proteins involved in growth regulation. Regimens derived from laboratory studies of biochemical modulation of antineoplastic agents[12] and monoclonal antibodies[13] that may serve as carriers of therapeutic isotopes or protein toxins are under active evaluation. These approaches require thoughtful preclinical development and demand careful clinical evaluation.

Will we make any progress through clincial trials? I believe that we will, but the path is likely to be long and frustrating. There will be rewards, however, for those who look to the advances in the biology of the disease, undaunted by the limited success we have had so far with empirically derived chemotherapeutic regimens.

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Quality Assurance in Cancer Treatment

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Report of a Working Party from the European School of Oncology

INTRODUCTION

QUALITY ASSURANCE in medicine is the process through which we attempt to monitor the actual quality of care given to an individual patient, to a patient group or to a population. When deficiencies are identified, measures taken for corrective action are formulated.

While this would seem an obvious process to be integrated in the process of health care, it appears that relatively few organised activities have taken place in this field. This is related in part to the fact that the results of health care are determined by a large number of processes and professional groups which all contribute in important ways in determining the final product. They include basic and clinical researchers, legislators, administrators, physicians and paramedical professions, each individual influence often being difficult to identify.

Apart from the complexity of the process, evaluation is also hindered by the frequent difficulty in defining adequately the aim that is pursued. For example, when considering outcome, cure is the most readily measurable parameter in statistical terms, while quality of life, palliation and patient satisfaction are difficult to quantify. It is, therefore, extremely important to define the different endpoints we need to assess. We also need to clearly identify the elements of the process to be considered separately and the mechanisms for implementing corrective action.

Different goals in quality assurance

The final value of a specific treatment can be analysed through five questions:

— is there efficacy in the treatment?
— is it effective in routine application?
— can we afford it, or does it have a good cost–benefit relation?
— is it available to all patients?
— is it applied correctly when given to a specific patient or patient group?

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Does it work? The ability of a given treatment agent to influence the course of the disease is termed its efficacy. It is investigated in basic research or determined through clinical investigation, mainly prospective (randomised) trials.

Does it work in routine application? A treatment hardly ever yields its full potential in routine practice, as the optimal technical conditions and human interactions are often not achieved. The more complex the technology and procedures for a certain treatment are, the further routine outcome will be from ideal results. The relation between the outcome in routine settings and the potential under optimal conditions is called effectiveness. The analysis of effectiveness should be done by global health care research.

Is it cost-effective? Not all effective procedures are worth implementing. Indeed, in a framework of the assessment of global health care priorities it will be necessary to measure the benefit and the cost of each procedure in order to be able to decide on the appropriateness of its application. If small improvements in results require unduly large expenditure, they may have to be rejected in favour of other procedures with better cost–benefit ratios. This means that quality in a population aims at optimal average use of resources, not the best potential use in every single case. This implies that a global assessment of cost-effectiveness is constantly necessary for old as well as new procedures. The elimination of suboptimal procedures thus becomes as critical for quality of health care as the activation of useful new procedures.

Is it available for all patients? The advent of a new procedure is often followed by a number of political and organisational decisions which will determine its availability to the patient population. This can also involve decisions on coverage by health insurance plans, regulation measures on which centres or which physicians are allowed to carry out the procedure and financial support for investments in the intra-structure. Distribution or accessibility of therapy is largely determined by political decisions and organisational measures. The question of equitable distribution can be studied through epidemiological or utilisation studies.

Is the procedure correctly carried out? (Table 1) This is quality control in the strict sense. This involves the investigation of the adequacy of treatment given to a specific patient or a group of patients in a well-defined setting, for example, a department or a hospital ward. This should also cover the selection of the treated population (do all patients who need the treatment get it and is the treatment withheld from patients for whom it will not be useful?), the prescription of treatment in its technical aspects, the process of treatment preparation (e.g. acquisition of patient data) and its execution. In cancer therapy, process analysis of treatment has largely been limited to radiotherapy with only minimal activity in the fields of surgery and chemotherapy.

Table 1.

Quality control of treatment procedures
Patient selection: diagnostic procedures and medical decision making
Treatment prescription
Treatment execution
Radiotherapy
Surgery
Chemotherapy
Supportive therapy

Quality assurance: field of research or routine activity?

It is important to distinguish these two aspects of quality assurance. As a routine practice, quality assessment looks at the level of care achieved in a defined setting. Quality assurance also comprises all the necessary steps to take corrective actions. The research activity in quality assurance tackles a number of additional aims. It tries to define the target which should be achieved in treatment and to collect hard data to support the validity of predetermined standards and the achievement of the intended aims. It attempts to identify the factors influencing quality of treatment, analyses the measurement techniques that can be applied and assesses the impact of corrective measures.

HOW DO WE ASSESS QUALITY?

Outcome

For patients, measurement of outcome, or the final result of the treatment is logically the most important parameter, but this proves to be a complex and contentious issue. Outcome covers a number of factors such as cure, side-effects and satisfaction of the patient. Cure and side-effects are parameters which, in oncology, can often only be assessed after many years. This means that when results become available they may no longer be relevant. Assessment of outcome on too small numbers and with too short follow-up times has often been counterproductive. Once outcome is measured, it only gives a limited result without indicating possible reasons for shortcomings. If outcome is less satisfactory than expected, it is necessary to reflect on and analyse the separate facets of the process to try to identify the reasons. Compared with the assessment of outcome, it is easier to appraise the structure or the process used to obtain the outcome. However, the value of this is uncertain because a direct relationship between these factors and outcome have usually not been convincingly demonstrated.

Assessment of structure

The rationale of the structural approach of quality analysis is logical as a good structure should be expected to facilitate a satisfactory process to ensure a good outcome. "Structure" can be defined as the way a centre treating patients is equipped and organised in all aspects. In the EORTC projects on "data quality control" and "chemotherapy quality control" a sizable part of the investigation has been aimed at establishing the reliability of the structure used in the participating centres. The assumption that the quality of structure influences process and that this is directly related to the treatment result is difficult to prove as outcome is likely to be confounded by other factors. Even the best structures can be abused, while some doctors may perform well in abysmal conditions. Hence, the influence of structure on outcome is not clearcut, making it difficult to directly validate the impact of this factor. The structural approach does strengthen the hand of regulatory bodies in dealing with unacceptable conditions.

Measurement of process

The "process approach" analyses the way treatment is actually given to patient groups or individual patients. This has been the most frequently used procedure in the EORTC quality control program in the recent years. Again, it is difficult to demonstrate a direct relationship between quality of process and outcome.

However, if for instance in radiotherapy one accepts the critical importance of adequate tumour coverage and of the dose effect relationships then one can presume that the identification of parts of the tumour uncovered by the radiation beam and the elimination of large dose deviations should have positive repercussions for improved tumour control as well as reduced incidence of treatment complications. However, such influences cannot be demonstrated in retrospective studies and ethical considerations are evidently obstacles to randomised studies on this aspect.

Quality assurance in cancer treatment is a constructive process in which the provision of health care is analysed systematically and critically. It entails setting standards of care, ensuring they are being fulfilled and the outcomes aimed for are achieved. Hence, areas where change is needed may be identified so that new standards can be set and again subjected to quality control. The process covers the environment in which care is delivered (structure), how operational standards are maintained (process) and what is achieved for patients (outcome).

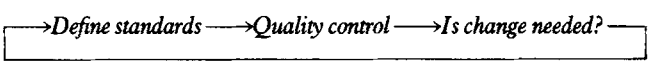
The implications for resource utilisation are important and an essential component for commissioners (purchasers) of health care who should expect to have evidence of quality control from the providers of these services.

NEED TO DEFINE STANDARDS OF CARE

Definitions of standards of care are essential prerequisites for the practice of any aspect of medicine. They establish the guidelines to which medical practitioners, nursing staff and other personnel should adhere and are a *sine qua non* for quality assurance. Without standards of reference, quality control is impossible.

It is necessary to set standards for the structures and processes which are aimed at achieving specified levels of outcome. The quality control process (audit) assesses, in a systematic and critical way, the precision with which standards are being followed and if outcome is satisfactory. It detects when defined objectives fail to be reached and so engenders a reappraisal of the predetermined standards. In this way we identify whether or not the standards have been fulfilled or if they need amending. If the need for change is demonstrated, this is implemented by setting new standards to close the "audit loop". Further quality control procedures ensue in this continuum of quality assurance, a process entirely dependent on the regular establishment and re-definition of standards of care.

The audit loop



RELATION BETWEEN FACTORS OF STRUCTURAL OR PROCEDURAL NATURE AND OUTCOME

Although it is very difficult to document the direct relation between factors potentially influencing the quality of the treatment and therapy result (outcome), there has been a rapidly expanding body of indirect evidence building over the past two decades. This can be divided into factors influencing the structure in which therapy is administered such as the cancer centre, the teaching hospital or the community hospital and factors steering the process itself such as guidelines, protocols and clinical trials. Nevertheless, we must be careful with the interpretation of these data as they can simply result from patient selection rather than differences in structure and procedure.

Structure

The apparent beneficial influence of an environment which encourages a large referral of patients with a specific disease or for a specific treatment has been documented several times. For paediatric solid tumours, clear differences have been shown in outcome between patients treated in specialised centres versus non-specialised centres [1–4].

Recently, similar differences have been demonstrated for outcome in ovarian cancer treated in either teaching or non-teaching hospitals [5]. In a comparison between a centre treating a large number of patients with testicular cancer and a series of centres with small numbers of patients, there was a significant survival advantage for those from the large centres [6]. It is noteworthy that all centres used the same trial protocol so that the procedures were supposedly identical, while often in the other studies, structures as well as procedures had been different.

Procedure

Treatment of patients in clinical trials has several important aspects. It always entails a detailed standardisation of treatment and often compares best convention treatment with a potentially better therapy. It usually implies the involvement of a physician interested in research, often in a cancer centre or a teaching hospital and usually has integrated quality control procedures.

The nearly constant better results that have been found for patients included in trials as compared with non-trial patients is of interest, but as there is usually considerable selection for trials, straightforward comparison with the general patient population is hazardous. Most data come from paediatric tumours, for which the proportion of patients treated in specialised centres is very high. Foremost are the studies on leukaemia (MRC working party on Leukemia in Childhood, 1971) [7, 8] where differences ranging from 10 to 40% in absolute survival have been identified. Also for nephroblastoma important differences were detected e.g. by Lennox *et al.* [9], who found values of 77 and 58% for children on study versus eligible but non-included patients. Of particular interest in this field is the later publication on overtreatment of the same type of patients outside paediatric oncology centres [10]. Similar differences have been found in adult patients with better results for treatment of myeloma [11] and for bronchial neoplasia [12] when patients are included in trials.

Attempts to improve the process by targetted educational efforts

Several projects have tried to identify the impact of specifically targetted, short-time educational efforts in order to improve the process in the treatment of certain oncological diseases by a whole community of physicians. Such a programme of distributing specific guidelines was carried out in Italy for ovarian cancer with disappointing results. No clinically relevant effect of the programme was detected [13]. A similar program (Community Hospital Oncology Programme) supported by the NCI in the USA led to similar conclusions, the data showing no evidence of diffusion of guideline principles to the majority of practicing physicians [14].

The number of years physicians had been in practice had an inverse relationship to patterns of care conforming to guidelines. Hence, selective, targetted educational efforts can be of little impact and to get results will probably require a continuous and broad-based effort. The results also stress that, ultimately, the impact of such a programme could be very large as evidently, from the above reports, essential elements of documentation cannot be found within patients' files and are thus probably

systematically not taken into account in the decision making process for treatment.

STRUCTURE NEEDED FOR CANCER TREATMENT

A multidisciplinary approach is mandatory in the diagnosis and selection of treatment for cancer patients. A single doctor, regardless of his personal competence, can no longer be in a position to take decisions alone which affect patients' outcomes in terms of potential for cure and quality of life. In addition, for many cancers, the choices made at the initial stage will strongly affect the chances of cure, while decisions taken after failure of an initial treatment will mostly interfere with quality of palliation rather than with probability of cure. Hence we must define:

- — the optimum environment for accommodating the various disciplines involved in cancer treatment,
- — the basic methodology for the decision process,
- — the minimum requirements for equipment in each discipline,
- — the criteria for optimal staff composition and expertise,
- — the major factors influencing the acceptable variations of these figures,
- — knowing these data, which mechanisms should allow the improvement of a given situation.

Optimum environment for cancer treatment

Cancer centres or structually integrated departments in general hospitals usually offer the optimum geographical environment for diagnosis and treatment at times most critical for a patient's future: the multidisciplinary discussions for the decision process on treatment strategy and planning.

The variability and complexity of each tumour type, location and stage of disease requires several multidisciplinary groups, involving experts from each involved discipline to:

(a) decide formally policies for management of specific diagnostic categories either within the framework of clinical research (choice of experimental protocols in recognised national and/or international structures such as the EORTC) or within structured routine practice.
(b) take appropriate decisions on individual cases before the delivery of treatment.

The existence of formal structures defining the cooperation between an integrated cancer centre and between medical personnel elsewhere is necessary to provide the framework in which quality assurance procedures can be applied to evaluate performance and propose improvements.

Formalisation of decision process and accessability to outside review procedures

Procedures to evaluate the performance of a medical structure involved in cancer diagnosis and treatment need to be implemented. An integrated cancer treatment unit and associated personnel in the community should be able to document the rationale and criteria for the choices made in each clinical situation, and, if applicable, for the selection of clinical research. It should also facilitate audit by external review performed by independent experts and provide them with access to all staff members and case records.

The minimum requirements for equipment

The acquisition, usage and maintenance of major infrastructure equipment is one of the keypoints to achieving optimal results and the best cost/quality ratio. Radiation therapy is taken as the principle example. However, the same considerations can be applied to chemotherapy and surgery. Although some European countries have defined what they consider optimum ratios between types of equipment and the population served, surveys have shown large variations between countries, highlighting the need to define minimum criteria for equipment and staffing [15]. For megavoltage radiation therapy equipment, the number of patients treated per machine per year varied from 325 to 833, with a standard deviation of 501. These figures then need to be compared with other sources both in Europe and North America to reach conclusions as to which recommendations should be made. The upper figures (600–800 patients per year) in the survey appeared to be a true obstacle for the implementation and practical application of minimum required quality assurance methodology [15]. The evaluation of the Simulator equipment showed even greater disparities with a range of 500–2500 patients per machine per year (mean 1185, S.D. 537). This pointed out a major lack of simulator equipment in many institutions since it is not possible for many radiotherapy patients to be treated adequately and to benefit from routine control procedures performed with simulators [15]. We need to establish standards not only for major equipment infrastructure directly used for treatment, but also for that necessary for the preparation and quality control procedures before and during therapy. As a direct consequence of these considerations, several countries have recently strengthened their policy for irradiation equipment and now impose a licensing programme for radiotherapy departments. Guidelines are given for the proportion of supporting equipment such as simulators, planning systems, mould room and dosimetry equipment as well as setting minimum criteria for levels of medical staff, physics support and radiological technicians (radiographers).

Criteria for staff number and competence

The same investigations dealing with heavy infrastructure equipment also addressed the staff needed to treat patients and operate this equipment. The figures collected by the EORTC Cooperative Group of Radiotherapy expressed as the number of patients treated per staff member per year are in Table 2 [15].

The remarkable range observed for the various categories of megavoltage equipment and staff in radiation oncology suggests that these aspects also need clarifying for chemotherapy and surgery before defining standards for quality assurance in cancer treatment.

Factors influencing these figures: acceptable variations

Variations in infrastructure, staff number and expertise are unavoidable to some extent, being influenced by the workload carried out by institutions in addition to routine cancer treatment of patients. Participation in clinical research, teaching of oncology to medical students, medical specialists and paramedical staff (nurses, technologists, etc.) creates additional needs when evaluating the optimum staff figures.

Table 2.

	Radiation therapist	Physicist and Dosimetrist	Radiation technologist
Average	328	482	117
Standard deviation	147	285	60
Range	130–770	186–1250	58–250

Correction mechanisms

It is essential to target our objectives of quality assurance in the areas where the conclusions drawn from experimental approaches can be easily transferred as applicable tools to improve standard practice outside of clinical research by all specialists involved in cancer treatment. This is the only way in the long run to obtain an impact of quality assurance on cancer control and quality of life in the whole patient population.

A typical example of this is the quality control programme for beam calibration and check on mechanical characteristics of all equipment used in a radiotherapy department. The procedure for this was developed in the framework of a quality control project of the DG XII (IV Medical and Health research program) by the Radiotherapy Group of the EORTC and has been taken over by national groups to apply it to all centres, including those not participating in clinical research.

A new programme is now being activated in the frame of "Europe against Cancer" to set up a structure of reference centres in different countries to which all centres can refer with a program of mailed TLD dosimetry.

MEASUREMENT OF PROCESS

Patient documentation

Record keeping is a fundamental condition for quality assurance. If the quality of medical and nursing records is poor, treatment quality will be low and quality assurance studies on cancer treatment are bound to fail because of lack of information.

In the interest of facilitating the use of the medical record, it is recommended that a minimal standardised format and standard language is used.

Essential items which should be accurately and fully documented in the patients' files are: patient demographic data, diagnosis and staging, documentation of the medical decision process, precise information on treatment prescription, treatment modality details including timing and dose for both radiotherapy and chemotherapy actually given, concomitant treatments given, treatment evaluation, both relating to toxicity and to the anti-tumour effect, follow-up.

Data quality control site visits, recently performed in a number of large centres entering patients in EORTC trials, showed striking differences between the type and the quality of the hospital file documentation. A mean of 30% of treatment information could not be checked due to lack of systematic recording of timing and doses of chemotherapy and treatment-related toxicity. In addition, the complex and variable nature of hospital files led to difficulty in extracting basic information [16].

Quality control of diagnosis

Diagnosis is the first major step in cancer treatment and it provides information on which the therapeutic decision is made. In view of the many technical aspects involved, diagnosis is very dependent on quality control. The proof of an effect of quality in diagnostic techniques on outcome approach is rarely acquired scientifically. This could be overcome by the wider use of prospective randomised trials to evaluate diagnostic procedures.

Interestingly, however, effects in outcome have been related to quality of the diagnostic procedure mainly in screening projects, for instance in Malmö, Edinburgh and Canada [17–19].

Standardising techniques and morphometry make quality control possible for aspects of work in pathology. An example of an activity in this field is the Manual for Clinical Research in Breast Cancer from the Breast Cancer Cooperative Group of the EORTC.

Quality control of cancer treatment

Surgery. In treatment of tumours, surgery plays a crucial role in a high proportion of curative treatment schedules. As surgery is a sequence of technical procedures, highly dependent on quality of performance, quality control (quality assurance) should be given a high priority for this aspect of cancer treatment [20–23].

Chemotherapy. Doses and schedules of chemotherapy are chosen on the basis of their tolerability (as determined by varying toxicity) balanced against their effectiveness (measured by tumour response, assessment of quality of life, and survival). For many types of tumours there is often no universally accepted optimal regimen of chemotherapy—trials are established to compare outcome variables between different regimens.

For some relatively rare tumour types (germ cell tumours, lymphomas, paediatric malignancies, acute leukaemias), chemotherapy is curative in a high percentage of patients. For a larger percentage of tumours, the major aim of treatment with chemotherapy is reduction of tumour volume, palliation of symptoms and a relatively modest prolongation of survival. Many tumours are refractory to cytotoxic agents and should only be treated in carefully monitored clinical trials in specialist centres.

Given the potential of chemotherapy, and the importance of appreciating the aims of its administration in the various types of malignancy, it is essential that the quality control of its use be optimal. There is evidence in some tumours that the dose intensity of the administration of cytotoxics (i.e. dose delivered in unit time) correlates with outcome (as measured by response, relapse-free survival and survival) [24–28]. The majority of this information is relatively unsatisfactory as it is derived from retrospective analysis of studies. Animal data and increasing numbers of prospective studies, however, indicate that optimal response and survival are correlated with the administration of full dose intensities of cytotoxics [28, 29].

Unlike surgery and radiotherapy, cytotoxic drugs may be freely prescribed by any medical practitioner—specialist and non-specialist. In oncology centres, clinical practice is often highly structured with many patients in clinical trials. These centres often have an excellent intrastructure of nurse specialists and counsellors. Attendance at such centres may be difficult for patients with advanced cancer when long distances are involved and, for these, local facilities may be more appropriate. However, away from specialist centres, experience of the use of cytotoxic chemotherapy will be less and expertise lower.

In a recently completed study of the EORTC Quality Control Group, adherence to protocol therapy in specialist centres was audited [16]. Deviations in dose and timing occured in 30% of courses of which 67% were avoidable and not related to toxicity. It must be emphasised that such shortfalls were measured in highly specialised centres and it will be important to extend this audit to other institutions.

The provision of a good chemotherapy service therefore involves considerable organisation and expertise. For these reasons, it is suggested that the majority of cytotoxic therapy be concentrated in specialist centres. Not only will this provide an optimal environment for the concentration of facilities and trained personnel, but there is also evidence that the outcome of treatment (in terms of response rate and survival) is improved in such specialist centres (see the section on Relation Between Factors of Structural or Procedural Nature and Outcome).

There is little information on the usage of chemotherapy

outside controlled clinical trials. Even within such trials, data on quality control of chemotherapy administration is limited and reveals a lack of standard process.

Once adequate documentation exists, an audit of chemotherapy administration (recording regimens used, dosages, timing) could occur in different centres—both specialist and non-specialist. This should include a recording of the facilities which exist such as the site of reconstitution, measures taken to protect personnel reconstituting cytotoxic drugs, checks on dosage prescribed and administered. A model for such a quality control programme has already been constructed [16] and could be adapted for such a wider project.

Radiotherapy. At present, radiation therapy is given through a variety of organisational structures and high variability in treatment methodology and procedures for treatment delivery exists. While some informal data are available, literature data demonstrating the influence of radiotherapy structure and treatment processes on treatment outcome are still rather scarce. However, a number of scientific organisations and countries have already formulated a number of guidelines for minimum criteria for necessary infrastructure. As for the definition of "process", radiotherapy is one of the few medical specialties where extensive guidelines have been published for treatment prescription, documentation, as well as for equipment quality assurance procedures.

Need for precision in radiotherapy—many experimental and clinical observations demonstrate that dose–response curves are quite steep in certain cases, and it is generally accepted that a 5% change in the dose to the target volume may result in a significant change in the probability of tumour control (ICRU Report No. 24). Similarly, such a dose change may result in a marked change in the incidence and severity of radiation-induced morbidity, for which some authors claim even steeper dose–response relationships [30–33].

In the past few years, several major incidents in radiotherapy, leading to major complications and even to the death of a number of patients, have been widely discussed in the media (e.g. in Exeter in 1988 and in Zaragossa in 1991) and the need for quality assurances has been stressed.

Radiotherapy structure—at present, the organisational structures in radiotherapy range from large departments, staffed by full-time personnel with high megavoltage equipment, to small offices staffed by part-time personnel with no higher energies than orthovoltage at their disposal [15, 34–37].

As the ability to carry out high-quality radiotherapy depends on the availability of a sufficiently large staff of well-trained and highly motivated individuals, recommendations as to suitable staffing levels were made by various national and international bodies (WHO Meeting of Investigators, 1980). Recently, the scientific community has put an important effort into the development of a curriculum for radiotherapy training and education [38].

Radiotherapy process—each and every step in the process of treatment preparation and delivery (basic dosimetry, treatment unit parameters, delineation of target volumes, planning and calculation methods and daily set-up of the patients) can contribute to the total uncertainty in the absorbed dose delivered to the patient [39–42].

Therefore, efforts have been made by various specialised organisations such as the AAPM, ICRU and WHO to recommend comprehensive quality assurance programmes, including periodic verifications of dosimetry, treatment unit, treatment simulator, beam accessory devices and treatment planning systems. A dosimetric intercomparison, performed by the EORTC in 17 departments entering patients in clinical trials, demonstrated acceptable dosimetric data for 85, 70 and 71% of the cobalt, X-ray and electron beams, respectively [43]. After this review, the uniformity between the visited institutions increased considerably, since they changed to methods which were recommended by the EORTC confirming the usefulness of such procedures.

Apart from basic dosimetry methods, inadequate treatment prescription can lead to a number of errors. Treatment prescription consists of the definition of the target volume and organs at risk, the total dose to be delivered and the overall treatment time and the treatment technique to be used. The need for uniform and unequivocal treatment protocols was confirmed by an interinstitutional intercomparison performed by the EORTC for head-and-neck cancer treatments [44]. Major problems were discovered in respect of the estimation of the target volume, the choice of treatment technique and non-optimal planning of the treatment.

Due to the large number of steps and the number of persons involved, the treatment preparation is a vulnerable part in the radiotherapy process. It has been demonstrated that errors due to inadequate transfer of information from one step to the next can seriously affect the final result of the treatment in 5% of the cases [45, 46]. Apart from failing communication patterns, inadequate procedures and material used during treatment preparation add to the final uncertainty in dose delivery.

Because it is extremely difficult and very time consuming to eliminate all the possible sources of errors, it is highly recommended to perform the final verification of the treatment on the patient during the first sessions of treatment delivery. The effectively irradiated volume can be checked by portal imaging [47–51]. The actually delivered dose can be checked by means of *in vivo* dosimetry [52–59].

Medical decision making

Agreement on best current management is important as it is the starting point for developing structure- and process-based surveys to assess the quality of patient care in cancer treatment. Moreover, a multidisciplinary approach, as in cancer care, can only be achieved through agreed policies and protocols, so that even if a new or follow-up patient is seen by one practitioner, the decision making is made within the context of a multidisciplinary approach to the patient's problem.

The basis of such an agreement can consist of expert opinion, results published in scientific journals, or results achieved in the best teaching hospitals.

The implication of "best current management" is that standards are set which define acceptable and unacceptable cancer care.

Ideal standards and criteria presume that we know in absolute terms what constitutes the best possible cancer treatment. Obviously, this cannot be achieved for most cancer sites and therefore the current medical knowledge and technology is used as the model on which to base the actual criteria. Recently, an attempt to define current good practice for the use of cytotoxic chemotherapy in the palliative treatment of advanced cancer has been made [60].

To set criteria for management is difficult. If "optimal care" is used as the reference, this may create an unrealistically high objective thus discouraging the majority of the physicians from trying to adjust to them. When, on the other hand, they are

based on previous practice or on averages, they encourage sub-optional medical care or perpetuate bad treatment habits, impeding for innovative developments. Therefore, the development of guidelines should be limited to general principles and specific practical aspects and not aim at all-encompassing rigid management principles.

The definitions of best current management must extend beyond rate and statistics to include patient preferences. Finally, it is applied to the measurement of the quality of cancer care, for which criteria and standards must be set against which to compare different treatment outcomes.

RESOURCE ALLOCATION

Optimal therapy requires proper financial support. Within limited resources we need a continuous process of eliminating suboptimal or useless procedures, thus freeing finances for worthwhile modalities. Additionally, within all available treatments with positive effects, priorities, based on cost–benefit analyses, will have to be set. This requires economic analyses of individual treatments, the effects in a whole population and, consequently, that on the global health budget. Not only do the financial consequences of a procedure have to be studied, but also predictions and/or follow-up measurements on frequency of usage. The financial support provided for a treatment can influence its use and *vice versa*. Until now, data on global costs of management decisions have been too sparse on which to build policies. Collection of such information is strongly encouraged.

The benefit part requires the development of procedures for quantitative analysis outcome. The easiest in absolute terms is the cure rate, although even here the translation of an increased cure rate into absolute benefit can be contentious, especially when weighed against adverse side-effects or complications.

In the benefit analysis, patients' perceptions should be built in, together with the objective data on cure, tumour-free survival and response rates—quality of life in the widest sense. The acquisition of information for these endeavours requires dedicated manpower which itself demands a high priority for resource allocation. Given the crucial importance of cost–benefit analysis, this is an area to which urgent consideration needs to be given for the appropriate funding of research and development in health care systems.

AREAS TO DEVELOP QUALITY ASSURANCE IN CANCER TREATMENT

Radiotherapy

Minimum requirements on the European level. In radiotherapy, there is already a large amount of information available from structure surveys, which deal both with equipment and staffing. In addition, the feasibility of some quality control procedures such as beam calibration and the check of treatment units, simulators and treatment planning systems has been tested by on-site visits or mailed procedures. Agreements, national or regional, do exist on the use of standardised treatment charts and for prescribing and reporting treatment data. For each of these items, it is of prime importance to develop minimal criteria or requirements on the European level. A European structure should be set up having the responsibility not only to set the minimum requirements but also to transfer them to national structures, which on their part will have the responsibility to distribute them on a national level.

Research projects. It has been shown that process-control procedures such as portal imaging and *in vivo* dosimetry reveal the weak points in the chain of radiation treatment. At present, efforts have been limited to individual centres trying to assess the feasibility, reliability, outcome and cost–benefit of specific quality control procedures.

Research projects should be focused on the further development of feasibility studies, philosophy analysis and implementation (both in small and large centres) of these process-related procedures such as portal imaging, *in vivo* dosimetry, the use of automatic verification systems, etc. At this stage, an important effort in further clinical research data in specialised centers is mandatory before minimum requirements can be set up.

Support in complex quality control procedures. Some quality control procedures for equipment and process control are of a high complexity both with regard to measurement equipment and to procedures. It is recommended that specialised centres can take the responsibility to offer technical assistance and procedural assistance by specifically trained personnel for reliable and accurate performance of these procedures to all centres interested and willing to perform these checks.

Chemotherapy

One of the major focuses should be aimed at assessing the facilities and staffing available and the degree of adherence to protocols in different centres where chemotherapy is used. As a first step, an inventory of the existing situation should be made, based on a questionnaire relating to facilities, including the presence of specialist nurses, site of reconstitution of drugs, steps taken to check the correct dispensing of the cytotoxics, methods of recording prescriptions, timing of administration and details of toxicity.

A wide range of types of centres should be covered as well as specialised cancer centres and general hospitals. As a result of this it should be possible to formulate guidelines as to the minimum criteria necessary for the environment in which chemotherapy can be given safely.

In a second step information can be gathered with the assessment of documented deviations from prescribed dose intensity (both dose reductions and time intervals) of chemotherapy, related to specific clinical studies.

Finally, a number of site visits can be carried out in which patient documentation will be checked as well as visits to available facilities including wards, pharmacies, data management offices.

Valuable information should be obtained on general parameters both of the factors related to the type of chemotherapy given and to the environment in which it is given.

Surgery

As for chemotherapy, information on the relation between the quality of the structure of the surgical departments and the outcome is scarce. The first step of a European project can be based on questionnaires sent to a variety of institutions in order to evaluate the staffing and organisation of facilities for surgical oncology. Tumour sites, for which centralised treatment is advisable, should be identified and a list of indications for centralised treatment should be composed.

In a step to address quality assurance of the surgical act, an attempt might be made to develop a methodology of audits for specific tumour sites by applying structured documentation procedures for two or three surgical acts such as, for instance, axillary clearance and tumorectomy for breast cancer.

In order to provide an incentive for standardising the procedures and their documentation, the different steps of the

operation shoud be described and case report forms developed. This would allow the production of lists containing all predetermined necessary information in operation reports.

The proposed forms can be tested in several pilot centers and guidelines produced based on the findings, for testing on a wider scale in a process combined with site visits to correlate documentation and third party observation during surgery.

Documentation of the cancer care process

Clear documentation of all aspects of care is a fundamental prerequisite of good cancer treatment. As a result of the Data Quality Control Programme performed by the EORTC, serious deficiencies in documentation were highlighted. Minimal guidelines should be drawn up for the documentation of the treatment decision process, the prescription, the actual treatment administered, the side-effects and the evaluation of the treatment effect. A framework for developing such guidelines needs to be initiated and will involve consensus by a group of specialists involved in each aspect of care. In some countries, minimal requirements for documentation of radiotherapy prescription and administration exist.

Given the potential toxicity of chemotherapy and the potential critical importance of administering full-dose intensity, it is surprising that no guidelines or requirements for documentation of chemotherapy exist. In many centres the dose actually administered will not be recorded and in the majority, toxicity recording does not occur or is unsatisfactory [16, 61]. Without such documentation, any audit of chemotherapy usage is impossible and measures of outcome are unsatisfactory or meaningless. In the chemotherapy treatment setting there is also need for clear documentation of pharmacy and nursing guidelines on the reconstitution, administration and potential toxicity of different cytoxic agents.

For surgery also, no criteria exist for documentation of operative procedures.

Multidisciplinary approach—basis for improvement of cancer treatment outcome

In many situations surgery, radiotherapy and medical oncology are effective, frequently additive in their effect on results, sometimes exchangeable. Joint therapy decision making avoids under-treatment or over-treatment, or a choice of wrong combinations. Multidisciplinary decision making is frequently lacking in medical practice, with probably an adverse impact on treatment outcome.

In an ideal setting, regular meetings of representatives of different disciplines should occur where:

— all cancer cases are discussed before treatment
— standard protocols for treatment in certain conditions are defined to be used in all cases at that hospital (or region).

A working project should design standards for such meetings and encourage their implementation by illustrating their usefulness. The current position could be established using a questionnaire to hospitals to look if and how such structures are functioning.

Medical decision making and outcome

Validation of medical audit. Clinical trials provide the best scientific approach for identifying the efficacy of treatment. This is necessarily a selective method and thus is limited as far as the generality of clinical practice is concerned. Hence, medical audit of outcome is needed to determine if efficacy can be translated into effectiveness.

Outcome endpoints vary according to the primary intention of treatment, but often interpretation of them could differ between patients and medical personnel (especially for palliative treatments).

As it is the latter who undertake audit, confirmation of its validity by gathering information from patients is essential if we are to be confident that audit works for patients. This is a field which should and can be subjected to clinical research. For example, the value of chemotherapy in the treatment of advanced gastric cancer is contentious. Here, information on patient's perceptions of various defined end-points can be collected by research nurses outside the treatment team. The patients' case records are subsequently subjected to audit by a team unaware of the patient survey results. A high correlation between two studies would give validity to the audit method and encourage its wider application.

Inappropriate non-use of treatment. A decision not to use an available treatment option is often difficult to make and may be in a patient's best interests. On the other hand, it is essential that patients are not wrongly denied potentially valuable treatment. Identifying such inappropriate non-use is difficult, but should be attempted. A way forward is to use cancer registries. For example, the withholding of palliative chemotherapy in breast cancer could be studied by looking at the records of patients registered and dying in a defined time-window. A simple questionnaire to hospitals could identify whether or not these patients were exposed to cytoxic drugs and, when not, an audit could be implemented to judge the appropriateness of the decisions made.

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ASSOCIATIONS

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Papers

The Impact of Received Dose Intensity on the Outcome of Advanced Ovarian Cancer

Lazzaro Repetto, Maurizio Pace, Serafina Mammoliti, Milena Bruzzone, Silvana Chiara, Cristina Oliva, Tiziana Guido, Pier Franco Conte, Elisabetta Campora, Alessandra Rubagotti, Paolo Bruzzi and Riccardo Rosso

It has been demonstrated that the prognosis of ovarian cancer is influenced by the dose intensity of cytotoxic treatment. The impact of received dose intensity of platinum-based combination chemotherapy on disease outcome was analysed in 226 stage III–IV ovarian cancer patients entered into two prospective randomised trials. All patients received either cisplatin or carboplatin and cyclophosphamide with or without doxorubicin for six courses after primary surgery. The impact of the received dose intensity of each drug (RDI), the average received dose intensity of the treatment regimen (ARDI) and the relative total drug dose (RTD) on progression-free survival (PFS) and survival were analysed. In the 198 patients receiving the full six courses of treatment, RDI of cisplatin or carboplatin, ARDI and RTD were > 0.76 in 74.2, 61.1 and 65.1% of cases, respectively. Although the differences were not significant, pathological complete response was more frequently observed in the group of patients with ARDI < 0.75, whereas the partial response rate was higher in the ARDI ≥ 0.76 group. Median survival and PFS were 19 and 13 months; 22 and 10 months; 23 and 13 months for the groups of patients receiving chemotherapy at a ARDI of < 0.75, ≥ 0.76–0.99 and > 1.00, respectively (*P* = not significant). It appears that modest dose modifications and brief treatment delays during first-line platinum-based chemotherapy do not affect response rate, survival and PFS in advanced ovarian cancer patients.
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INTRODUCTION

IN EXPERIMENTAL models, a steep dose–response curve has been demonstrated for several cytotoxic agents [1–3]. Recently, the planned dose intensity (DI) of a cytotoxic regimen, that is, the amount of drug scheduled to be delivered per unit of time, has been correlated to clinical outcome in solid tumours such as breast, lung, colon and ovarian cancer [4–11]. The majority of reports examine the impact on prognosis of the planned DI and do not take into account treatment delays and/or drug dose modifications that may occur in patients receiving multiple cytotoxic courses. The received dose intensity (RDI), i.e. dose of drug actually administered per unit of time, has been shown to predict the outcome of stage II breast cancer more accurately than planned DI [7].

Even if the outcome of ovarian cancer has been correlated to the planned DI of cisplatin-containing cytotoxic regimens [6], no study published to date has addressed the relationship between prognosis and RDI.

In order to analyse the impact of RDI on survival and disease-free survival (DFS) of stage III–IV ovarian cancer patients treated with cisplatin or carboplatin-containing chemotherapy, the clinical charts of 289 patients, entered into two consecutive randomised trials, were reviewed.

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