Healthcare Cost-Effectiveness Analysis for Older Patients: Using Cataract Surgery and Breast Cancer Treatment Data

Chapter 4

Clinical Trials in Older Cancer Patients: An overview of obstacles in generating evidence-based data.

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Introduction

The randomized trial comparing cataract surgery versus watchful waiting discussed in the previous chapters illustrates that clinical trials are feasible in older populations. Few alternatives other than clinical trials exist to determine treatment benefit in disease such as cataract surgery where the majority of patients are elderly. Even though the cataract trial was feasible, there were numerous issues that complicated its implementation and analysis. First, it was a laborious effort to recruit sufficient patients onto the trial, which limited the power of the clinical trial. Moreover, since the effectiveness outcome was quality-adjusted life years, generic instruments were used to determine subjective valuations of patient’s health. Using subjective responses in an elderly population required limiting the trial to English speaking patients with adequate hearing and mental functioning. These exclusion criteria may limit the generalizability of the study findings to a community population. Even with these inherent difficulties, valuable information was derived from the trial. Is the experience from this cataract surgery trial similar to other areas of medicine? A good focus area for comparison is cancer treatment.

Cancer incidence increases with age and cancer clinical trials form the largest proportion of clinical trials performed in the U.S. A review of cancer trials between 1993 and 1996 performed by the Southwest Oncology Group (SWOG) demonstrated that the percentage of patients over the age of 65 in clinical trials, 25%, underrepresented the percentage of elderly U.S. patients, 63%, with cancer [1]. Elderly patients were underrepresented in all categories of cancer clinic trials to varying degrees. For example, in prostate cancer, elderly patients represented 64% of cancer trial participants but 77% of all U.S. patients with prostate cancer. Differential participation by age was more prominent in colorectal cancer (40% clinical trials versus 72% U.S.) and lung cancer (39% clinical trials versus 66% U.S.). This under-representation was most dramatic in breast cancer where only 9% of trial patients were over 65 even though 49% of U.S. breast cancer patients were over 65 [1] (See Figure 1).

The SWOG data are only from one cooperative group so some clinicians argue they are not representative of clinical trials in general. Furthermore, the above study did
not distinguish participation of elderly patients by type of trial (Phase I, II, or III) or by stage at presentation. A more recent study examined the participation of older patients in National Institute of Cancer (NCI) sponsored cancer trials active from 1997 through 2000 using data from multiple cooperative groups. The results were very similar to the earlier SWOG data showing that older patients were under-represented in all clinical trials in oncology [2]. One of the largest discrepancies in participation was in breast cancer trials were even though the elderly represented 49% of U.S. breast cancer patients; they represented less than 20% of clinical trial patients [2]. In this study, the percentage of older patients were underrepresented but participation did not differ based Phase of clinical trial or stage of cancer.

There are many reasons that might explain why older women were not a part of breast cancer trials. Three major categories are (a) lack of referral by physicians, (b) lack of willingness to participate by patients, and (c) exclusion criteria inherent in the structure of the trials. Although these categories are listed separately, significant overlap exists between them.

Attitudes and Perceptions of Clinical Trials (Physicians and Patients)

Reluctance by oncologists and surgeons to refer and recruit breast cancer patients to clinical trials was recently studied. Factors were identified as to (1) why physicians are generally reluctant to participate in clinical trials and (2) why participating physicians refer only a small percentage of their patients [3]. Physicians were more likely to refer patients to a clinical trial when they knew which trials the patient was eligible for or when patients were more involved in decision-making. Attitudinal factors that were important in determining likelihood of referral to a clinical trial included: (a) comfort in explaining trials to patients, (b) perceived level of patient interest in a clinical trial, (c) perception that patients would remain in the local community and followed closely, (d) whether paper-work associated with a clinical trial was considered to be too time-consuming, or (e) if there was a belief that trial entry requirements were too stringent [3]. Interestingly, the only patient characteristic that predicted referral to a clinical trial was the patient’s age, with the older patients being less likely to be referred.
Equally important as physician attitudes towards clinical trials in breast cancer are the attitudes of breast cancer patients. One in-depth study using focus groups and surveys on 60 consecutive patients, the majority of which had breast cancer, at an outpatient cancer clinic found that patient knowledge about randomized trials was not high. The three most important factors in willingness to join a clinic trial were (1) patients perception, favorable or unfavorable, of their physician, (2) their personal attitude towards experimentation and uncertainty, and (3) whether their was a perception that clinical trial participation would be inconvenient or represent a loss of control [4]. A larger study on patient’s attitudes using cross-sectional surveys of women attending a breast clinic demonstrated that women who would consider participating in a randomized clinical trial were younger, more likely to want an active role in decision-making, and more knowledgeable about randomized clinical trials [5].

Only recently has research focused specifically on barriers to participation of older women with breast cancer in clinical trials. A recent study evaluated 77 pairs of younger (mean age 50.4 years) and older (mean age 76.5 years) women with breast cancer matched on physician type (surgeon, medical oncologist, or radiation oncologist), stage (early or late) who were eligible for at least on open trial in their institution and treated within one year of the study date. Both physicians and patients were surveyed [6]. A significantly greater number of patients in the younger group, 51%, were offered a clinical trial option compared to the older group, 35%. Patients with a higher number of comorbidities were less likely to be offered clinical trial participation [6]. After controlling the number of comorbidities and functional status †, age still significantly predicted whether patients were offered a clinical trial. Factors that influenced physician referral for older patients included: (a) the presence of comorbid conditions not excluded by the clinical trial but that the referring physician felt would have affected the patient’s response to treatment, and (b) a perception that the clinical trial regiment was too toxic [6].

Surprisingly, patient’s difficulty in understanding and costs of the clinical trial, transportation issues, and shorter life expectancy did not influence physician’s clinical

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† Functional Status refers to the ability of an individual to perform required daily tasks at home and at work. It reflects the level of physical strength, mobility, and energy level of an individual.
trial referral decisions for either younger or older patients. Of patients offered a clinical trial, there was no difference among younger and older patients in the percent who consented, 56% versus 50%, respectively [6]. Therefore, the failure of clinicians to offer a clinical trial to eligible older patients is a significant barrier to enrollment.

**Exclusion Criteria: Age, Comorbidity, and Functional Status**

As a result of demographic changes in the U.S. population that have and will further increase the proportion of older patients seeking cancer treatment, the U.S. Food and Drug Administration (FDA) published “Guidelines for the Study of Drugs Likely to be Used in the Elderly” in 1989 [7]. These guidelines state that the population studies should reflect the population likely to be treated. Nevertheless, there is a significant discordance between the “study” patient and the “ordinary” patient when it comes to clinical trials [8]. This discordance increases with age since most cancer clinical trials set an upper age bound at 70, and exclude patients with multiple comorbidites or functional impairment. Since pharmaceutical companies, whose primary goal is to demonstrate efficacy of their drug to the FDA, sponsor many clinical trials, selection criteria for trials reflect a desire for a younger healthier population in order to provide clear and convincing proof of drug benefit.

A study reviewing the protocol exclusion criteria in over 500 Phase II and III NCI sponsored cooperative group trials demonstrated that over 80% had exclusion criteria based on hematological, hepatic, and renal functioning [2]. In addition, over 90% had an exclusion based on a minimal level of functional status with over 60% requiring patients to be able to perform all Activities of Daily Living (ADLS) [see subsequent discussion] [2]. It is therefore worthwhile to examine the relationship of age, comorbidity, functional status, and treatment outcome.

Comorbidity increases with age. One study on colon cancer patients demonstrated that patients aged 55-64 had an average 3 comorbid conditions with an addition of one comorbid condition on average per additional decade of age [9]. Patients 75 and over, therefore, had a mean of 5 comorbid conditions (See Figure 2). Comorbidity can influence treatment in two ways: (1) by decreasing the resilience that patients have to the
toxic effects of treatment or (2) by affecting treatment selection [10]. Furthermore, comorbidity can be split into “covert” comorbidity which is not recognized by the physician and “overt” comorbidity, which is recognized usually integrated into clinical trial exclusion criteria [10].

Baseline comorbidity has been shown to be predictive of mortality in a population-based study [11]. In cancer patients, there is a relationship between overall survival and total comorbidity, with mortality risk ratios ranging from 1.33-1.85 in those with 3 or more comorbidities [9]. In a study of older patients with early breast cancer patients, only 51% of deaths were due to breast cancer showing the mortality effect of multiple competing illnesses in patients [12].

Complications caused by comorbid condition during treatment may exceed the expected benefit from the treatment itself. It is often difficult to separate patients who will recover from the morbidity of treatment and those whose health will decline and eventually die. Furthermore, patients with comorbid conditions get less optimal treatment. Among patients with early breast cancer, patients over 70 were significantly less likely to receive therapy consistent with the National Institute of Health (NIH) consensus statement for the treatment of breast cancer [12]. Therefore, it is difficult to use observational data to determine whether comorbidity or treatment selection leads to poor outcome. The association between comorbid condition and less treatment selected may be biased since other factors such as age bias may be the driving force in their connection [13].

A separate yet intertwined criteria in evaluating a patient’s acceptability for a clinical trial is functional status or impairment. Functional impairment is the inability to perform daily life activities normally. Several scales have been used to measure functional impairment.

Geriatricians, physicians involved in the general medical care of older patients, break functional status into: (a) activities of daily living (ADLs) and (b) instrumental activities of daily living (IADLs). ADLs are a measure of 6 basic functions: bathing, dressing, toileting, continence, transferring, and feeding [14]. IADLs are a measure of eight higher level functions: using the telephone, traveling, shopping, preparing meals, laundry, doing housework, taking medicine, and managing money [15]. The number of
impairments in ADLs and IADLs increases with age (See Figure 3). A recent survey indicated that 10-13% of older persons between the age of 65-69 have difficulty getting out of bed and between 6-10% need help with routine care. With age this need increases, with 24-29% of those over the age of 80 requiring help getting out of bed, and 29-42% requiring help with routine care [16].

Oncologists use alternative functional assessment instruments such as the Karnofosky Performance Scale (KPS) or the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale. The ECOG scale has 6 possible scores: 0 (fully active), 1 (restricted in physically strenuous activity, but ambulatory and able to carry out light work), 2 (ambulatory and capable of all self-care) but unable to carry out work activities, 3 (capable of only limited self care, confined to bed or chair >50% of waking hours), 4 (completely disabled), and 5 (dead) [17]. The ECOG scale correlates well with ADLs but any deficiency in ADLs makes a 3 the highest score possible on the ECOG. Most clinical trials limit patients to those with ECOG scores of 2 or lower. As a result many older patients are excluded from clinical trials due to functional limitations.

Functional status is also related to treatment outcome. Medical conditions may present first (or only) as a functional disturbance. In addition, functional loss affects the quality of life** of older patients. Furthermore, functional losses may lead to further disability and institutionalization. Lastly, functional impairment is a predictor of morbidity and mortality. In a study of 189 older individuals living in a rural community, the relative death risk from going from independence to dependence in on or more ADLs, adjusted for other illnesses, was 6.5 [18]. There was an interaction between age and functional status with the relative risk of death being 12.02 and 13.60 in those aged 80-84 and over 84 respectively. Patients with two impairments in ADL had a relative risk of death of 13.66 [18]. This data demonstrates that independent of age and health condition, functional status is a predictive factor for short-term mortality in non-institutionalized older individuals.

** Quality of Life is a subjective measure of one’s overall enjoyment of life. It includes some of the components of functioning, similar to Functional Status, but also includes other physical (pain, nausea,…), social, and emotional components. Therefore, even though an individual may objectively have a poor functional status, they may rate their overall quality of life high, or vice versa.
Conclusion

Unlike cataract surgery where any clinical data requires the enrollment of older individuals, the treatment guidelines for cancer, and more specifically breast cancer, are largely derived from trials of patients under the age of 70. There may be many reasons for the lack of adequate representation of older patients in clinical trials including: the lack of referral from physicians or the lack of willingness to participate from patients. In most cases, though, clinical trials have criteria that exclude patients over the age of 70 and patients with significant comorbidities or functional impairment. As a result, the “study” patients are often not reflective of the typical older breast cancer patient, and data derived from these trials are not easily generalizable to community practice involving older cancer patients. In the future, clinical trials will need to be designed to include older patients and a broader range of baseline health conditions/status. Until these trials are designed and data is generated, alternative approaches are needed in determining the care of older cancer patients. Modeling involving different assumptions of treatment benefits and costs while incorporating the impact of age, comorbidity, and functional status maybe helpful in guiding care in older breast cancer patients and may even help direct where clinical trials are most critical. An example of this type of approach is outlined in the next chapter.
Figure 1: Older Persons Under-represented in clinical trials; SWOG – Clinical trials of Southwestern Oncology Group; US – U.S. patients with specific cancer.

Figure 2: Mean number of comorbidities per age bracket: 55-64, 65-74, 75+.

Figure 3: Percentage of individuals with functional disabilities in ADL (Activities of Daily Living) or IADLS (Instrumental Activities of Daily Living).
References


2. Kilgore M: The participation of patients 65 years of age and older in cancer clinical trials, Personal Communication to Naeim A, Santa Monica, 2002


7. Administration. UFaD: Guidelines for the Study of Drugs Likely to be Used in the Elderly, in, Rockville, MD, Food and Drug Administratrion/Center for Drug Evaluation and Research, 1989

