

PATIENT REPORTED OUTCOMES ARE IMPORTANT IN ONCOLOGY

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Abstract

Cancer is a major health problem in Australia. As such, improving cancer outcomes is a priority. Traditionally, cancer outcomes such as mortality, survival rates and local recurrence rates have dominated clinical decision making. The past several decades has seen a paradigm shift in that there has been an increased emphasis on patient reported outcomes, both in the research arena as well as clinical practice. However, despite the rapidly expanding volume of outcomes research, uptake into clinical practice has been slow. As treatments in oncology often involve complex tradeoffs between survival and functional sequelae, it is important that the patient is involved in clinical decision making. In order to allow patients to make an informed decision, patient reported outcomes need to accompany and complement traditional objective outcomes such as survival and treatment efficacy.

Measuring the success of any organisation is critical, regardless of the nature of the organisation. Although somewhat over-simplistic, the key index of performance in private companies is usually measured in terms of profits. Unlike the private sector however, measuring outcomes in health care is much more complex and multi-dimensional. Depending on the perspective adopted and the outcomes one is interested in, individual patient outcomes, clinician performance, outcomes for specific diagnostic groups, compliance to system processes or even cost effectiveness of the system can and have all been measured.^{1, 2} Contributing to the complexity of measuring health outcomes in patients is the fact that health is not a dichotomous state, but a subjective perception that resides on a continuum which is in turn influenced by the individual's expectations and environment.^{3, 4}

Measuring and understanding outcomes in oncology is important because of the burden of disease that cancer imposes on our society. According to a recent report by the Australian Institute of Health and Welfare, one in two Australian men and one in three Australian women will be diagnosed with cancer by the age of 85, and one in five Australians will succumb because of cancer.⁵ As a cause of disability, cancer overtook cardiovascular disease in 2003 as the single most important contributor to the total burden of disease in Australia and is a major source of health care expenditure, itself accounting for 9% of Australia's gross domestic product.⁶ It is not surprising that cancer was declared a national priority area that is directly reportable to health ministers.⁷ The problem posed by cancer is not unique to Australia. Most developed countries and even some developing countries are facing similar problems, with an increasing burden of disease from cancer as the population ages and the pool of patients seeking treatment continues to expand. Improving cancer outcomes is therefore important, be it from the point of view of a consumer seeking high

quality health care, a health practitioner at the coal face of clinical oncology, or a policy maker trying to ensure a sustainable and equitable health care system.

Traditional outcomes measures in cancer

Traditionally, cancer outcomes have been measured in terms of survival, mortality, treatment efficacy (cure rates) and recurrence rates. These outcomes are concrete and objective, and lend themselves well to conventional methods of measurement. As cancer is a disease that can pose a direct threat to life, survival or mortality as endpoints are logical and are often favoured by policy makers as 'hard' endpoints, because they are intuitive in demonstrating performance in health care. While longitudinal trends in survival and mortality are helpful to inform the overall effectiveness of cancer services, a major limitation with these studies is that they are ecological in nature and generally do not demonstrate cause and effect.⁸ Further, unlike data on cancer incidence, which is generally comprehensive and complete due to mandatory reporting,⁵ mortality data is generally derived from death certificates where information may be less accurate, particularly in elderly or infirm patients where post-mortems are less likely to be performed and others where co-morbidities exist.⁹⁻¹¹ Cancer related mortality in Australia has decreased by 16% over the past 20 years as a result of a combination of increased cancer awareness, uptake of cancer screening and widespread use of effective multi-modal therapy.⁵ While further reductions in cancer related mortality are expected with ongoing scientific and technological advancement, there may come a time when the ceiling is reached such that further reductions in mortality will be hard earned and slow coming, making mortality a less useful endpoint in clinical trials. With increased survival, the goal of cancer treatment can no longer be restricted to survival alone. Instead, treatment goals need to be expanded to

include improving the quality of cancer survivorship. This is particularly important in oncology because most cancer treatments can be associated with long-term functional sequelae. This is not to say that the 'hard' outcomes are no longer important benchmarks in oncology, it is simply recognising that a good oncological outcome is not merely being alive or free of cancer. As summarised aptly by the World Health Organisation, health is a "state of complete physical, social and mental well-being and not merely absence of disease or infirmity."¹²

Patient reported outcomes

Patient reported outcomes (PROs) is an encompassing term that includes any outcomes measure directly elicited from the patient without interpretation from the treating doctor, carer or other health care professional.¹³ Within PROs are measures such as symptoms, functional outcomes, satisfaction and treatment preferences.¹⁴ The drive to develop PROs stems from a number of factors including the spiraling cost of health care, recognition of disparities in quality of care and the appreciation that clinicians and patients often have different opinions and treatment preferences.¹⁵ Further, by their very nature, subjective outcomes such as improved symptoms, reduced anxiety or quality of life are often intangible to everyone else other than the patient themselves, making PROs a logical complement to traditional outcome measures in the assessment of treatment efficacy.

Measuring health related quality of life

To accurately quantify health related quality of life (HRQoL) and the impact that illness or treatment has on the patient, novel measures had to be developed. The important attributes of a HRQoL measure are that it needs to be relevant to the condition in question (content validity, construct validity and criterion validity), reliable (test/re-test reliability and internal consistency), sensitive to change, acceptable to patients and easy to administer.¹⁶

Broadly speaking, there are three types of HRQoL measures – generic, condition specific measures or patient specific measures.¹⁷ Generic measures such as SF 36, EQ-5D (EuroQoL) or AQoL (Assessment of Quality of Life) assess the individual's global sense of well-being.¹⁶ These measures usually combine symptoms with function in domains that are accepted as being necessary for health, such as physical, social and emotional subscales.^{14,16,18} Generic measures allow comparison of quality of life across different conditions, however unlike condition specific measures, they are also not sensitive enough to detect clinically meaningful changes in domains relevant to specific conditions to enable treatment related changes.¹⁶ As such, numerous condition specific measures have been developed over the years. Considering the time and cost associated with the development of each instrument, it is also not surprising that many condition specific instruments are developed by modifying existing generic measures, so as to capture additional condition specific concerns that are not evaluated in the generic measure.¹⁶ Patient specific measures allow individual choice of outcome measures such as the direct questioning of objectives.

Selecting a suitable HRQoL instrument depends on the intended use of the measure and the clinical context. Ease of access to the instrument is also a practical consideration,

as the preferred instrument may not be available because of language barriers or maybe culturally inappropriate. Costs associated with the use or scoring of a measure also limits its utility, especially when repeated use is necessary. Finally, the exponential growth in number of instruments over the past two to three decades has made it somewhat difficult for clinicians to stay abreast with instruments that are available.¹⁹ Recognising this problem, the Mapi Research Foundation established an online database to house all known HRQoL instruments on a website known as Patient Reported Outcome Quality Of Life Instrument Database, or PROQOLID for short.¹⁹ The website enables researchers and clinicians to perform multi-field searches of the database so as to facilitate identification of and access to the desired HRQoL instrument.²⁰

Patient preferences and decision making

Most treatments in oncology, be it chemotherapy, hormonal therapy, radiotherapy or surgery, can be associated with significant short-term side-effects or long-term functional tradeoffs. Some treatments, such as surgery, are obviously irreversible. Quality of life measures in surgery often reflect informed consent and may not reflect true patient preferences made at the time of decision making (ie. cognitive dissonance deduction). Therefore, prospective measures of patient preference and equipoise studies are important.²¹ The use of multimodal therapy often increases toxicity for only modest gains in survival. Whether or not the survival benefit outweighs the potential toxicity of treatment to justify a certain treatment option is a decision best judged by the patient. In order to make an informed decision, patients need to be suitably counselled about available treatment options, treatment efficacy, as well as the pros and cons of each option. Notwithstanding this, not all patients will be comfortable with making treatment decisions themselves, even when all options are fully explained. Studies have shown that older patients and those with certain personality traits seem more reluctant to make treatment decisions, preferring instead to defer decision making to their doctor.²²⁻²⁴ To facilitate patient participation in clinical decision making, there has been a growing interest in the use of decision aids. These tools come in a variety of formats (pamphlets, decision boards, audio tapes, interactive websites) and can be used either in preparation for a consultation or at the time of consultation with the treating doctor. Although decision aids do provide factual information, they differ from educational pamphlets in that they are also preference sensitive – that is, they help patients clarify their treatment preferences.²⁵

In a recent Cochrane review, decision aids were found to improve knowledge, reduce decisional conflict, improve patient participation in shared decision making and reduce the proportion of patients who remain undecided.²⁵ Although the positive effects of decision aids are encouraging, their use in clinical practice remains in its infancy. Barriers in uptake in clinical practice include time constraints, concerns about the impact decision aids may have on doctor-patient relationship and fear that patients may be overwhelmed by the amount of information provided, or may not comprehend the concept of a decision aid.²⁶ Whether or not decision aids will benefit all patients equally (low literacy patients, different age groups or different personalities with different decision making styles), and whether they have any beneficial flow on effects on cost or reducing litigation, is

currently unknown and warrants further evaluation. Further, barriers to implementation also need to be addressed before decision aids will be taken up by clinicians.

Cost-effectiveness of interventions

An important aspect of the health care system is to ensure that the resources available are used in an equitable and efficient manner. Cancer related expenses have increased over the years because of an increased pool of patients requiring treatment, as well as rising cost of treatment per patient.²⁷ The rate at which cancer related treatment expenses are increasing is somewhat alarming. In Canada, oncology drug spending is increasing at a disproportionately high rate compared to the incidence of cancer.²⁸ In the United States, where total health care expenditure represents about 16% of their national gross domestic product (compared to 11% in France, 8.9% in Australia, 8.4% in the United Kingdom and 4.1% in the Netherlands), there is a concern that further increments in cancer treatment costs could outpace inflation, contributing to the rapidly rising total health care expenditure, which has been postulated to approach 20% of their national gross domestic product by 2020.^{27, 29} Yet, despite the disparately different health care expenses, life expectancies and cancer outcomes seem remarkably similar between United States and other countries.²⁷

The costs of the new chemotherapeutic agents in particular have attracted the most attention in recent years.³⁰⁻³² Considering the marginal benefits conferred by some of these novel targeted therapies, it is essential that all new interventions are thoroughly evaluated before approved for widespread use. In 1993, Australia was the first country to introduce the requirement for a formal cost effectiveness analysis prior to approving a medication for public use.³³⁻³⁵ Today, most major drug approving agencies, including the Food and Drug Administration in the US, National Institute of Clinical Excellence in the UK and European Medicines Agency in the European Union, have all adopted similar policies demanding either evidence of cost effectiveness or improved HRQoL before a drug can be licensed for use.³⁶⁻³⁸

Developments in adjuvant therapies for colorectal cancer highlight the importance of a comprehensive assessment process prior to approving a medication. Prior to the introduction of new chemotherapy agents, 5-fluorouracil and leucovorin were the two most widely utilised agents costing under \$100 for a six month course,²⁹ and have been shown in several trials to result in a 22-33% relative reduction in mortality.³⁹⁻⁴¹ In the past 10 years, six new drugs have become available for the treatment of colorectal cancer. In a study from the US, the addition of oxaliplatin to 5-fluorouracil and leucovorin increased costs by \$30,000 for a six month course for a much more modest increase in overall survival – from 76% to 79% – and disease free survival from 67% to 73%.^{29,42} A more recent Australian study found that the addition of oxaliplatin increased drug costs alone by \$12,035 per course of chemotherapy, excluding costs associated with medication preparation and administration, which requires an infusional pump.⁴³ Notwithstanding this, combinational treatment with 5-fluorouracil, leucovorin and oxaliplatin was deemed cost-effective and is now widely available for patients with Stage III colorectal cancer around the world.^{44, 45} The same study also found that the addition of novel targeted monoclonal

antibodies, such as bevacizumab and cetuximab, further escalated costs by \$24,000 and \$50,000 respectively, for overall survival and disease free survival benefits measured in months.⁴⁶⁻⁴⁸ Cost effectiveness analyses have found both not to be cost-effective and as such, they are only available for use in patients with metastatic colorectal cancer on grounds of terminal cancer treatment and are not offered in all countries.^{49,50}

Due to the large sample sizes required in randomised control trials for oncology studies, several studies in recent years have used surrogate endpoints such as disease free survival or progression free survival, in anticipation that survival benefit will eventuate with longer follow-ups.^{27,51} However, findings of a large randomised trial of tamoxifen in breast cancer and bevacizumab have not found this to be a valid approach.^{52,53}

One major challenge with cost effectiveness analyses is to determine the threshold at which an intervention or a medication is deemed 'value for money'. Although different countries have different thresholds above which drug approval is unlikely,^{54, 55} this is also subject to other factors within the assessment, such as the importance of the disease or the availability of other treatment alternatives. More recently, there has been an evolving concept that cost-effectiveness analyses should take into consideration social concerns, such that the cost-effectiveness analysis may account for social inequalities so as to prioritise the disadvantaged.⁵⁶ Several approaches have been proposed, but how this can be accomplished in practice remains under investigation.⁵⁷

Patient reported outcomes in practice

Although PROs are increasingly used as primary or secondary endpoints in oncology trials,^{2, 58-60} a recent review by Macefield et al suggests that the uptake of PROs as an endpoint in cancer trials remains slow.⁶¹ Knowledge gleaned from PRO studies has provided invaluable information to guide patient decision making and has enabled clinicians to counsel patients appropriately by providing oncological data alongside HRQoL data. For example, the Dutch TME (total mesorectal excision) trial, comparing surgery alone versus radiotherapy plus surgery for rectal cancer, found that radiotherapy had no impact on overall survival, although it did halve the likelihood of local recurrence at the expense of detrimental effects on post-operative sexual and bowel function.^{58,62} The inclusion of some form of PRO outcome measure in randomised control trials is advocated by many cancer agencies, including the Clinical Oncology Society of Australia.

The ultimate goal of PRO research is to translate research knowledge into clinical practice and to collect routine PRO data in daily practice, so as to improve patient care.⁶³⁻⁶⁵ In a study by Velikova et al, routine PRO data collection immediately prior to a clinic consultation led to a statistically and clinically significant improvement in HRQoL, especially when the HRQoL information was fed back to the clinician during consultation.⁶⁴ Pre-consultation PROs also prompted discussion of non-specific chronic symptoms, without prolonging the consultation or altering patient management with more investigations or treatments.⁶⁴ Although the study has shown that routine PRO measurements can improve patient outcomes, there remain barriers to implementation, such as the mode of administration (touch screen

handheld computers or paper questionnaires), concerns for time required for data collection or interpretation and resources necessary to enable routine use of PROs. As a demonstration that routine collection of PRO data was feasible, the US Centres for Medicare and Medicaid Services launched a time limited project whereby medical oncologists were eligible to receive an additional payment of US\$130 per patient for collection and submission of data on nausea, vomiting, pain and fatigue.⁶⁶ Although unlikely as an ongoing undertaking by the government, the experiment demonstrated that routine PRO data collection was feasible, especially if there was incentive for the clinician to do so.

Conclusions

PROs complement traditional hard oncological outcomes and are important for decision making at all levels. At a macro level, HRQoL outcomes and cost-effectiveness analyses ensure rational use of limited health dollars. For clinicians, PROs can inform while patients are responding to treatment, whereas for patients, their experience and preferences are paramount. Better integration of the conventional hard oncological outcomes and basic science research with patient reported outcomes is needed to not only improve survival, but improve the quality of this survivorship.

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