Reporting Results of Cancer Treatment

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On the initiative of the World Health Organization, two meetings on the Standardization of Reporting Results of Cancer Treatment have been held with representatives and members of several organizations. Recommendations have been developed for standardized approaches to the recording of baseline data relating to the patient, the tumor, laboratory and radiologic data, the reporting of treatment, grading of acute and subacute toxicity, reporting of response, recurrence and disease-free interval, and reporting results of therapy. These recommendations, already endorsed by a number of organizations, are proposed for international acceptance and use to make it possible for investigators to compare validly their results with those of others.

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ADVANCES IN CANCER THERAPY are made by continual investigation and evaluation of treatment results and their incorporation in the practice of oncology. This requires comparisons between results and necessitates the availability of appropriate data in a suitable form. Thus, standardization of assessment and of reporting of results is an important step that aims at increasing the amount of usable therapeutic information at the disposal of the physician. It has, therefore, become necessary to develop a "common language" to describe the results of cancer treatment and to agree upon internationally acceptable general principles for reporting and assessing data.

On the initiative of the World Health Organization, two meetings on the Standardization of Reporting Results of Cancer Treatment have been held in Turin, 1977 and in Brussels, 1979 with representatives of the European Organization for Research on Treatment of Cancer, the National Cancer Institute USA, the International Union Against Cancer, the Council for Mutual Economic Aid (COMECON), as well as members of several other organizations (ECOG, MRC, SAKC, SWOG, VA). This report is a summary of the conclusions and recommendations resulting from these combined efforts. A WHO technical report has been published in handbook form by the World Health

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Organization.[8] The guidelines given here are meant to be minimal requirements, leaving the investigator free to add any variable he deems necessary.

Baseline Data

Minimum sets of patient and tumor characteristics are necessary for identification of the patient population under therapy. This minimum allows for a more complete evaluation of the reported data and results. Useful for this purpose are some of the recommendations in the WHO Handbook for Standardized Cancer Registries.[7]

Minimum Data about the Patient

The minimum data should include name of the patient, address, hospital number or other identification number, sex, year of birth, birth place, height and weight, relevant medical history, all prior antitumor therapy, and performance status.

Performance status classification can be according to the Karnofsky scale (10 points)[4] or preferably using a 5-grade scale[9]: grade 0—able to carry out all normal activity without restriction; grade 1—restricted in physically strenuous activity but ambulatory and able to do light work; grade 2—ambulatory and capable of all self-care but unable to carry out any work. Up and about more than 50% of waking hours; grade 3—capable of only limited self-care, confined to bed or chair more than 50% of waking hours; grade 4—completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

It is often helpful to obtain additional data such as nutritional status, specific habits, and socioeconomic status. These and similar factors, which may influence the behavior of the neoplasm or the antitumor therapy, should be specified when indicated.

Data about the Tumor

The minimum data set desirable follows.

Site of the primary: ICD-O is recommended for topography coding.[3]

Measurability of the disease: Mention should be made whether the tumor or lesions are measurable: measurable, bidimensional; measurable, unidimensional or non-measurable but evaluable.

Measurable, bidimensional: Malignant disease measurable (metric system) in two dimensions by ruler or caliper with surface area determined by multiplying the longest diameter by the greatest perpendicular diameter (*i.e.*, metastatic pulmonary nodules, lymph nodes, and subcutaneous masses). Institutions performing life-size liver scans may use clearly defined biopsy-proved malignant hepatic nodules measuring greater than 5 cm in diameter as measurable disease.

Measurable, unidimensional: Malignant disease measurable (metric system) in one dimension by ruler or calipers (*i.e.*, mediastinal adenopathy, malignant hepatomegaly, or abdominal masses).

Mediastinal and hilar involvement may be measured, if a preinvolvement chest x-ray is available, by subtracting the normal mediastinal or hilar width on the preinvolvement x-ray from the on-study width containing malignant disease.

Malignant hepatomegaly may be measured if the liver descends 5 cm below the costal margin by adding the measurements below the costal margins in the midclavicular line and the tip of the xiphoid. Measurements below the costal margins should be made in the midclavicular lines or at other specifically defined points during quiet respiration.

Nonmeasurable, evaluable: Malignant disease evident on clinical (physical or radiographic) examination, but not measurable by ruler or calipers (*i.e.*, pelvic and abdominal masses, lymphangitic or confluent multinodular lung metastases, skin metastases).

When applicable, photographs should be taken before and during therapy to document response (*i.e.*, skin and subcutaneous metastases, inflammatory breast cancer, intraoral lesions, or recurrent rectal cancer).

Chemical values and biologic markers should be measured during therapy but are not used to evaluate response, unless specifically stipulated in individual protocols.

Histopathology, tumor type, grade, and stage: The ICD-O morphology codes should be used.[3]

Anatomical extent of the disease: Clinical staging should be recorded before the start of therapy. The UICC TNM system should be used whenever applicable.[6] Where surgery has been used to complete the staging, the extent of the disease, what was examined and what was found, and the resulting surgicopathologic stage should also be recorded.

Laboratory and radiologic data: It is suggested that the following be included: complete blood count, renal and liver function tests, pertinent radiologic assessment and tumor markers, if any.

Reporting of Treatment

Since the treatment methods should be reproducible, it is necessary to report sufficient information to interpret and evaluate the therapy used. It is important to indicate whether the specific therapy, be it a single

mode or a combined modality, is used to induce an antitumour effect or to maintain a condition.

In this report, the term "adjuvant therapy" is not used. What can be considered as adjuvant to primary therapy today may become primary tomorrow. It is therefore recommended that the term "combined modality therapy" be used when more than one form of treatment is used.

Surgery

Precise description of the surgical procedures should be given, preferably in the following categories.

1. Local excision of the tumor without excision of regional lymph nodes.
2. Local excision of the tumor with excision of the regional lymph nodes.
3. Excision of the tumor with the involved organ without excision of the regional lymph nodes.
4. Excision of the tumor with the involved organ with excision of the regional lymph nodes.
5. Excision of the tumor extended to adjacent organs. This can include removal of the involved organ where applicable.
6. Partial excision of the tumor (reduction, debulking, or other).
7. Excision of the metastatic lesions.
8. Reconstructive surgery.
9. Surgery for alleviation of symptoms only.
10. Other surgery, *i.e.*, exploratory, second look.

Whenever relevant, it is recommended that the surgeon states at the end of the operation whether the procedure is potentially curative or not. Major complications following surgery must be reported.

Radiotherapy

The following minimum specifications and descriptions are recommended: treatment plan; indications of whether the intent was curative or palliative; and the methodology, including the following.

1. Source of radiation (e.g., isotope, treatment machine).
2. Type of radiation (e.g., photon, neutron).
3. Energy of radiation.
4. Method of application (e.g., external beam, interstitial).
5. Sites treated including field sizes.
6. Dosage-time relationship, specifying: total dose, individual doses, dose rate, fractionation scheme, and overall time.

When treatment is not completed, the reason(s) for this should be stated. Radiosensitizers or protectors should be described when used.

Chemotherapy including Hormonal Therapy

Precise description should be given of treatment plan and drugs.

Description of drug administration should include drug name (use of nonproprietary name is recommended); routes and duration of administration; dosages (specify per kg of body weight or body surface in square meters and amount, e.g., mg, g); schedule and duration. Specify whether the drugs used are given singly, concurrently, or in sequence.

Give the proportion of planned doses actually administered if possible, and explain the reasons for dosage modifications or delays in drug administration.

Immunotherapy

Precise description should be given of agents or materials used; sources and strains; routes and duration of administration; dosage; and frequency of administration.

Combined Modality Therapy

Each of the modalities should be described individually. The time relationship of the different forms of therapy should be clearly specified, whether given concurrently, sequentially, during primary therapy, maintenance, or other.

Reporting of Toxicity

The management of malignancies frequently requires the use of treatment modalities that are associated with significant toxic effects. The acceptability of specific therapy can be assessed by comparing its benefits with its potential cost in terms of toxicity. For this reason, the documentation of toxicity is a crucial part of reporting treatment results. For purposes of classification, toxicities are best divided into acute plus subacute and chronic or late, rather than into specific treatment modalities.

Acute and Subacute Toxicity

Grading of acute and subacute toxicity has several important advantages: it permits comparison of toxicity between treatment programs, it permits computerized storage and analysis of toxicity data, and it allows uniform treatment modification within the therapeutic programs.

The attachment of clinical significance to a grade should be avoided, e.g., life threatening. A five grade system is recommended for general use, grades 0

TABLE 1. Recommendations for Grading of Acute and Subacute Toxicity

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic (Adults)					
Hemoglobin (g/100 ml)	≥11.0	9.5–10.9	8.0–9.4	6.5–7.9	<6.5
Leukocytes 1000/cmm	≥4.0	3.0–3.9	2.0–2.9	1.0–1.9	<1.0
Granulocytes 1000/cmm	≥2.0	1.5–1.9	1.0–1.4	0.5–0.9	<0.5
Platelets 1000/cmm	≥100	75–99	50–74	25–49	<25
Hemorrhage	none	petechiae	mild blood loss	gross blood loss	debilitating blood loss
Gastrointestinal					
Bilirubin	≤1.25 × N*	1.26–2.5 × N	2.6–5 × N	5.1–10 × N	>10 × N
SGOT/SGPT	≤1.25 × N	1.26–2.5 × N	2.6–5 × N	5.1–10 × N	>10 × N
Alkaline phosphatase	≤1.25 × N	1.26–2.5 × N	2.6–5 × N	5.1–10 × N	>10 × N
Oral	none	soreness/erythema	erythema, ulcers, can eat solids	ulcers, requires liquid diet only	alimentation not possible
Nausea/vomiting	none	nausea	transient vomiting	vomiting requiring therapy	intractable vomiting
Diarrhea	none	transient <2 days	tolerable but >2 days	intolerable requiring therapy	hemorrhagic dehydration
Renal, bladder					
BUN or blood urea	≤1.25 × N	1.26–2.5 × N	2.6–5 × N	5–10 × N	>10 × N
Creatinine	≤1.25 × N	1.26–2.5 × N	2.6–5 × N	5–10 × N	>10 × N
Proteinuria	none	1+, <0.3 g/100 ml	2–3+, 0.3–1.0 g/100 ml	4+, >1.0 g/100 ml	nephrotic syndrome
Hematuria	none	microscopic	gross	gross + clots	obstructive uropathy
Pulmonary	none	mild symptoms	exertional dyspnea	dyspnea at rest	complete bed rest required
Fever-Drug	none	fever <38 C	fever 38 C–40 C	fever >40 C	fever with hypotension
Allergic	none	edema	bronchospasm, no parenteral therapy needed	bronchospasm, parenteral therapy required	anaphylaxis
Cutaneous	none	erythema	dry desquamation, vesiculation, pruritus	moist desquamation, ulceration	exfoliative dermatitis, necrosis requiring surgical intervention
Hair	none	minimal hair loss	moderate, patchy alopecia	complete alopecia but reversible	nonreversible alopecia
Infection (specify site)	none	minor infection	moderate infection	major infection	major infection with hypotension
Cardiac					
Rhythm	none	sinus tachycardia >110 at rest	unifocal PVC atrial arrythmia	multifocal PVC	ventricular tachycardia
Function	none	asymptomatic, but abnormal cardiac sign	transient symptomatic dysfunction, no therapy required	symptomatic dysfunction responsive to therapy	symptomatic dysfunction nonresponsive to therapy
Pericarditis	none	asymptomatic effusion	symptomatic, no tap required	tamponade, tap required	tamponade, surgery required

TABLE 1. (*Continued*)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Neurotoxicity					
State of consciousness	alert	transient lethargy	somnolence <50% of waking hours	somnolent > 50% of waking hours	coma
Peripheral	none	paresthesias and/or decreased tendon reflexes	severe paresthesias and/or mild weakness	intolerable paresthesias and/or marked motor loss	paralysis
Constipation†	none	mild	moderate	abdominal distention	distention and vomiting
Pain‡	none	mild	moderate	severe	intractable

* N = upper limit of normal.

† Constipation does not include constipation resulting from narcotics.

‡ Pain—only treatment-related pain is considered, not disease-related pain. The use of narcotics may be helpful in grading pain, depending upon the tolerance level of the patient.

through 4 (Table 1). No attempt has been made to be all inclusive and investigators will undoubtedly need to add some toxic manifestations.

Several forms of cancer treatment can result in or contribute to death. Such deaths must be reported separately.

Chronic and Late Toxicity

Chronic and late toxicities are becoming more common as more effective treatments result in longer survival. The severity of these toxicities is less easily quantified than acute states. It is suggested that the following be reported: organ site or system affected; timing in relation to presumed causative therapy; nature of toxicity or disability (include second malignancy); magnitude of symptoms; impact on performance status; therapy required; response to therapy.

Patients should be evaluated annually for chronic and late toxicity.

Reporting of Repsonse

The guidelines proposed by the Breast Cancer Task Force in the USA[1], and those proposed for breast cancer by the UICC project[2] have in large measure been the basis for the criteria of response recommended in this report.

In the past, some groups and investigators have reported decreases of less than 50% in tumor size as responses. Often, it does not seem possible to determine this with precision.[5] It is recommended that only complete or partial responses as defined in this report be used.

While it is recognized that in some treatment trials shorter durations of response may be useful, in general four weeks should be used as the minimum duration of reported response.

Objective response can be determined clinically, radiologically, biochemically, or by surgicopathologic restaging. The method of determining response should therefore always be specified.

A 25% increase in one or more measurable lesions and appearance of a new lesions are recommended for defining progression of disease. This percentage should not necessarily be regarded as influencing the management of the patient.

Definitions of Objective Response

Measurable disease: Complete response (CR)—The disappearance of all known disease, determined by two observations not less than four weeks apart.

Partial response (PR)—50% or more decrease in total tumor load of the lesions that have been measured to determine the effect of therapy by two observations not less than four weeks apart. Bidimensional: single lesion, greater than or equal to 50% decrease in tumor area (multiplication of longest diameter by the greatest perpendicular diameter); multiple lesions, a 50% decrease in the sum of the products of the perpendicular diameters of the multiple lesions. Unidimensional: greater than or equal to 50% decrease in linear tumor measurement. In addition there can be no appearance of new lesions or progression of any lesion.

No change (NC)—A 50% decrease in total tumor size cannot be established nor has a 25% increase in the size of one or more measurable lesions been demonstrated.

Progressive disease (PD)—25% or more increase in the size of one or more measurable lesions or the appearance of new lesions.

Non-measurable disease: Complete response (CR)—Complete disappearance of all known disease for at least four weeks.

Partial response (PR)—Estimated decrease in tumor size of 50% or more for at least four weeks.

No change (NC)—No significant change for at least four weeks. This includes stable disease, estimated decrease of less than 50%, and lesions with estimated increase of less than 25%.

Progressive disease (PD)—Appearance of any new lesions not previously identified or estimated increase of 25% or more in existent lesions.

Bone Metastases

A separate set of response criteria are necessary for bone metastases.

Complete response (CR)—Complete disappearance of all lesions on x-ray or scan for at least four weeks.

Partial response (PR)—Partial decrease in size of lytic lesions, recalcification of lytic lesions, or decreased density of blastic lesions for at least four weeks.

No change (NC)—Because of the slow response of bone lesions, the designation of no change should not be applied until at least eight weeks have passed from start of therapy.

Progressive disease (PD)—Increase in size of existent lesions or appearance of new lesions.

Occurrence of bone compression or fracture and its healing should not be used as the sole indicator for evaluation of therapy.

Determination of Overall Response in Solid Tumors

Progression in any site indicates disease progression, despite objective responses in other sites.

If the organ site complete and partial responses are greater than no change designations, the overall response will be partial.

No change of evaluable disease does not detract from complete or partial responses in measurable sites, but the patients overall response will be partial.

Duration of Response

The period of complete response should last from the date the complete response was first recorded to the date progressive disease was first noted.

In those who only achieve partial response, only the period of overall response should be recorded. The period of overall response lasts from the first day of treatment to the date of first observation of progressive disease.

Subjective Response

Definition of subjective response is difficult because there are so many factors that can influence it. Despite this difficulty a response (*e.g.*, weight gain or decrease in pain) can nevertheless be of great importance to the patient and may alert the physician to the possibility of an objective response.

Reporting of Recurrence, Relapse, Disease-Free Interval, and Disease-Free Survival

The terms "recurrence" or "relapse" are here used to indicate reappearance of disease after complete eradication and are preferentially applied for patients with early stage disease; whereas, the term "progression" is usually reserved for patients with advanced disease.

Date of First Recurrence

This should be based on the onset of a sign. The date of first detection of a palpable lesion is acceptable only when the diagnosis of tumor involvement is subsequently established. The diagnosis of recurrent disease by x-rays or scans should be dated from the first positive record, even if determined in retrospect. Disease specific markers and disease specific symptoms may be used to back-date the time of recurrence.

To define the time of recurrence as accurately as possible, one should specify the frequency of examination and duration of follow-up. Time to recurrence or death should be measured from the first day of therapy.

All dates should be recorded by those responsible for the care of the patient. Dates of first recurrence, relapse, metastasis and death should be confirmed by an independent reviewer whenever possible. Data based on suspicion alone should be reviewed to establish their accuracy. In addition, the case records of patients not reported as having recurrent disease should be scrutinized annually.

Diagnosis

One or more of the following must be positive for a diagnosis of recurrent disease to be acceptable: histology or cytology; progression of lesion originally considered suspicious only; response of lesion(s) to specific therapy; and autopsy.

Classification of Recurrence

Lesions can be categorized broadly as locoregional or distant. A precise description of the sites of recurrence or metastasis should be given. Where radiotherapy has been employed, distinction should be made on whether disease has reappeared within the irradiated volume or not.

Classification of Cases

At the time of analysis the following outcomes are possible for each case: alive without recurrence; alive with recurrence; alive, recurrence unknown; dead without recurrence; dead with recurrence; dead, recurrence unknown; lost without recurrence; lost with recurrence; and lost, recurrence unknown.

Disease-Free Interval and Disease-Free Survival

Disease-free interval or disease-free survival cover the period when there is no evidence of disease activity. The time elapsed between randomization or date of start of treatment and recurrence or death for each patient must be carefully recorded.

Reporting Results of Therapy

In the reporting of results, a division can be made into two broad categories.

Frequency. The frequency of an event is usually the first factor computed to evaluate a treatment. It is the ratio between the number of events of interest over the total number of units at risk. It can represent the frequency of recurrences following primary therapy, the proportion of responders, the proportion of survivors, the frequency of treatment failure, etc.

Duration. The duration of several parameters can be important. Examples are the duration of time to recurrence, duration of response, duration of survival.

Consideration of both frequency and duration will improve the completeness of reports. For instance, following the treatment of a primary cancer, it is useful to learn not only the frequency of recurrence but also the time elapsed between treatment and recurrence as well as the survival. On the other hand, when advanced disease is being treated, it is necessary to determine the proportion of responders, the duration of the responses, as well as survival. Thus, the appropriate use of parameters can vary with the disease, the stage of that disease, and the treatment.

Numerators and denominators: The numerator is the number of patients in whom events occur during a given period of observation. The denominator is the total number of patients at risk during that same period. Many authors do not clearly define the numerator or denominator used to report their results. Often a denominator is used from which many patients in the original sample have been deleted. Reasons for deletion include loss to follow-up, early death, inadequate data, failure to complete therapy due to toxicity, and refusal by the patient of further therapy. Such deletions can lead to a falsely high frequency or duration for a group.

At least two of the following three denominators are recommended for reporting results: 1) Eligible and registered, or randomized. The reasons for ineligibility and the number of patients entered on study but subsequently found to be ineligible must be reported. 2) Eligible, registered or randomized and treated . This includes all patients who were eligible, were registered, and were given therapy regardless of how little or how much therapy was given. 3) Eligible, registered or randomized and adequately treated.

When other denominators are used, these should be clearly defined.

Maturity of data: When a large proportion of patients has been followed for a short length of time, the reporting of duration may be meaningless. Similarly, the frequency of recurrence may be low and as yet of limited importance. It is important, therefore, to ensure that data have matured long enough to provide precision in the reported results while the completeness of data should always be specified in reports. The length of observation period required will tend to vary with different tumors.

Accuracy of dates: There are many forms of inaccuracy that can distort reported treatment results. A very important one is in the follow-up. If this is infrequent or poor, patients may be considered lost to follow-up or even alive and healthy when in reality they may be dead. Before reporting results, therefore, every effort should be made to confirm the state of the patient's health as well as the date on which an event occurs.

The problem of cure: The definition of "cure" is difficult and by many considered impossible. One definition used is when a group of patients has a survival experience identical to that of the general population with the same distribution of demographic factors, *i.e.*, when the relative survival ratio is one. Some prefer the term "recovered" for those patients for whom it is known that there is a low probability of subsequent death from the initial neoplasm. Another option is to regard the patient as cured when he or she has survived in a disease-free state long enough to

enter a group with a known low probability of developing a recurrence.

Patient Population

The patients to be considered in reporting results can be classified as follows: patients available for treatment; patients considered eligible and registered for a given therapy (criteria for eligibility and noneligibility should be specified); patients treated with a given therapy; patients adequately treated (the definition of adequate should be stated before therapy is started and not at the end of a study); and patients evaluable for efficacy of therapy.

The term "evaluable" is often not defined. This is one of the reasons different results from the same therapy are given in separate reports. Therefore, it is necessary to describe clearly those patients not considered evaluable. Patients evaluable for toxicity may not be evaluable for response.

Duration

The best method to summarize frequency and duration is the life table method because it takes into account the experience of all patients entered into a study. The method can be used to calculate survival, duration of response, disease-free interval and other sets of time intervals. Investigators not fully acquainted with the methods of calculation are encouraged to enlist the assistance of a medical statistical unit.

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