Risk assessment for cancer surgery in elderly patients

Hodigere SJ Ramesh[1]
Tom Boase[2]
Riccardo A Audisio[1,2]

[1]Department of Surgery, Whiston Hospital, Prescot, Liverpool, Merseyside, UK; [2]University of Liverpool, Liverpool, Merseyside, UK

Abstract: Global growth of the elderly population is requiring healthcare providers to cater for an expanding elderly cancer subpopulation. The aggression with which cancer should be treated in this subpopulation is an ethical dilemma and is an ongoing debate, as surgeons have feared increases in postoperative morbidity and mortality. As a result elderly patients often receive suboptimal cancer treatment. The need for standardization of cancer surgery is well recognized despite the difficulties in view of heterogeneity of the group. In this article, epidemiological changes, tumor biology specific to elderly cancer are visited, operative risk assessment tools are discussed, and interim results of ongoing multinational investigation ie, PACE (Preoperative Assessment of Cancer Elderly) revealed.

Keywords: Elderly, cancer, co-morbidity, surgery, PACE, operative risk

Introduction

The definition of "elderly" is controversial. The traditional demographic definitions include those patients exceeding 65 years of age. Census statistics show that this age group is expected to rise. Agreement on what constitutes the elderly cancer patient is particularly vital since the community age structure is very dynamic (Taueber 1993). Functional deterioration is more frequently apparent beyond the age of 70 years (Yancik et al 1998). No two elderly individuals are same: they differ in their physical fitness, cognitive level, and presence of co-morbidities, quality of life, and life expectations. Surprisingly, few objective instruments have been made available to categorise age-related pre-existing chronic illness; age related functional physical decline, or preoperative risk status (Copeland et al 1991; Yancik et al 1998; Ogle et al 2000).

Ageism is defined as a "prejudice towards, stereotyping of and/or discrimination against any person or persons directly and solely as a function of their having attained a chronological age which the social group defines as old" (APA 2005). Ageism attitudes are deep-rooted in mankind and are reflected in language, attitude, beliefs, behaviours, and policies (Penson et al 2004). Healthcare providers, including surgeons, are no exception to ageist bias. Age frequently affects the overall cancer treatment plan, including the surgeon's view towards operative strategy and multi-modal treatment (Ogle et al 2000). The majority of surgical oncologists seem to be aware of the burden of elderly patients affected by cancer and are not biased by an ageist approach. However there is disturbing evidence of a wide variety of treatment options offered, ranging from a minimalist approach to over-treatment (Audisio, Osman, et al 2004).

Cancer is a disease of the aging. Solid tumors predominantly affect the aged and most cancer-related deaths occur within this age group (Brookes 1937; Wallach and Kurtz 1990; Alexander et al 1991). The elderly receive substandard cancer treatment in comparison with the young although the quoted reasons are many (Welch 1948;

Correspondence: Riccardo A Audisio
Consultant Surgical Oncologist, Honorary Reader, University of Liverpool, Whiston Hospital, St Helens and Knowsley NHS Trust, Warrington Road, Prescot, L35 5DR, UK
Tel +44 151 430 1079
Fax +44 151 290 4113
Email raudisio@doctors.org.uk

Greenfield 1975; Boyd et al 1980; Greenburgh et al 1985; Samet et al 1986; Brow et al 1991; Fallahzadeh and Mays 1991; Firat, Bousamra, et al 2002; Audisio, Bozzetti, et al 2004). This has prompted several surgical oncologists to review their series. Outcomes of these are superimposable long-term cancer-related outcome across all age groups and short term complications and mortality which do not seem to differ in a highly selected patient group undergoing cancer surgery (Vercelli et al 1998; Firat, Byhardt, et al 2002).

Surgery for elderly cardiac, orthopaedic, and vascular diseases is increasingly accepted. Yet, the reluctance to offer optimal cancer surgery continues (Alexander et al 1991) although it remains the primary treatment for solid cancer (Wallach and Kurtz 1990). Our limited knowledge of the elderly sub-population is due to the exclusion of onco-geriatric patients from clinical trials (Brow et al 1991; Fallahzadeh and Mays 1991; Firat, Bousamra, et al 2002). There is an urgent need for expanding our understanding of cancer behavior and cancer management for this unique group. Better understanding will come with elderly patients taking part in clinical research and by encouraging clinicians to take part in scientific meetings dedicated to onco-geriatrics.

Epidemiology

The median life expectancy of population among industrialized countries has dramatically expanded in recent years. An effect of an absolute rise in geriatric population among populous countries (ie, China, India, and Brazil) despite smaller in proportion (11% to 15%), and a higher proportionate rise (20%) in developed countries by 2020, is likely to lead to geriatric population explosion (Day 1996; US Census 1996; Kalache and Keller 2000). At the end of the 19th century, the average life expectancy was 40 years, but has now doubled to 81 years of expected survival for females, and 76 years for males in the UK. A 60 year old subject is now expected to survive for 24 years and an 80 year old is expected to survive for 6 years in Western Europe (Lag et al 1999). On the other hand, the risk of developing cancer increases with age. According to the Cancer Incidence, Mortality and Prevalence in the European Union (EUCAN) 90 data, 58% of cancers, and 69% of cancer deaths, affect subjects aged 65 years or more. When all tumors are taken into account, the risk of developing cancer among persons older than 65 is 2.9-fold for males and 2.2-fold for females, in comparison with 55 to 64 year olds (Coeburgh 2001). According to the SEER (Surveillance Epidemiology and End Results) data, the prevalence of cancer is 207.4 cases/100 000 in the <65 year old subjects, and 2163.9/100 000 in ≥65 year old subjects in the US. Mortality in this survey was 68.8 and 1076.2/100 000 subjects, respectively. This means cancer prevalence is 10 times, and mortality 15 times higher in the ≥65 year olds (Lag et al 1999).

Le Quintree et al (2005) concluded the methodological quality of randomized controlled trials (RCT) in very elderly subjects is equivalent to that of RCT in the general adult population. Nevertheless, RCT are very scarce and neglect certain diseases. RCT in elderly should be strongly encouraged (Le Quintree et al 2005). Since only a small sub-setting of geriatric patients are being entered into clinical trials (De Rijke et al 1996, 2000, 2002; Barchielli and Balzi 2000), elderly patients are still being managed on the assumptions and outcomes derived from a younger cancer patient.

Despite this epidemiological "time bomb" (Masoro 1997; Redmond and Aapro 1997), there is concern that the scientific community has so far been unable to develop a significant amount of evidence-based knowledge.

Tumor biology

The increase in incidence of cancer with age is related to a number of biologic factors. Age-related etiological factors includes decreased immune surveillance, longer duration of carcinogenic exposure, increased susceptibility of cells to carcinogens, decreased DNA repair, oncogene activation or amplification, and defects in tumor-suppressor genes. The biological behaviour of neoplasm, once initiated, may vary in different age groups depending on tumour type, immune system status, and alterations in other regulatory factors such as angiogenesis. Attention to age-related biological changes are essential to the designing of successful therapy (Cohen 1994).

The biology of cancers differs in various age groups, with variations in growth patterns, and doubling times, intrinsic hormonal receptor expression, DNA ploidy, tumor angiogenesis, percentage of cells in S-phase, p53 expression, and extracellular matrix protein expression (Piantanelli 1988; Cutler and Sensei 1989; Cristofalo et al 1994; Osiewicz and Hamann 1997). The microenvironment of senescent tissue is less capable of supporting rapid tumor growth. Histologically identical tumor in older patients may behave differently (Olshansky et al 1990; Holmes et al 1991; Eppenberger-Castori et al 2002; Anisimov 2003). The subcellular changes involved in the aging process and the effect of particular aging 'phenotype' has on cancer susceptibility is ill-understood (Thigpen 1998; Ling et al 2000). The correlation between immune system and cancer development/progression are currently poorly understood (Ling et al 2000; Schindowski et al 2002; Zhang et al 2002). Prolonged tumor-associated antigen exposure associated with immune 'exhaustion' and absence of repair genes is the predominance of a 'frail' gene variant (Baramiya 2000; Franceschi et al 2000; Ling et al 2000).

Age influences the predilection of cancer for disease site and histology type, ie, higher incidence of adeno-carcinoma of the distal esophagus, well-differentiated gastric tumors, right-sided colonic cancer, and low-grade lobular or mucinous type breast tumors in the elderly population have been reported (Audisio, Veronesi, et al 1997). Similarly a higher incidence of larger thyroidal tumour with Hürthle cell variant, extra-thyroidal growth and metastases at presentation are noted in elderly (Audisio and Zbar 2002). Elderly patients have greater frequency of tumors with more indolent histology and an overall favorable tumor profile (Hayman and Muss 2003): Older women with breast cancer tend to have more estrogen receptor-positive tumors (Wyld and Reed 2003). These basic pathological differences will inherently affect outcome (Franceschi et al 2000). For most types of solid epithelial tumors, old age itself does not appear to function as an independently negative prognostic variable for cancer-specific survival; a finding evident in recent studies assessing colorectal cancer (Audisio, Cazzaniga, et al 1997; Staudacher et al 2000; Chiappa et al 2001), gastric cancer (Lo et al 1996; Kitamura et al 1999), esophageal carcinoma (Jougon et al 1997; Poon et al 1998), liver (Chiappa et al 1999), head & neck (Robinson 1994; Rapidis et al 1998) and breast cancers (Veronesi et al 1988; Desch et al 1993; Newschaffer et al 1996; Siliman 1996).

More complex issues, however, impact on different age groups and affect their overall and disease-free survival.

Surgical risk assessment

The most important responsibility a surgeon is asked to take is to decide whether to operate or not (Jones and de Cossart 1999; de Cossart 2001). This is particularly true when the patient is a high surgical risk.

The decision-making process is complex in a poor surgical candidate or frail and elderly: on one side, a nihilistic approach has been repeatedly reported, which results in intolerably poor cancer management and outcomes; on the other, the surgical oncologist must balance the operative risk against benefits.

A number of factors, including a greater need for information, a more effective utilization of available resources, and advances in peri-operative management and surgical techniques, demand an improved risk definition to be shared between the surgeon and the patient.

Unfortunately there seems to be no laboratory test capable of predicting postoperative adverse outcomes (Balducci et al 2001).

None of the risk classifications aimed at predicting outcomes in specific conditions used by surgeons are completely reliable. More importantly, no scoring method has ever been attempted specifically in the elderly population and a "CGA-snap-shot" of senior patients undergoing surgery has never been attempted.

The recommendations of the consensus meeting held during the 6th International Conference on Geriatric Oncology (Balducci et al 2001) was that any elderly cancer patient should firstly be assessed on his/her frailty, and then considered for appropriate cancer management. We consecutively endeavor on holistic assessment of this cancer sub-setting.

Currently available risk assessment tools include American Society of Anesthesiologists (ASA) scoring system. The ASA scoring system does not measure operative risk, rather it globally assess the degree of sickness or physical state prior to anesthesia and surgery.

Sensitivity of ASA scoring to differentiate the proportion of patients belonging to ASA II vs III (Leung and Dzankic 2001), where both groups show a similar mortality under elective conditions (15%) is poor.

The assessment of cardiac risk is addressed by the Goldman Cardiac Risk Index (CRI) (Goldman et al 1977); an instrument designed to assess cardiac risk in noncardiac surgery but is rarely used by surgeons (Michaels et al 1996). Respiratory complications were analyzed by Kroenke and colleagues (1993) who identified the following as associated with postoperative respiratory complications: 1) age over 70; 2) peri-operative broncho-dilator use; 3) abnormal chest x-ray; and 4) high ASA grade. Lawrence et al (1994) identified four preoperative variables that were associated with postoperative respiratory complications: 1) abnormal respiratory examination; 2) abnormal chest x-ray; 3) Goldman CRI; and 4) the Charlson co-morbidity index (Charlson et al 1987). These have not been formalized as a score or validated.

The Acute Physiological and Chronic Health Evaluation (APACHE) is the best known physiological scoring system (Knaus et al 1981). It is based on 34 physiological variables taking the worst values in the first 24 hours from the patient's admission to an intensive care unit (ICU). Various modifications of this APACHE system are now available: APACHE II (Knaus et al 1985) uses 12 physiological variables; it is currently being used in general and surgical intensive care patients. Its application in the ICU seems very appropriate, but its utility to general surgical patients who may not require respiratory support in the ICU is limited.

A relatively popular risk assessment tool especially in UK is POSSUM (Physiological and Operative Severity Score for EnUmaration of Mortality and Morbidity) as well as Portsmouth modification (P-POSSUM) (Prytherch et al 1998). The weakness of the tool is to overestimate mortality rate for low risk procedures, inability to predict postoperative outcome in preoperative setting and is affected by surgeon dependent factors rather than intrinsic difficulty of the case (Bann and Sarin 2001; Sutton et al 2002). Age is an independent risk factor built into above mentioned risk prediction tools.

Preoperative Assessment of Cancer in Elderly (PACE)

PACE is a prospective multicenter, international cooperative investigation which aims at defining the general health condition of onco-geriatric surgical candidates. PACE is designed to assess the functional activities of geriatric patient and hence to assess the functional life of an onco-geriatric patient. We propose this will help in predicting the individualized risk of cancer surgery. The pilot study has proven PACE is feasible, inexpensive and well accepted by the patient (Warner 1998). Our study population constituted of ≥70 years age patients undergoing moderate, major and major + elective cancer surgery whose Mini Mental Score is ≥18 (ability to give written informed consent). The end points of the study are 30 days morbidity, 30 days mortality, and hospital bed days. The aim is to predict preoperatively the probable outcome of cancer surgery treatment in elderly. The tools incorporated in the PACE are detailed in Table 1.

Results

213 patients were prospectively recruited for the study from July 2003 to September 2004. The postoperative outcome is assessed using a morbidity checklist (Table 2). The interim analysis results (Table 3) show median age was 76 years (70–100 years). Postoperative complications were noted in 64 (30%). The median number of co-morbidity was 2 in

Table 1 Validated instruments used with PACE

Mini Mental State Examination (MMS)
Satariano's Modified Index of Comorbidities
Activities of Daily Living (ADL)
Instrumental Activities of Daily Living (IADL)
Geriatric Depression Scale (GDS)
Brief Fatigue Inventory (BFI)
Eastern Co-operative Oncology Group Performance Status (PS)
American Society of Anesthesiologists Physical Status (ASA)
Physiological and Operative Severity Score for EnUmeration of Mortality and Morbidity (POSSUM)
Portsmouth POSSUM Modification (P-POSSUM)

Abbreviations: PACE, Preoperative Assessment of Cancer in Elderly.

Table 2 30 days morbidity check

Complications	Absent	Minor	Major
Respiratory			
Cardiac failure			
Renal failure			
Generalized sepsis			
Stroke/Neurological problems			
Hemorrhage and bleeding			
Nutritional problems			
Other organ failure			
Wound infection/dehiscence			
Thromboembolic problems			
Hepatic failure			
Urinary retention			
Anastomotic failure			
Peripheral ischemia			
Endocrine failure			
Pressure sores			
Analgesic problems			
Others			

Table 3 PACE Interim analysis: association of PACE with postoperative morbidity

Components	Complications (64 patients)	No Complications (149 patients)	p
Median (IQR)			
Comorbidities	2 (0–3)	1 (0–2)	0.024
MMS	28 (27–30)	28 (26–30)	0.917
GDS	3 (1–6)	2 (1–4)	0.018
BFI	2.2 (0.2–4.4)	1.2 (0–4.4)	0.156
Number of patients (%)			
PS = 0	30 (46.9)	122 (81.9)	<0.0001
ADL (Dependent)	38 (59.4)	55 (36.9)	0.005
IADL (Independent)	38 (59.4)	114(76.5)	0.043
ASA = 1 or 2	29 (45.1)	72 (49.0)	0.449

Abbreviations: ADL, activities of daily living; ASA, American Society of Anesthesiologists scoring system; BFI, Brief Fatigue Inventory ; GDS, Geriatric Depression Scale; IADL, independent activities of daily living; IQR, interquartile; MMS, Mini Mental State; PS, performance status.

complications group and 1 in complications-free group. Functional assessment using performance status (PS), ($p<0.0001$) and activities of daily living (ADL) ($p<0.005$) achieved statistical significance in predicting postoperative morbidity. Aspects of PACE relating to psychological well being (Geriatric Depression Score, Mini Mental State) do not appear to be significantly associated with post operative morbidity. The number of co-morbidities, ASA, instrumental activities of daily living (IADL) which failed to achieve statistical significance will be a reassessed on a larger sample. Recruitment to the study is currently ongoing and full results will be revealed on completion.

How to improve our understanding of elderly cancer patients?

It is estimated that up to a third of cancer deaths is preventable by the promotion of education. An emphasis should be on the dangers of a delayed diagnosis, as well as the erroneous interpretation of misleading symptoms in the presence of co-morbidities (Audisio et al 2003). Educational endeavours for elderly should target specialists and general practitioners alike. Optimizing management of cancer in elderly requires better understanding. This could be achieved by encouraging elderly to take part into clinical trials specifically developed for onco-geriatric series. Elderly cancer patients should be encouraged to enroll with the same vigor as their younger counterpart. Elderly wish to participate in trials in contrast to present perceptions (Silliman et al 1993). It is also desirable to make cancer management decision within a dedicated multidisciplinary (MDT) meeting, comprising of onco-surgeon, oncologist, radiation therapist, geriatricians, anesthesiologists with interest in geriatric surgery, and other support staff involved in elderly patient care. Educational opportunities like International Society of Geriatrics Oncology (SIOG 2006) conferences and the European School of Oncology (ESO 2004) courses should be utilized to enhance our knowledge and to discuss issues pertaining to management of elderly cancer. Further learning modules should be included in the medical curriculum in order to learn to look beyond age.

Conclusions

An increase in elderly surgical cancer workload is inevitable in the coming years. The special needs of elderly cancer patient should be taken into consideration prior to treatment planning. Provision of care should honor patients' preferences across all age groups. More progress in optimization of surgery for cancer in elderly could be achieved with the availability of validated tools capable of predicting postoperative outcomes. Clinical trials should be specifically developed for onco-geriatric series and elderly cancer patients should be encouraged to enroll. A multidisciplinary approach is the way forward. Educational opportunities like SIOG and ESO should be utilized to enhance our understanding of this unique subgroup. Learning modules should be created to look beyond age in cancer treatment planning. Developments in the surgery and expansion of our elderly cancer knowledge base are the way forward to optimize cancer surgery for elderly.

References

Alexander HR, Turnbull AD, Salomone J, et al. 1991. Upper abdominal cancer surgery in the very elderly. *J Surg Oncol*, 47:82–6.

Anisimov VN. 2003. The relationship between aging and carcinogenesis: a critical appraisal. *Crit Rev Oncol Hematol*, 45:277–304.

[APA] American Psychological Association. 2005. Resolution on ageism [online]. Accessed 15 December 2005. URL: http://www.apa.org/pi/aging/ageism.html.

Audisio RA, Bozzetti F, Gennari R, et al. 2004. The surgical management of elderly cancer patients: recommendations of the SIOG surgical task force. *Eur J Cancer*, 40:926–38.

Audisio RA, Cazzaniga M, Veronesi P, et al. 1997. Elective surgery for colorectal cancer in the aged: a clinico-economic evaluation. *Br J Cancer*, 76:382–4.

Audisio RA, Gennari R, Sunouchi K, et al. 2003. Preoperative assessment of cancer in elderly (PACE) patients: a pilot study. *Supportive Cancer Ther*, 1:55–60.

Audisio RA, Osman N, Audisio MM, et al. 2004. How do we manage breast cancer in the elderly patients? A survey among members of the British Association of Surgical Oncologists (BASO). *Crit Rev Oncol Hematol*, 52:135–41.

Audisio RA, Veronesi P, Ferrario L, et al. 1997. Elective surgery for gastrointestinal tumours in the elderly. *Ann Oncology*, 8:317–26.

Audisio RA, Zbar AP. 2002. Updates in surgical oncology for elderly patients. *Crit Rev Oncol Hematol*, 43:209–17.

Balducci L, Barnabei R, Albrand G, et al. 2001. Consensus on comprehensive geriatric assessment. 6th International Conference on Geriatric Oncology, 14–15 September, Lyon, France.

Bann SD, Sarin S. 2001. Comparative audit: the trouble with POSSUM. *J R Soc Med*, 94:632–4.

Baramiya MG. 2000. Aging and carcinogenesis – insufficient metabolic cell repair, the common link. *Gerontology*, 46:328–32.

Barchielli A, Balzi D. 2000. Age at diagnosis, extent of disease and breast cancer survival: a population-based study in Florence, Italy. *Tumori*, 86:119–23.

Boyd JB, Bradford B Jr, Watne AL. 1980. Operative risk factors of colon resection in the elderly. *Ann Surg*, 192:743–6.

Brookes B. 1937. Surgery in patient of advanced age. *Am Surg*, 105:481–501.

Brow SCW, Walsh S, Abraham JS, et al. 1991. Risk factors and operative mortality in surgery for colorectal cancer. *Ann Roy Coll Surg Engl*, 73:269–72.

Charlson ME, Pompei P, Ales KL, et al. 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*, 40:373–83.

Chiappa A, Zbar AP, Bertani E, et al. 2001. Surgical outcomes for colorectal cancer patients including the elderly. *Hepatogastroenterology*, 48:440–4.

Chiappa A, Zbar AP, Biella F, et al. 1999. Survival after repeat hepatic resection for recurrent colorectal metastases. *Hepatogastroenterology*, 46:1065–70.

Coebergh JW. 2001. Epidemiology in Europe. *EJC*, 37(Suppl 7):S175–227.

Cohen HJ. 1994. Biology of ageing as related to cancer. *Cancer*, 74(7 Suppl):2092–100.

Copeland GP, Jones D, Walters M. 1991. POSSUM: a scoring system for surgical audit. *Br J Surg*, 78:355–60.

Cristofalo VJ, Gerhard GS, Pignolo RJ. 1994. Molecular biology of aging. *Surg Clin N Am*, 74:1–21.

Cutler RG, Sensei I. 1989. Development, cancer and aging: possible common mechanisms of action and regulation. *J Gerontol*, 44:25–34.

Day JC. 1996. Population projections of United States, by age, sex, race and Hispanic origin: 1995 to 2050. US Govt Printing Office, Washington, DC. p 25–1130.

De Rijke JM, Schouten LJ, Hillen HF, et al. 2000. Cancer in the very elderly Dutch population. *Cancer*, 89:1121–33.

De Rijke JM, Schouten LJ, Schouten HC, et al. 1996. Age-specific differences in the diagnostics and treatment of cancer patients aged 50 years and older in the province of Limburg, The Netherlands. *Ann Oncol*, 7:677–85.

De Rijke JM, Van der Putten HW, Lutgens LC, et al. 2002. Age-specific differences in treatment and survival of patients with cervical cancer in the Southeast of the Netherlands, 1986–1996. *Eur J Cancer*, 38:2041–7.

De Cossart L. 2001. Patient assessment and risk stratification. In: Paterson-Brown S, (ed). Core topics in general and emergency surgery. 2nd Ed. London: WB Saunders Co Ltd, p 389–407.

Desch CE, Hillner BE, Smith TJ, et al. 1993. Should the elderly receive chemotherapy for node-negative breast cancer? A cost-effectiveness analysis examining total and active life-expectancy outcomes. *J Clin Oncol*, 11:777–82.

Eppenberger-Castori S, Moore DH Jr, Thor AD, et al. 2002. Age-associated biomarker profiles of human breast cancer. *Int J Biochem Cell Biol*, 34:1318–30.

[ESO] European School of Oncology. 2004. Cancer in the elderly [online]. Accessed 15 December 2005. URL: http://www.cancerworld.org/CancerWorld/eventDetail.aspx?id_sito=1&id_stato=1&id=351.

Fallahzadeh H, Mays ET. 1991. Pre-existing disease as a predictor of the outcome of colectomy. *Am J Surg*, 150:65–70.

Firat S, Bousamra M, Gore E, et al. 2002. Comorbidity and KPS are independent prognostic factors in stage I non small – cell lung cancer. *Int J Radiat Oncol Biol Phys*, 52:1047–57.

Firat S, Byhardt RW, Gore E. 2002. Comorbidity and Karnofksy performance score are independent prognostic factors in stage III non-small – cell lung cancer: an institutional analysis of patients treated on four RTOG studies. Radiation Therapy Oncology Group. *Int Radiat Oncol Biol Phys*, 54:357–64.

Franceschi C, Bonafe M, Valensin S, et al. 2000. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci*, 908:244–54.

Goldman L, Caldera DL, Nussbaum SR, et al. 1977. Multi-factorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med*, 297:845–50.

Greenburgh AG, Saik RP, Pridham D. 1985. Influence of age on mortality of colon surgery. *Am J Surg*, 150:65–70.

Greenfield LJ (ed). 1975. Surgery in the aged. Saunders Golden series. Philadelphia: WB Saunders, p 2-25

Holmes CE, Muss, HB. 2003. Diagnosis and treatment of breast cancer in the elderly. *CA Cancer J Clin*, 53:227–44.

Holmes FF, Wilson J, Blesch KS, et al. 1991. Biology of cancer and aging. *Cancer*, 68:2525–6.

Le Quintree JL, Bussy C, Golmard JL, et al. 2005. Randomized controlled drug trials on very elderly subjects: Descriptive and methodological analysis of trials published between 1990 and 2002 and comparison with trials on adults. *J Gerontol Series A: Biol Sci Med Sci*, 60:340–4.

Jones HJS, de Cossart L. 1999. Risk scoring in surgical patients. *Br J Surg*, 86:149–57.

Jougon JB, Ballester M, Duffy J, et al. 1997. Esophagectomy for cancer in the patient aged 70 years and older. *Ann Thorac Surg*, 63:1423–7.

Kalache A, Keller I. 2000. Population ageing in developing countries: demographic aspects. In: Evans JG, Williams TF, Beattie BL, et al (eds). Oxford Textbook of Geriatric Medicine. 2nd ed. New York: Oxford Univ Pr. p 26–32.

Kitamura K, Sugimachi K, Saku M. 1999. Evaluation of surgical treatment for patients with gastric cancer who are over 80 years of age. *Hepatogastroenterology*, 46:2074–80.

Knaus WA, Draper EA, Wagner DP, et al. 1985. APACHE II: a severity of disease classification system. *Crit Care Med*, 13:818–29.

Knaus WA, Zimmerman JE, Wagner DP, et al. 1981. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. *Crit Care Med*, 9:591–7.

Kroenke K, Lawrence VA, Theroux J, et al. 1993. Postoperative complications after thoracic and major abdominal surgery in patients with and without obstructive lung disease. *Chest*, 104:1445–51.

Lag R, Eisner MP, Kosary CL, et al (EDS). 1999. SEER Cancer Statistics Review 1973–1997. *Cancer in the EU* (1995). IARC.

Lawrence VA, Dhanda R, Hilsenbeck SG, et al. 1996. Risk of pulmonary complications after elective abdominal surgery. *Chest*, 110:744–50.

Leung JM, Dzankic S. 2001. Relative importance of preoperative health status versus intra-operative factors in predicting postoperative adverse outcomes in geriatric surgical patients. *L Am Geriatr Soc*, 49:1080–5.

Ling J, Rees E, Hardy J. 2000. What influences participation in clinical trials in palliative care in a cancer centre? *Eur J Cancer*, 36:621–6.

Lo SS, Wu CW, Hsieh MC, et al. 1996. Relationship between age and clinical characteristics of patients with gastric cancer. *J Gastroenterol Hepatol*, 11:511–14.

Masoro EJ. 1997. Aging: current concepts. In: Masoro EJ (ed). Handbook of physiology: aging. New York: Oxford Univ Pr. p 73–84.

Michaels JA, Payne SPK, Galland RB. 1996. A study of methods used for cardiac risk assessment prior to major vascular surgery. *Eur J Vasc Endovasc Surg*,11:221–4.

Newschaffer CJ, Penberthy L, Desch CD, et al. 1996. The effect of age and comorbidity in the treatment of elderly women with non-metastatic breast cancer. *Arch Intern Med*, 156:85–90.

Ogle KS, Swanson GM, Woods N, et al. 2000. Cancer and comorbidity: redefining chronic diseases. *Cancer*, 88:653–63.

Olshansky SJ, Carnes BA, Cassel C. 1990. In search of Methuselah: estimating the upper limits to human longevity. *Science*, 250:634–40.

Osiewicz HD, Hamann A. 1997. DNA reorganization and biological aging. A review. *Biochemistry (Mosc)*, 62:1275–84.

Penson RT, Daniels KJ, Lynch TJ 2004. Too old to care. *Oncologist*, 9:343–52.

Piantanelli L. 1988. Cancer and aging: from the kinetics of biological parameters and the kinetics of cancer incidence and mortality. *Ann N Y Acad Sci*, 521:99–101.

Poon RT, Law S, Chu KM, et al. 1998. Esophagectomy for carcinoma of the oesophagus in the elderly. Results of current surgical management. *Ann Surg*, 227:357–64.

Prytherch DR, Whitley MS, Higgns B. 1998. POSSUM and Portsmouth POSSUM for predicting mortality. Physiological and Operative Severity Score for EnUmeration of Mortality and Morbidity. *Br J Surg*, 85:1217–20.

Rapidis AD, Keramidis T, Panagiotopoulos H, et al. 1998. Tumors of the head and neck in the elderly: analysis of 190 patients. *J Craniomaxillofac Surg*, 26:153–8.

Redmond K, Aapro MS. 1997: Cancer in elderly, a growing problem. In: Veronesi U, Aapro MS (eds). Cancer in elderly. ESO Scientific updates–2. Amsterdam*: Elsevier*, 2:3–14.

Robinson DS. 1994. Head and neck considerations in the elderly patient. *Surg Clin N Am*, 74:431–9.

Samet J, Hunt WC, Key C. et al. 1986. Choice of cancer therapy varies with age of patient. *JAMA*, 255:3385–90.

Schindowski K, Frohlich L, Maurer K, et al. 2002. Age-related impairment of human T lymphocytes' activation: specific differences between CD4(+) and CD(8+) subsets. *Mech Ageing Dev*, 123:375–90.

Silliman RA, Balducci L, Goodwin JS, et al. 1993. Breast cancer in old age: what we know, don't know and do. *J Natl Cancer Inst*, 85:190–9.

Silliman RA. 1996. Breast cancer in old age: where do we go from here? *J Natl Cancer Inst*, 88:701–3.

[SIOG] International Society of Geriatric Oncology. SIOG website [online]. Accessed 15 December 2005. URL: http://www.cancerworld.org/cancerworld/home.aspx?id_sito=3&id_stato=1.

Staudacher C, Chiappa A, Zbar AP, et al. 2000. Curative resection for colorectal cancer in the elderly. Prognostic factors and five-year follow-up. *Ann Ital Chir*, 71:491–7.

Sutton R, Bann S, Brooks M, et al. 2002. The surgical risk scale as an improved tool for risk adjusted analysis in comparative surgical audit. *BJS*, 89:763–8.

Taueber CM. 1993. Current Population Reports. Special Studies. In: Sixty-five plus in America: Rev ed. US Govt Printing Office, Washington DC. p 23–178 RV.

Thigpen JT. 1998. Gynaecologic cancer. In: Balducci L, Lyman GH, Ershler WB, (eds). Comprehensive geriatric oncology. Harwood Acad, Amsterdam. p 721–32.

US Census; US Govt Printing Office. 1996. US Census Bureau [online]. Accessed 15 December 2005. URL: http://www.census.gov/.

Vercelli M, Qualglia A, Casella C, et al. 1998. Relative survival in elderly cancer patients in Europe. *Eur J Cancer*, 34:2264–70.

Veronesi U, Robertson JF, Todd JH, et al. 1988. Sentinel lymph node dissection. Comparison of mastectomy with tamoxifen for treating elderly patients with operable breast cancer. *BMJ*, 297:511–14.

Wallach CB, Kurtz RC. 1990. Gastrointestinal cancer in the elderly. *Gastroenterol Clin N Am*, 19:419–32.

Warner JP. 1998. Quality of life and social issues in older depressed patients. *Int Clin Psychopharmacol*, 13:S19–S24.

Welch CS. 1948: Surgery in the aged. *N Engl J Med*, 238:821–32.

Wyld L, Reed MWR. 2003. The need for targeted research into breast cancer in the elderly. *Br J Surg*, 90:388–99.

Yancik R, Wesley MN, Ries L, et al. 1998. Comorbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients. *Cancer*, 82:2123–4.

Zhang X, Fujii H, Kishimoto H, et al. 2002. Aging leads to disturbed homeostasis of memory phenotype CD 8(+) cells. *J Exp Med*, 195:283–93.