American Society of Anesthesiologist physiological status scoring system (ASA). Mechanical and antibiotic prophylaxis was administered as well as heparin to prevent infections, venous thrombosis and pulmonary embolism. In elective as in emergency, sphincter-saving restaurative proctectomy was the only procedure performed and only in the post-operative time stoma were fashioned to treat complications. Except for 24 patients, in all other, silicone transanal tube NO COIL ®, 60-80 mm long, 2 mm thick with a calibre of up to 2 cm, was applied and secured to the perineal skin by two stitches, then removed on the seventh postoperative day if no signs of leakage occurred [20]. All elective patients with T_{3-4} underwent short course neoadjuvant radiotherapy (RT) or chemoradioterapy (CHT). The clinico-pathological features of patients are summarized in Table I and Table 3. Main clinical and pathological data, morbidity, clinical anastomotic leakage, reoperation rate, 30-day mortality, overall survival, and cancer-related survival were assessed and compared (Table II). The follow-up interval was calculated in months and defined as the time between the date of surgery and the date of the event. Signed consent from individual patients were obtained to conduct the study.

Statistical analysis

Overall and cancer specific survival were estimated by the Kaplan-Meier product limit method [21]. *T-test* was used to statistically compare means. Correlations among the all analyzed parameters and the main clinico-pathological features were performed by Chi-square test (χ^2). $p<0.05$ was considered significant. With absolute frequencies less then 5 units, test of Fisher was used. All statistical analyses were performed with the SPSS statistical software package (SPSS, Inc., Chicago, IL).

Results

Significant differences between the two groups were detected with regard to the American Society of Anesthesiologists classification, comorbidities and the emergency presentation. Overall morbidity rate was

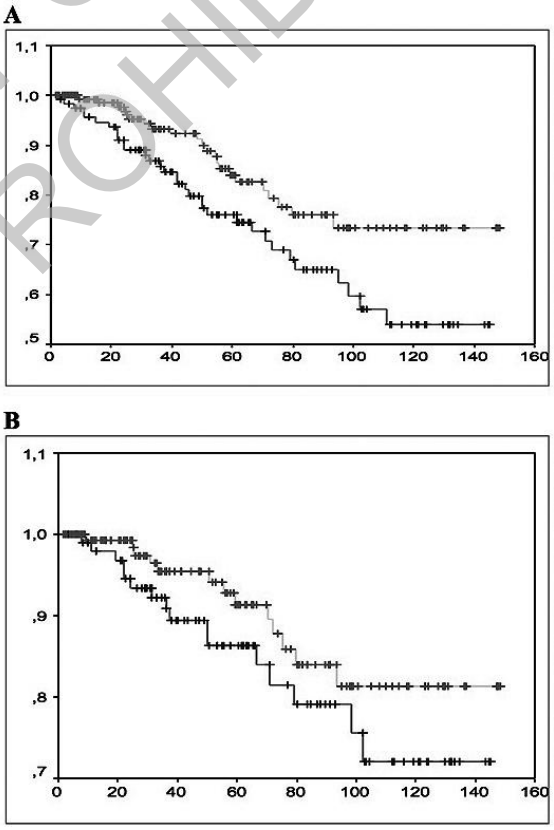

Fig. 1: (**A**). Overall survival of patients (excluding operative mortality). Blue line represents group 1 (patients aged ≥ 75 years); red line represents group 2 (patients aged <75 years). The overall 5-year survival rate: 76 % in group 1, 84 % in group 2 (P = 0.0223)
(**B**). Cancer-specific survival of patients operated on with a curative intent. Blue line represents group 1 (patients aged ≥ 75 years); red line represents group 2 (patients aged <75 years). The cancer-specific 5-year survival rate: 86 % in group 1, 91 % in group 2 (P =0.0179).

30.4% and 20.2% in group 1 and group 2, respectively. Clinical anastomotic leakage rate was 6.1% in group 1 while 10.9% in group 2. The reoperation rate was 7.1% and 9.9% respectively in group 1 and group 2, mainly related to anastomotic leakage. The operative mortality rate was 6.1% in group 1 and 1.3% in group 2 (Table II). The Kaplan-Meier overall survival showed a significant difference between the two groups of patients with overall 5-year survival rate of 76 % in group 1, 84 % in group 2 (P = 0.0223), and cancer-specific 5-year survival rate of 86 % in group 1 while 91 % in group 2 (P =0.0179) (Fig. 1 A-B).

Discussion

Rectal cancer is one of the most representative diseases whose incidence correlates directly with increased age. In literature, there are few evidence-based data for surgical rectal cancer management in elderly patients. Most studies, are single-centre series from specialized surgical centres, with inherent selection biases. They include mainly elderly people experiencing successful ageing with no serious comorbidity. Most frail elderly patients with rectal cancer also are not referred to surgeons or are spontaneously excluded from some surgical indications [22-24]. Advantage age should not rule out patients from undergoing curative rectal resection. Elderly patients had significantly more comorbidities than did younger patients. Comorbidity, rather than age, increases mortality and the occurrence of complications after curative surgery for rectal cancer in elderly patients. However, despite higher risk of post-operative mortality and reduced overall survival, selected elderly patients benefit from radical surgery for rectal cancer [25-29].

Age alone should not be a contraindication to restorative rectal resection. Older adults are know to have a deterioration of the pelvic diaphragm muscles and exter-

TABLE I - *Clinical features of patients*

	Overall population n=400	<75 AA n =302	%	≥75 AA n=98	%	*P value*
SEX						
M	248	188 M	62.2%	60 M	61.2%	
F	152	114 F	37.8%	38 F	38.8%	0.8556**
Comorbidities	239	158	52%	81	83%	<0.05
Neoadjuvant treatment						
RT-CHT	80	64	21.2%	16	16.3%	0.295
NO RT-CHT	315	238	78.8%	82	83.7%	
RT	5					
LEVEL OF TUMOR						
HIGH	191	136	45.03%	55	56.1%	0.127
MEDIUM	98	80	26.5%	18	18.3%	
LOW	111	86	28.5%	25	25.5%	
ASA SCORE *	204	157	51,99%	39	39,80%	<0.05
I-II	196	145	48,01%	59	60,20%	
III-IV						
CLINICAL SETTING						
ELECTIVE		285	94.3%	72	73.4%	
EMERGENCY		19	6.4%	26	26.5%	<0.05
Occlussion		18		25		
Perforation		1		1		
RADICALITY	309	231	76.5%	78	79.5%	0.524**
R0						
R1-R2	91	71	23.5%	20	20.4%	
TYPE OF ANASTOMOSIS						
CAA	101					
CPA	219					
CJPAA	80					

** statistically not significant

Table II - *Surgical Outcomes*

	OVERALL POPULATION	<75 AA		≥75 AA		p
	n= 400	n = 302	%	n= 98	%	value
LEAKAGE	41	35/302	10.9%	6/98	6.1%	0.508*
OVERALL 30-DAY MORTALITY	10	4/302	1.3%	6/98	6.1%*	Overall 0.984**
LEAKAGE-RELATED	2	2		0		Test of Fisher
NO LEAKAGE-RELATED	8	2		6		
REOPERATIONS	37	30/302	9.9%	7/98	7.1%	Reoperation 0.407
LEAKAGE-RELATED	29	24/30	80%	5/7	71.4%	
NO LEKAGE-RELATED	8	6/30	20%	2/7	29.6%	
LEAKAGE-TREATMENT						0.967**
STOMA	29	24	68.5%	5	80%	Test of Fisher
CONSERVATIVE	12	11	31.5%	1	20%	
CHT ADJUVANT	130	112		18		
CHT-RT ADJUVANT	20	17		3		
RT ADJUVANT	3					

* Statistically not significant
** Absolute frequencies less then 5 units: Test of Fisher

Table III - *Pathological data of patients*

	Total	%	<75 AA		≥75 AA		p
			n= 302	%	n= 98	%	value
Stadio 0	38	9.5	27	8.9	11	11.2	0.503*
Stadio I	75	18.7	59	19.5	16	16.3	0.479
Stadio II	86	21.5	64	21.2	22	22.5	
A	74	86	55	85.9	19	86.3	0.792*
B	12	14	9	2.9	3	13.6	
Stadio III	103	25.7	76	25.1	27	27.5	
A	8	7.7	7	9.2	0	/	0.639*
B	46	44.6	31	40.7	16	59.2	
C	49	47.5	38	50	11	40.7	
Stadio IV	98	24.5	76	25.1	22	22.4	0.587*

* statistically not significant

nal anal sphincter, leading to a greater incidence of continence and defecation disorders. Sphincter function, assessed clinically and if necessary after manometry, is an essential element to consider in the pre-operative assessment and the decision-making procedure. If sphincter function assessment is found acceptable, low colorectal anastomosis, coloanal anastomosis and intersphincteric resection are possible in selected elderly patients and are associated with a good functional results and quality of life [30-35].

Results of studies of rectal surgery by laparotomy in the elderly patients, have drawn attentions to the increased risk of cardiac and pulmonary post-operative complications. These patients, seem to benefit more from a laparoscopic approach than do younger patients [36-39].
For these reasons, we think that, a multidisciplinary cooperation, involving oncologists, gastroenterologists, radiotherapists, anaesthetists, radiologist, pathologists and surgeons, is essential in elderly patients. In these patients, after oncogeriatric assessment taking into account physi-

ological age, presence of geriatric syndrome, comorbidities, the patient's general condition, and estimated life expectancy, mayor curative rectal cancer surgery similar to that undertaken in younger patients can be done [40-43]. In our experience advanced age itself is not a contraindication to surgery, although it is associated with higher morbidity and mortality. No laparoscopy approach but open sphincter-saving restaurative proctectomy without stoma was the only procedure performed. Each patient was classified by the American Society of Anesthesiologist physiological status scoring system (ASA). Antibiotic and heparin prophylaxis was administered to prevent infections, venous thrombosis and pulmonary embolism in elective as in emergency cases. Our data demonstrated also, that survival is lower in patients over 75 age, but cancer-related survival is not different between the two groups

Riassunto

Il tumore del retto ha un'alta incidenza nei pazienti anziani ma pochi dati sono presenti in letteratura rispetto al tumore del colon. L' obiettivo del nostro studio è quello di comparare i risultati in termini di dati clinici e patologici post-operatori, di sopravvivenza e di sopravvivenza cancro-correlata, tra due gruppi di pazienti (gruppo 1: ≥ 75 anni, n =98; gruppo 2: <75 anni, n= 302) affetti da tumore del retto sottoposti ad intervento di proctectomia restaurativa con rispetto dell' integrità anatomo-funzionale dello sfintere anale. I nostri risultati non mostrano nessuna differenza statisticamente significativa tra i due gruppi, in particolar modo per il dato della sopravvivenza cancro-correlata. La sopravvivenza globale risulta essere inferiore nel gruppo dei pazienti anziani rispetto ai pazienti con eta minore dei 75 anni.

References

1. Rutten HJ, den Dulk M, Lemmens VE, van de Velde CJ, Marijnen CA: *Controversies of total mesorectal excision for rectal cancer in elderly patients.* Lancet Oncol, 2008; 9(5):494-501

2. Law WL, Chu KW: Anterior resection for rectal cancer with mesorectal excision: A prospective evaluation of 622 patients. Ann Surg, 2004; 240(2):260-68.

3. Vironen JH1, Sainio P, Husa AI, Kellokumpu IH: C*omplications and survival after surgery for rectal cancer in patients younger than and aged 75 years or older*. Dis Colon Rectum, 2004; 47(7):1225-231.

4. Mulcahy HE1, Patchett SE, Daly L, O'Donoghue DP: *Prognosis of elderly patients with large bowel cancer.* Br J Surg, 1994; 81(5):736-38.

5. Singh J, Stift A, Brus S, Kosma K, Mittlböck M, Riss S: *Rectal cancer surgery in older people does not increase postoperative complications. A retrospective analysis*. World J Surg Oncol, 2014, 12:355.

6. Ramesh HS1, Pope D, Gennari R, Audisio RA: *Optimising surgical management of elderly cancer patients*. World J Surg Oncol, 2005; 3(1):17.

7. Endreseth BH, Romundstad P, Myrvold HE, Bjerkeset T, Wibe A: *Norwegian Rectal Cancer Group: Rectal cancer treatment of the elderly*. Colorectal Dis, 2006; 8(6):471-79.

8. Bufalari A, Giustozzi G, Burattini MF, Servili S, Bussotti C, Lucaroni E, Ricci E, Sciannameo F: *Rectal cancer surgery in the elderly: A multivariate analysis of outcome risk factors*. J Surg Oncol, 2006; 93(3):173-80.

9. Baci D, Durut I, Bukvi N, Cepi I: *Transanal endoscopic microsurgery (TEM) alternative or a method of choice in treating tumors of the rectum with appropriately selected patients?* Coll Antropol, 2014; 38(4):1127-30.

10. Ács B, Szász AM, Kulka J, Harsányi L, Zaránd A: Is *it radical enough? Transanal endoscopic microsurgery for the treatment of rectal neoplasia: Clinicopathological view point.* Magy Seb, 2014; 67(6):329-33.

11. Quarto G, Sivero L, Benassai G, Bucci L, Desiato V, Perrotta S, Benassai G, Massa S: *Early rectal cancer: local excision by Transanal Endoscopic Microsurgery (T.E.M.).* Ann Ital Chir, 2013; 84(4):437-39.

12. Quarto G, Sivero L, Benassai G, Bucci L, Desiato V, Perrotta S, Benassai G, Massa S: *TEM in the treatment of recurrent rectal cancer in elderly*. Ann Ital Chir, 2014; 85(1):101-4.

13. *Summaries for patients. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation*. Ann Intern Med. 2008; 149(9):I-44.

14. Ugolini G, Ghignone F, Zattoni D, Veronese G, Montroni I: *Personalized surgical management of colorectal cancer in elderly population*. World J Gastroenterol, 2014; 20(14):3762-777

15. Habr-Gama A, Sabbaga J, Gama-Rodrigues J, São Julião GP, Proscurshim I, Bailão Aguilar P, Nadalin W, Perez RO: *Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management?* Dis Colon Rectum, 2013; 56(10):1109-117.

16. Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U Jr, Silva e Sousa AH Jr, Campos FG, Kiss DR, Gama-Rodrigues J: *Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy*: *Long-term results.* Ann Surg, 2004; 240(4):711-17.

17. Angenete E, Correa-Marinez A, Heath J, González E, Wedin A, et al: *Ostomy function after abdominoperineal resection-a clinical and patient evaluation.* Int J Colorectal Dis, 2012; 27(10): 1267-274.

18. Astler VB and Coller FA: *The prognostic significance of direct extension of carcinoma of the colon and rectum*. Ann Surg, 1954; 139(6): 846-52.

19. Ratto C and Ricci: *Potential pitfalls concerning colorectal cancer classification in the seventh edition of the AJCC Cancer Staging Manual*. Dis Colon Rectum, 2011; 54(8):e232.

20. Montemurro S, De Luca R, Caliandro C, Ruggieri E, Rucci A, Sciscio V, Ranaldo N, Federici A: *Transanal tube NO COIL® after rectal cancer proctectomy. The "G. Paolo II" Cancer Centre experience.* Tumori, 2012; 98(5):607-14.

21. Kaplan ER, Meier P: *Non parametric estimation for incomplete observation*. J Am Stat Assoc, 1958; 227:457-81.

22. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, Lichtman S, Mor V, Monfardini S, Repetto L, Sørbye L, Topinkova E: *Task Force on CGA of the International Society of Geriatric Oncology: Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG*). Crit Rev Oncol Hematol, 2005; 55(3):241-52.

23. Extermann M, Hurria A: *Comprehensive geriatric assessment for older patients with cancer.* J Clin Oncol, 2007; 25(14):1824-831.

24. Hurria A, Lichtman SM, Gardes J, Li D, Limaye S, Patil S, Zuckerman E, Tew W, Hamlin P, Abou-Alfa GK, Lachs M, Kelly E: *Identifying vulnerable older adults with cancer: integrating geriatric assessment into oncology practice*. J Am Geriatr Soc, 2007; 55(10):1604-608.

25. Phillips PS, Farquharson SM, Sexton R, Heald RJ, Moran BJ: *Rectal cancer in the elderly: patients' perception of bowel control after restorative surgery*. Dis Colon Rectum, 2004; 47(3):287-90.

26. Jung B, Påhlman L, Johansson R, Nilsson E: *Rectal cancer treatment and outcome in the elderly: An audit based on the Swedish Rectal Cancer Registry 1995-2004*. BMC Cancer, 2009; 9:68.

27. Manceau G, Karoui M, Werner A, Mortensen NJ, Hannoun L: *Comparative outcomes of rectal cancer surgery between elderly and non-elderly patients: A systematic review*. Lancet Oncol, 2012; 13(12):e525-36.

28. Pala C, Serventi F, Paliogiannis P, Trignano E, Attene F, Scognamillo F, Trignano M*: Functional sequelae after low anterior rectal surgery.* Ann Ital Chir, 2009; 80(3):193-97.

29. Pata G, Casella C, Nascimbeni R, Cirillo L, Salerni B: *Modifiable risk factors in colorectal surgery: Central role of surgeon's volume*. Ann Ital Chir, 2008; 79(6):427-32.

30. Ito M, Saito N, Sugito M, Kobayashi A, Nishizawa Y, Tsunoda Y: *Analysis of clinical factors associated with anal function after intersphincteric resection for very low rectal cancer*. Dis Colon Rectum, 2009; 52(1):64-70.

31. Denost Q, Laurent C, Capdepont M, Zerbib F, Rullier E: *Risk factors for fecal incontinence after intersphincteric resection for rectal cancer.* Dis Colon Rectum, 2011; 54(8):963-68.

32. McNamara DA, Parc R: *Methods and results of sphincter-preserving surgery for rectal cancer.* Cancer Control, 2003; 10(3):212-18.

33. Bretagnol F, Rullier E, Laurent C, Zerbib F, Gontier R, Saric J: *Comparison of functional results and quality of life between intersphincteric resection and conventional coloanal anastomosis for low rectal cancer.* Dis Colon Rectum, 2004; 47(6):832-38.

34. Coco C, Valentini V, Cogliandolo S, Cosimelli MO, Picciocchi A: *Surgery and radiotherapy in rectal cancer: indications for anal sphincter conservation.* Ann Ital Chir, 2001; 72(5):611-17.

35. Giglio MC, Persico M, Quarto G, Benassai G, Luglio G, Tarquini R, Celentano V, Sollazzo V, Bucci L: *Intersphinteric resection for rectal cancer: role in fecal continence and Quality of Life.* Ann Ital Chir, 2013; 84(3):287-90.

36. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM; *MRC CLASICC trial group: Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled tria*l. Lancet, 2005. 365(9472):1718-26

37. Zhao JK1, Chen NZ1, Zheng JB1, He S1, Sun XJ: *Laparoscopic versus open surgery for rectal cancer: Results of a systematic review and meta-analysis on clinical efficac*y. Mol Clin Oncol, 2014. 2(6):1097-1102

38. Aziz O, Constantinides V, Tekkis PP, Athanasiou T, Purkayastha S, Paraskeva P, Darzi AW, Heriot AG: *Laparoscopic versus open surgery for rectal cancer: a meta-analysis.* Ann Surg Oncol, 2006; 13(3):413-24.

39. Nussbaum DP, Speicher PJ, Ganapathi AM, Englum BR, Keenan JE, Mantyh CR, Migaly J: *Laparoscopic versus open low anterior resection for rectal cancer: results from the national cancer data base.* J Gastrointest Surg, 2015; 19(1):124-31.

40. PACE participants, Audisio RA, Pope D, Ramesh HS, Gennari R, van Leeuwen BL, West C, Corsini G, Maffezzini M, Hoekstra HJ, Mobarak D, Bozzetti F, Colledan M, Wildiers H, Stotter A, Capewell A, Marshall E: *Shall we operate? Preoperative assessment in elderly cancer patients (PACE) can help. A SIOG surgical task force prospective study*. Crit Rev Oncol Hematol, 2008; 65(2):156-63.

41. Repetto L, Fratino L, Audisio RA, Venturino A, Gianni W, Vercelli M, Parodi S, Dal Lago D, Gioia F, Monfardini S, Aapro MS, Serraino D, Zagonel V: *Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: An Italian Group for Geriatric Oncology Study.* J Clin Oncol, 2002; 20(2):494-502.

42. Pope D, Ramesh H, Gennari R, Corsini G, Maffezzini M, Hoekstra HJ, Mobarak D, Sunouchi K, Stotter A, West C, Audisio RA: *Pre-operative assessment of cancer in the elderly (PACE): a comprehensive assessment of underlying characteristics of elderly cancer patients prior to elective surgery.* Surg Oncol, 2006; 15(4):189-97.

43. Owusu C, Berger NA: *Comprehensive geriatric assessment in the older cancer patient: Coming of age in clinical cancer care.* Clin Pract (Lond), 2014; 11(6):749-62.