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EDUCATIONAL SECTION

Risk analysis in surgical oncology—Part I: concepts and tools

D. A. Rew

Consultant Surgeon and Honorary Senior Lecturer, Southampton University Hospitals, UK

'The fear of harm ought to be proportional not merely to the gravity of the harm, but also to the probability of the event'

Logic 1662 Paris

All clinical procedures invoke risk. Many interventions in cancer management carry a particularly high element of risk, expressed through morbidity and premature death. Formal risk analysis is a discipline which is fundamental to engineering, to finance, to the airline industry and many other sectors of public life. Clinical risk analysis involves risk prediction, risk management and risk avoidance.

Risk analysis is rarely invoked or taught in the clinical sciences, and management appraisals on individual patients almost never include a formal estimate of risk. Clinical decisions tend to be guided by qualitative judgements, and by the personality interactions of patients and clinicians. A formal evaluation of risk on a case by case and procedural basis might reduce morbidity and cost in surgical oncology practice. This article introduces the concepts, the spectrum and history of risk analysis and the tools for risk prediction.

Key words: **risk analysis; moral hazard; clinical governance.**

Introduction

Risk is the possibility of incurring misfortune or loss. Risk is unavoidable. It affects the decision making of individuals, of groups, of organizations and societies. All human life is encompassed by risk and by the certainty of death within a definable period. Conscious and cognitive decisions on risk will thus be taken by all individuals and encompassed by the human life span. Indeed, life is inconceivable without risk, the driving force of Darwinian evolution. Risk aversion may be essential to survival. Conversely, excessive risk aversion would not be a successful life strategy in a competitive world. Risk is not well understood in medicine, surgery and oncology. A more rigorous appreciation and examination of risk should help reduce the morbidity in surgical practice and provide a more rational basis for therapeutic decision making.

Risk analysis is the judgement of the extent to which the past determines the future, based upon the use of numbers and the implementation of choice. Risk analysis underpins all human actions. It is founded upon the concept of the future, and our need to anticipate eventualities and the consequences of our actions. Risk, risk management and risk taking determine our current behaviour in anticipation of future consequences and outcomes. In risk, the future is not infinite, because human life and decision cycles are finite. Risk may thus be defined as the probability of an event which may have beneficial or detrimental consequences for the individual or party concerned with a decision.

The tools of risk analysis and risk mitigation are more highly developed and more rigorously applied in other branches of science and engineering than in clinical medicine. These fields include flight and air traffic control systems, nuclear systems and structural engineering. The statistical and mathematical tools of risk analysis encompass game theory, probability theory, economic planning, gambling, stock and commodities market strategies and insurance, engineering, and actuarial life tables.

Just as risk is a key determinant of decision making in the physical, social and economic world, so every decision in medicine and surgery is overshadowed by risk. For a subject which is so all-embracing in our clinical and oncological practice, relatively little effort has been put into systematizing the clinical study of risk. Risk analysis invokes the prediction of risk, for which mathematical tools and historical data sets are required; the management of risk, for which appropriate administrative systems are required; and the avoidance of risk, for which appropriate training, clinical practices and evidence-based protocols are required. The challenge of clinical risk management is to minimize the clinical variability due to human factors in an environment which is man—rather than machine—driven and in which

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biological variables are considerable, unlike many engineering systems.

Patients with cancer present particular problems in the evaluation and management of risk. There is a high probability of a fatal outcome in a finite time. The risks of intervention must nevertheless be properly weighed against the probable consequences of each diagnostic and therapeutic option. It is thus appropriate to attempt to systematize the language and concepts of risk in surgical oncology. We need to find agreed definitions of risk and the tools for its analysis. Modern concepts of professional clinical governance and evidence-based medicine are predicated upon risk and its reduction.

The mathematics of risk

The history of risk analysis has been recorded in detail by Bernstein.[1] Risk analysis is enabled by a system of abstract numerical mathematics such as was not possible with Roman numerals. Fibonacci's book 'Liber Abaci' (1202) introduced numerical mathematics to the West from India and Arabia in mediaeval times. Practical predictive number theory was developed by Blaise Pascal (1654). This addressed the mathematics of outcomes of games of chance. Jacob Bernoulli's Law of Large Numbers (1713) assessed probabilities. It observed that the true average measure of an event (or risk) will be more closely given by a large rather than a small number of events. Daniel Bernouilli's 'New Theory on the Exposition of Risk' (1738) observed that the *value* of an item is not based on its *price*, but on its *utility* yield. Thus, the satisfaction resulting from a small increase in wealth is inversely proportional to the wealth previously possessed. This utility concept quantifies the willingness to take risk and the motivations of the selector. Bentham developed utility theory in his book on 'the principles of morals and legislation' (London, 1789). He recognized the primacy of pain and pleasure in determining human actions. Jevons considered that value depends entirely upon utility, expressed in the 'Theory of Political Economy' (London, 1871). He also proposed that the more refined and intellectual our needs become, the less they are capable of satiety.

Abraham de Moivre described in the 'Doctrine of Chances' (London, 1730) the normal distribution curve and the standard deviation, from which were developed the Law of Averages. Bayes's theorem of the mid-17th century addressed the change in probabilities with time. Life and health insurance and the concept of insurance risk are predicated upon population risk analysis. The analysis of life expectancy was introduced by John Graunt in London in 1662, in his 'Natural and Political Observations' made upon the bills of mortality. Life insurance tables, life annuities and marine insurance were developed in the early 18th century. Britain's first population census was conducted in 1801.

Galton (1875) described the regression to the mean. This suggests why hereditary trends do not tend towards extremes. Markowitz (1952) described the diversification of risk. Games theory was developed by von Neumann in the 'Theory of Games and Economic Behaviour' (1953). Games theory assumes that uncertainties arise from the intentions of others behaving rationally. Chaos theory and non-linear mathematics are a modern contribution to risk analysis, through the systematic analysis of unpredictable outcomes.

Information and time as key components of risk

Risk taking is predicated upon information, and the time available for its collation. The greater the available information, the more it may be possible to mitigate risk. Many decisions are irreversible, and are made on the basis of incomplete information. Action pre-empts the receipt of new information which may alter the perception of risk. Procrastination may thus have real value in mitigating risk. Thus, in surgical decision making, we must balance the probability of risk from a procedure against the risk to the patient of not intervening. We cannot always be sure that the intervention mitigates risk, or achieves the correct balance of risk to benefit.

Time creates risk, because the absence of a future would also abolish risk from the decision making process. The status of the system may change during the time taken for information gathering. Time also provides more opportunity to compensate for risk during the collation of information. However, the timescale of clinical risk is often compressed and the magnitude of risk to patients is often greater, less abstract and more immediate in decision making in the face of cancer than in most aspects of daily life.

The individual and the point of decision

Risk analysis reaches a point of decision, at which the risk is accepted or rejected. Effective decision making requires access to objective facts, and a clear view of the utility value of the desired outcome. Decisions in cancer treatment are a complex balance of interactions between the clinician and the patient. Decisions on utility value find their absolute expression in matters of impending death, because the utility of additional cognitive life to the individual is so absolute in comparison to the state of death.

We are often poor subjective judges of risk. Individuals seem to be particularly inconsistent in the assessment and execution of health risk, both as clinicians and patients, such that better approaches are needed. For example, smoking remains a widespread health damaging activity, while the cost of efforts to eliminate bovine spongiform encephalopathy with a $1/10^6$ individual risk seems to have been hugely disproportionate to the real magnitude of the risk to health.

The risk assessments of the advising clinician and of the patient are unlikely to be in harmony, as the starting conditions and perceptions vary with each individual. We thus need to understand and systematize the factors in the clinical decison making process in order to minimize risk. As patients and their advocates become better informed, so the interactions in clinical risk evaluation change.

The patient and health risk analysis

Each personal decision in all aspects of life, including health matters, carries an element of risk and uncertainty. Perception of risk varies considerably between individuals, with age and experience, and given the starting point of physical and mental well being. Personal health risk assessment is not entirely random, as we can perceive clear patterns of individual choice which govern decision making in matters of health. Given physical security and good health at the outset, the option of a longer healthy life will be the key determinant of choice for most individuals. Anomalous and irrational behaviours must also be recognized in risk analysis.

Physiological and biological factors are core determinants of risk and behaviour. These include comfort, security and nutrition. We may well be innately programmed to assess risk and to accept a balance of risk in our lives in the attainment of core biological functions, such as the attainment of reproductive success, for example. Where ill health is the starting point, decision making on medical interventions by the patient will be increasingly skewed towards the early attainment of well-being rather than late longevity as the severity of the starting conditions (disease, disability, pain, emotional torment) increases.

Undue weight is often given to the component parts of a problem rather than to the whole. Interactive factors (covariance) are often underestimated or undervalued. Factors which may influence the decision point include the competency of the mental accounting process, fear of 'decision regret', aspects of self-control, loss aversion or a gambling tendency. Some extremes of human behaviour ignore demonstrable personal risk to an excessive degree.

The surgical oncologist and practical risk analysis

Professional assessment of risk in medical and surgical strategies, including those in surgical oncology, is often poor. It is subject to the risk taking personality and the experience of the individual clinician or the endemic culture in any one surgical unit. The surgeon can bring greater knowledge of the probabilities of outcomes for any given disease pattern or technical intervention, but this knowledge of risk (or foresight of complication) cannot be absolute. Opinions and beliefs can be highly discontinuous in the face of inconclusive, complex or poorly synthesized evidence. This is a particular problem where huge volumes of published data, each with different starting points and population subsets, assail the clinician, as for example in breast cancer management. Clinicians thus cling to, or overemphasize, their knowledge of particular studies and conclusions which may not be consistent with the generality of knowledge, not least because this generality of knowledge may for practical, day to day purposes be unfathomable.

Some factors determining cancer outcomes are outside the immediate control and influence of either patient or clinician. These include genetic and hereditary risk, and environmental risk. The surgical oncologist thus wishes to answer a series of questions when making any therapeutic decision. What are the consequences of my proposed intervention for this patient/condition? What factors are influencing my decision? Is this an appropriate judgement for me to make, or are others better qualified to do so? What are the odds of favourable and unfavourable consequences? How will I define these consequences? How does my proposed treatment compare with each and every alternative, including non-intervention?

The public perception of risk

The consequences of clinical risk impinge particularly upon the clinician at the interface with the general public and the media. The determination of cancer treatment strategies for individual patients often include high risks of iatrogenic morbidity and mortality. Publicity about the scientific application of clinical data to clinical and cancer management strategy has now become a professional and political imperative. Public and media perceptions are particularly ill informed about clinical risk, at least in part in consequence of the complexities of risk analysis for clinicians themselves. Thus, expectations of 'perfect', 'scientific' outcomes produce an intolerance of seemingly unsatisfactory results and morbidity, which may be expected to have a considerable and continuing bearing on clinical practice in the coming years. The interpretation of risk has considerable medicolegal ramifications, as poor interpretation of data may lead to unfair and inappropriate judgements on individual practice.

The spectrum of risk in surgical oncology

Most clinical risk is borne by patients in respect of clinical outcomes. Morbidity and mortality are integral to the process of cancer progression. We can nevertheless increase morbidity and accelerate death by inappropriate or misjudged interventions. The hospital is a high risk environment, and additional risk to the patient and to the clinician may be generated along numerous axes of oncological practice. Western hospitals have developed robust procedures and practices over many years to mitigate general risks, such as of error of identification, infection control and antithrombotic prophylaxis. However, the zero error culture and error intolerance which dictate practice in civil aerospace engineering, for example, has not generally permeated hospital and surgical practice. Clinicians are often fault and error tolerant. The individual clinician remains the key to minimizing error, for which we must consider greater use of Human Factor Analysis in future. This will help titrate the individual's knowledge, training, experience and skills to the problem in hand. For example, factors such as technical inexperience, over-optimism or aggression, fatigue, overwork, timings and an unsatisfactory environment (unfamiliar staff or equipment) can collectively influence surgical outcomes adversely. In the technical sphere of adjuvant therapy, faults and miscalibrations of radiotherapy equipment, or misjudgement of doses and regimes of cytotoxic drugs, cause high profile problems.

Tools and statistical methods in oncological risk prediction

Usable information is a critical requirement. We generate huge quantities of data in the form of clinical notes and records, and patient activity, but this is rarely captured, stored or analysed in a form which facilitates risk analysis. We need a system which can store, collate and analyse data from the totality of clinical experience in any one discipline, to give an aggregate picture of the morbidity and outcomes of each and every intervention in each and every case. The systems and processes exist to address this problem. Many large businesses use software systems which analyse huge volumes of data to extract commercial trends, as for example supermarkets which track and analyse the sale (treatment) of each and every item of goods (patient) in each and every store (hospital).

Potentially useful clinical data sets for risk analysis are collected at various levels of practice in surgical oncology. Closest to the patient, many individual clinicians keep personal records on patients in categories of special interest. Such data sets are usually highly selective. They are useful for identifying trends and problems in personal practice, but are of little value in the systematic comparison of risk betwen one clinician or patient population and another.

The next level of clinical data is that held collectively by departments (such as oncology units) and by hospitals. Such data can cover the totality of clinical workload in any one centre, and allow detailed evaluations of local practice if the data is held in analysable form. They may allow for comparative performance assessment of groups of clinicians.

The next level of cancer data collation is that collated by regional cancer intelligence units within individual countries such as the UK. This data can be fed into national and international registries and censuses. These allow for the analysis of general trends, for identification of specific subsets of patients, and for general comparisons of clinical performance between individuals and units. However, a general rule of data management is that the further the point of collation and analysis of the data from its collection, the less accurate and informative it becomes, and the less sensitive to local factors which may have a considerable bearing on interpretation.

Clinical trials and meta-analyses are a highly refined form of data collection and investigation. The limitations of clinical trials are well recognized, in that they report on selected patient categories, treatment regimes and outcomes rather than the totality of treatment of populations. They are nevertheless an important aid to risk analysis, in that they clarify decision points.

Mathematical tools for risk and hazard analysis

Risk can be measured as an event rate over a given time period. We commonly and unconsciously use risk measures in the form of predictive factors in cancer management, most commonly in the histological description and node status.

There are many mathematical tools which facilitate the analysis of outcomes in appropriately collected clinical data and which thus contribute to risk analysis. They are often inconsistently applied. Their potential has been hugely enhanced in recent years by the power of computers and software packages. Computers allow the analysis of huge data sets for defined and unexpected trends (Data Mining), and the assessment of trends to decide future strategies (Forecasting). They allow the modelling of treatment strategies and prediction of outcomes with increasing numbers of variables. They can calculate probabilities and odds, the odds on an outcome being the ratio of favourable outcomes to unfavourable outcomes.

Conventional survival analyses such as Kaplan–Meier survival function plots are a valuable and underused tool for comparing outcomes for risk analysis. Cox Regression tools allow the calculation of proportional hazards with time dependent covariates. These tools may be used with actual data from study populations, or with predictive data from standard populations and epidemiological studies.[2,3] Survival analysis can usefully be applied to therapeutic decision making. For example, Shaha *et al.* (1995)[4] reported a selective approach to management of follicular carcinoma of the thyroid based upon an analysis of historical outcomes of 228 patients with follicular carcinoma of the thyroid treated at The Sloan–Kettering Cancer Center.

Survival data nevertheless needs to be treated with great caution, as one data set can be used to produce seemingly different survival figures, illustrated by Schofield *et al.* in 1986.[5] Conventional survival techniques need tuning when applied to cancer management, as the expected survival will be influenced by the age of the patient and by pre-existing conditions, for which adjustment must be made. For example, this may be achieved by couching survival estimates in terms of the fraction of the normal remaining life span.[6]

Bayes' theorem aids decision making because it shows how probability distributions, which reflect current assumptions, can be modified by new information. It also allows for the study of the effect of a variable such as a treatment intervention on multiple subgroups.[7,8] Bayesian methods recognize that unknown quantities such as population means have probability distributions rather than fixed values. Computers permit the complex calculations and statistical manipulations such as were not practical when 'conventional' statistical methods were developed by Bland.[9] Bayesian methods may thus be a powerful tool for risk analysis in cancer management, and provide an underutilized tool for the evaluation of clinical practice.[10]

Cluster analysis is another technique linked to Bayesian methodology which may find applications in cancer management risk analysis. It is a tool currently used to identify environmental hazards to populations. A cluster is a (geographically) bound group of occurrences of sufficient size and concentration to be unlikely to have occurred by chance.[11,12] Thus, for example, we could identify for further research particular patterns of cancer events or outcomes in one health area or population.

Whichever tools are used, risk analysis is a continually evolving and dynamic process which must address new data. Over the past century, life styles, life expectancy, dietary habits, disease profiles and environmental hazards have changed dramatically, and society is constantly re-evaluating avoidance strategies for individual cancer hazards, such as reduction in smoking and environmental pollution to reduce the incidence of lung cancer, or asbestos control for mesotheliomas. The denominator populations do not remain stable with time.

Risk management

All medical strategies invoke risk. Some strategies will therefore fail to produce the anticipated improvements to health. Our objective must thus be to reduce clinical risk to a realistic minimum rather than to eliminate it entirely. Risk management aims to maximize and optimize the factors which we can control, while minimizing factors which we cannot control. How are we to optimize rational, scientifically driven and risk averse behaviour in oncological decision making? Can we modify individual characteristics of risk aversion or risk seeking through subspeciality training, for example?

Risk reduction also imposes costs, both for the acquisition of information and for the implementation of preventative strategies. These costs are a real constraint upon risk reduction which must be taken into account when appraising outcomes. For example, is the skills mix of fully trained, fully qualified clinicians properly resourced? Are the investigative techniques adequately funded to allow early diagnosis? Are the treatment regimes resourced to allow optimum outcomes? What is the impact upon morale of inadequate resourcing, and the consequence for the development of a risk averse culture?

The terminology of clinical risk

The communication of the concepts of clinical risk both to professionals and to the public has undoubtedly been clouded by the terminology, particularly in relation to relative and absolute risk.[13] Relative risk describes a simple ratio of events in the high risk (the numerator) to the low risk (the denominator) population. The ratio can substantially exceed unity, and thus can give the impression of a very high risk where the actual numbers of events are in fact very low. Relative risk also allows simplistic comparisons and generalizations between and across very different populations and age ranges, and across multiple risk factors and multifactorial analyses.

In contrast, the absolute risk is measured in units which accurately describe the incidence of an event and allow the direct calculation of absolute numbers in a given population, and hence the resources to be diverted to prevention or treatment. Perversely, absolute risk may have much less impact in conveying the message. Thus, for example, an environmental factor such as hormone replacement therapy (HRT) may increase the incidence of an epithelial cancer from 30 to 60 cases per 10 000 women in a given age group and over a given period. This may be presented as a very small absolute additional risk of incurring the condition to any one woman contemplating the use of HRT, or it may be presented as a very substantial relative risk to discourage use of HRT. The absolute risk can nevertheless be misleading if not applied strictly to the case in hand. Thus, for example, a '1 in 12' absolute lifetime risk of breast cancer to a Western woman disguises huge age related differences in the risk of developing the disease. These terminologies become particularly important when advising patients on familial and genetic risk, as they may provoke inappropriate or excessive prophylactic interventions.

Concluding comments

A strategy for clinical risk analysis is beginning to emerge, the key to which is better information collation and management. Powerful and networked digital computer systems, the universality of the personal computer, new software models for data analysis, and modern data entry systems such as bar code readers should bring accurate and time and resource efficient data collection closer to the clinician and the clinic, while allowing massive high level interrogation of data over entire populations and health delivery systems. The creation of an awareness of the challenges and opportunities of risk analysis, zero error tolerance, human factor analysis and human systems engineering is the first step to developing and assessing new models and attitudes to working practice.

The management of cancer patients will always involve risk and usually takes place in the knowledge and certainty of premature death. This may have made us unduly tolerant of a high risk case management culture which may increase morbidity and early mortality. Moral hazard is the acceptance of risk, and it is a burden accepted by all cancer clinicians. In a discipline which is so dependent upon human factors of skill and judgement, we may not expect to achieve the levels of fault intolerance demanded in other fields of human endeavour. However, failure to address these matters robustly will make our patients continue to pay a high price and will have medicolegal and political consequences. Risk analysis is a discipline whose time has come in clinical and oncological practice. In the next article, we address in greater detail the issues of risk management as they affect the practising surgical oncologist.

Key Learning Points

Risk and uncertainty influence all human decision making
Information and time mitigate risk
Risk analysis is a mathematical and scientific discipline
The consequences of failure to make adequate judgement of risk in surgical management of cancer are generally borne by patients
Clinical governance and medicolegal judgements are transferring this risk to clinicians
Survival analysis, Bayesian probabilities and cluster analysis are some of the established tools for clinical risk and outcome analysis
Massive health data set analysis will permit better risk evaluation across the spectrum of clinical practice

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