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Quality control in multicentric clinical trials. An experience of the EORTC Gynecological Cancer Cooperative Group

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Abstract

Data Quality is a central requirement of scientific research and external monitoring is essential in multicentric clinical trials (MCT). A quality control (QC) study was conducted in the main Institutions participating in EORTC-GCCG Protocol number 55863 — randomised phase III trial of vindesine, cisplatin, bleomycin and mitomycin-C (BEMP) versus cisplatin (P) in disseminated squamous cell carcinoma of the uterine cervix — in order to assess the impact of variations in data quality on the conclusions of the trial. The reliability of the different centres in following the protocol was investigated by a questionnaire covering drug prescription, local facilities and the procedure for preparation and administration of chemotherapy. The 'treatment protocol adherence' was evaluated by recalculation of the ideal protocol dose and its comparison with the actual delivered dosage at each cycle of chemotherapy. 'Data quality control' was assessed by comparison of data on case report forms (CRFs) with the corresponding items in the medical records. Eleven centres participating in the trial were visited by the same team of reviewers. Striking differences were noted in the chemotherapy administration procedures and between the type and quality of hospital files. Overall, there was an acceptable level of data quality and protocol compliance. Data accuracy was 81.8% (range: 65.6–97%) of the 4424 items checked. Incorrect data were found in 7.0% (2.3–14.5%), data were missing on the form in 3.6% of cases (0–12%) and data was on the form but not in the file in 7.6% of cases (0.7–17.5%). Causes of inaccuracy were analysed. Both problems in data management but also in a lack of clarity of the protocol and/or CRFs were to blame. Training and supervision of data managers, precision in writing protocols, standardisation of some aspects of CRFs and the use of a checklist for chemotherapy data and treatment toxicities would have avoided many of these errors. The need for QC in all collaborative groups performing MCT is emphasised. A literature review on QC in MCT dealing with chemotherapy is included.

Keywords: Quality control; Multicentric trials; Chemotherapy

1. Introduction

Scientific quality is an ethical obligation of clinical research [1]. Clinical studies are aimed at improving the quality of management of the patients and, ideally, the treatment results of a certain disease. The way in which clinical research protocols are handled in the collaborating centres of multi-institutional studies can vary greatly and major inadequacies in treatment execution may alter the outcome of the study. In the 1980s the European Organization for Research and Treatment of Cancer (EORTC) received several grants from the European Community to perform quality control (QC) projects at different levels. Many variables were investigated in QC studies including diagnostic techniques, treatment modalities, tumour response assessment and, more recently, quality of data management [2–14].

Since 1988, the EORTC Study Group on Data Management (SGDM) has focused its efforts on establishing

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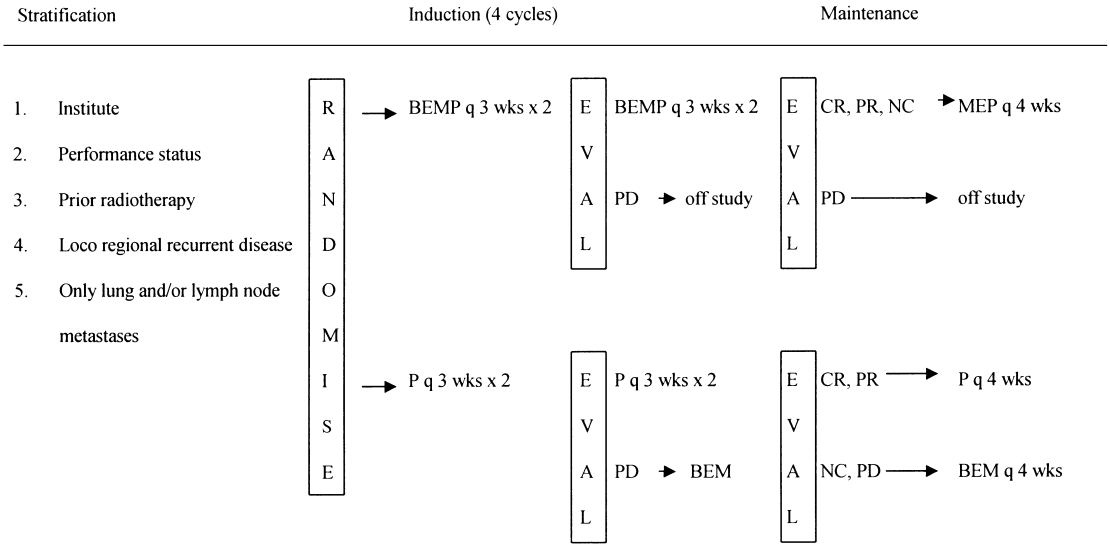
a method for data quality control in clinical trials. After a pilot phase based on site visits in 20 centres [7], a complete procedure for assessing both the capacity of a given institution to conduct clinical trials and its quality of data management was established [15]. In addition, a 'chemotherapy QC programme'' was developed in order to improve chemotherapy management and overcome the pitfalls which may occur as a result of poor drug prescription and dispensing [16–18]. The first step of the chemotherapy QC programme was to develop a reproducible procedure applicable for all chemotherapy regimens. This covered the main steps of chemotherapy handling, from drug prescription and preparation, to administration.

Both the validity of 'chemotherapy QC' and 'Data Management QC' needed to be tested by different EORTC Groups performing multicentre chemotherapy trials. Thus far, three Cooperative Groups have been involved in this programme: the Soft Tissue and Bone Sarcoma Group, the Head and Neck Cancer Cooperative Group and the Gynecological Cancer Cooperative Group (GCCG). The present report summarises the experiences of the EORTC-GCCG with the chemotherapy QC programme.

2. Patients and methods

The EORTC Protocol number 55863 was ''a randomised phase III trial of vindesine, cisplatin, bleomycin and mitomycin C (BEMP) versus cisplatin (P) in patients with disseminated squamous cell carcinoma of the uterine cervix' which was initiated by the GCCG in September 1986. A total of 254 patients were randomised by 39 centres in 14 different countries. The design of this study is shown in Fig. 1.



BEMP:	Vindesine:	3	mg/m² i.v. day 1, 8
	Cisplatin:	50	mg/m² i.v. day 1
	Bleomycin:	15	mg/day (infusion), day 2-4
	Mitomycin C:	8	mg/m² i.v. day 5 (cycle 1 and 3)
P:	Cisplatin	50	mg/m² i.v. day 1
MEP:	Vindesine	3	mg/m² i.v. day 1, 8
	Mitomycin C	8	mg/m² i.v. day 1 (alternate cycles)
	Cisplatin	50	mg/m² i.v. day 1
BEM	Vindesine	3	mg/m² i.v. day 1,8
	Bleomycine	15	mg/day (infusion), day 1-3 (deleted after 5 cycles)
	Mitomycin C	8	mg/m² i.v. day 4

Fig. 1. Randomised phase III trial of BEMP versus P in disseminated squamous cell carcinoma of the uterine cervix (EORTC protocol number 55863). q, every; eval, evaluate; PD, progressive disease; CR, complete response; PR, partial response; NC, no change.

The main participating centres were visited by a team consisting of the Protocol and the QC project coordinators. Centres to be visited were informed at least 1 month in advance and a questionnaire was sent to these centres, which had to be completed before the site visit and was further discussed during the site visit with the local investigators (responsible physician and data manager). The protocol oriented structure reliability within the GCCG was assessed by this questionnaire which was divided into two parts. In the first part, general aspects of drug preparation and administration were covered, as described earlier [15]. The second part of the questionnaire was protocol-specific and related to drug reconstitution, timing and mode of administration (Fig. 2). Details of antiemetic therapy and the centre's process to record side effects were also investigated and discussed during the site visit. This information was expected to give a picture of the group's reliability in following protocol guidelines both in drug handling and in toxicity recording. In addition, for this protocol-specific part the discipline involved (medical oncology, gynaecology, radiotherapy) and the type of centre involved (cancer centre, university hospital, general hospital) was taken into account.

2.1. Protocol adherence (chemotherapy quality control)

Essential aspects of the protocol included not only an early change in the treatment regimens depending on the response evaluation after two and/or four treatment cycles but also the separation of an induction phase from a maintenance phase. Chemotherapy cycles were repeated every 3 weeks during the induction phase and every 4 weeks during the maintenance phase. Moreover, mitomycin C was given on alternate cycles in BEMP and MEP, but every cycle in BEM. The sequence of drug administration, specified in the protocol for some of the administered agents, was assessed during the site visits in selected patients. In addition, depending on the availability of information in the medical record, a comparison of the calculated and administered dose per cycle versus that prescribed by the protocol dose was made. A 100% protocol dose was recalculated, based on the weight and height of the patient before each cycle. The actual dose was noted on the quality control forms. Deviations from the intended dose were calculated and presented as percentages. The reasons for any dose reduction or dose delay, if any, were coded.

2.2. Data quality control

At each site visit, the informed consent procedure was examined, the quality control of key data was done and a review of submitted data was performed as described earlier [15]. The presence or absence of a toxicity summary in the medical record was also documented. Toxic effects and grades reported on the case report forms (CRFs) were reviewed in 5 out of 11 centres. Moreover, in all institutions, the percentage of requested laboratory tests actually performed was assessed.

Finally, the organisational structure of local data management was determined and information concerning CRF processes for completion and data management supervision was documented. This allowed a comparison of data obtained in centres with data managers with those without.

After each site visit a detailed confidential report, signed by the QC co-ordinator, was sent to the protocol co-ordinator and to the visited centre (responsible physician and data manager). In order to guarantee anonymity each institution was given an identification number.

3. Results

Eleven EORTC institutions belonging to 7 European Countries participating in the GCCG (Italy 3, Netherlands 2, France 2, Belgium 1, Spain 1, Portugal 1 and Poland 1) were visited from March 1990 through June 1991. Six gynaecology (GYN) departments, five medical oncology (MED) units and one gynaecological oncology unit of a radiotherapeutic institute (RT) were involved (Table 1). In one university hospital, both the gynaecological department and the medical oncology unit were involved in giving the chemotherapy. In only three institutes were professional data managers employed.

The mean working time was 10 h for each site visit (range: 7–12 h). The mean number of medical records reviewed was 5 (range: 3–7) and the number of charts reviewed 59 (38% of the 156 patients enrolled by the 11 visited centres, range: 23–50%).

Table 1
Characteristics of the 11 visited centres[a]

Code number	Discipline giving CT	Patients		Professional data manager
		Enrolled	Checked (%)	
551	GYN	14	7 (50)	–
552	GYN	26	6 (23)	–
553	GYN	16	7 (44)	–
554	MED	19	6 (32)	+
555	MED	14	5 (36)	–
556	GYN	19	6 (32)	–
557	GYN	8	4 (50)	–
558	GYN/MED	6	3 (50)	+
559	MED	11	5 (45)	+
560	MED	12	5 (42)	–
561	RT	11	5 (45)	–

[a] GYN, gynaecologist (oncologist); MED, medical oncologist; RT, radiotherapist; CT, chemotherapy; +, professional data manager employed.

3.1. General evaluation report

Data on chemotherapy prescription, preparation and administration collected by the questionnaire are summarised in Table 2. The exact protocol dose was prescribed in one institution only; in three the dose was rounded up, in one rounded down and in three it was rounded up or down. In the remaining three centres the

Reconstitution of protocol products

Vindesine	1 = glucose
Cisplatin	2 = saline
Bleomycin	3 = combination
Mitomycin C	4 = other: .....

Timing of drugs

Vindesine	1 = 5 min push
	2 = slow push within 15 min
	3 = prolonged over ..... min

Cisplatin given in .... hrs ..... min
1 = inpatient
2 = outpatient

Bleomycin given in .... hrs ..... min

Mitomycin C	1 = over 15 min
	2 = shorter = ... min
	3 = longer = ... min

Mode of administration

Vindesine	1 = IV, peripheral
Cisplatin	2 = IV, peripheral catheter
Bleomycin	3 = IV, central catheter
Mitomycin C	4 = IV, via port-a-cath
	5 = other: .....

Please complete sequence of drug administration

Cycle 1, day 1

BEMP scheme	MEP scheme
1 = Vindesine, Cisplatin	1 = Vindesine, Mito C, Cisplatin
	2 = Mito C, Vindesine, Cisplatin
	3 = Mito C, Cisplatin, Vindesine
	5 = Cisplatin, Vindesine, Mito C
	6 = Vindesine, Cisplatin, Mito C

Approximate time delay (minutes) between preparation to administration of drugs in protocol 55863

..... min Vindesine ..... min Cisplatin Unknown?*
..... min Bleomycin ..... min Mitomycin C

General anti-emetic policy for first line chemotherapy patients? Y/N*
If yes, detail anti-emetics:

Dexamethasone/other steroids as antiemetics Y/N*

Toxicity: are side effects recorded in the hospital file? Y/N*
If yes, is a special form used Y/N*
Is data recorded as descriptive/coded/both* (please enclose a copy of any form used)

Data: ..... Signature: .....

Fig. 2. Drug reconstitution, time and mode of administration. Mito, mitomycin.

Table 2
General information on prescription, preparation and administration of chemotherapy

Prescription by:				
Specialist	7	Checked:	Yes	9
Junior doctor	1		No	2
Combination	3			
Preparation by:				
Nurse	8	Location:	Ward	8
Pharmacist	2		Pharmacy	2
Doctor	1		Other[a]	1
Administration by:				
Specialised nurse	6			
Doctor	2			
Nurse or doctor	3			

[a] Laboratory with laminar flow.

exact procedure was unknown. A similar picture was obtained with respect to drug preparation. The exact prescribed dose was prepared in three institutions, but mostly dosages were rounded up or down (seven institutions). In one institution this was unknown. Most of the time, chemotherapy residue was discarded (64%), but in 36% it was used again for other patients. Protective clothing (and gloves) was usually worn during preparation, but goggles were used in only 18% of the institutions. However, on several occasions a glass wall was present and, in fact, an exhaust canopy or laminar flow facilities were used in 82% of institutions.

3.2. Quality of adherence to protocol chemotherapy

Reconstitution and dilution of the four drugs was done according to protocol instructions in all centres. Timing and sequence of drug administration are summarised in Table 3. Large differences in timing were observed only for cisplatin and bleomycin, probably because of the desire to complete infusions in an outpatient setting. The sequence in which the drugs were administered was always correct in case of BEMP or BEM, but in four centres (557, 558, 559, 560) the sequence of drug administration in MEP varied considerably, for no clear reason. Overall, dosages given, expressed as median per cent doses (see Table 4), ranged from 98–100%. However, important deviations were observed for both bleomycin and mitomycin C. For bleomycin, major deviations could be easily explained (refusal of the patients; physician's error); for mitomycin C, however, this was due to protocol violations. Compliance in switching chemotherapy regimens after two or four cycles based on response evaluation was also poor in several institutes (551, 552, 556, 560). In particular this was seen when the protocol required changing from cisplatin alone to BEM. The frequency and causes of changes in the treatment intervals are summarised in Table 5. Occasional patients had treatment given earlier than specified, but the majority of deviations (48 of a total of 54) were prolonged. The shorter intervals without exception were observed in the cisplatin alone arm, the prolonged intervals in mainly the combination chemotherapy regimen, both in the induction phase and in the maintenance phase, illustrating the difference in tolerability of the two arms of the study. Out of the total of 54 altered treatment intervals 19 could have been avoided (35%). In particular, treatment delays were found to have been avoidable in 13 of the 48 instances (27%). Although some of the institutes were less compliant than others, there was no indication that the discipline giving the chemotherapy had any influence on this behaviour.

3.3. Data quality control

In this protocol, written informed consent was not compulsory. In the centres where written consent was not obtained, patients were to have had the study explained and were to give oral informed consent. In five centres nothing could be found in the medical records about informed consent and in three of them the investigator stated that it had never been requested.

Table 3
Timing and sequence of drug administration

Timing/sequence of drugs	Protocol instruction	Protocol adherence in 11 centres		
		Yes	No	Deviation
Timing	⩽5 min	7	4	15 min
Cisplatin (DDP)	3–4 h	7	4	2 h (3), 30 min (1)
Bleomycin (BLM)	3×24 h	9	2	20 min (1), 12 h (1)
Mitomycin (MMC)	⩽5 min	4	7	15 min (7)
Sequence in				
BEMP	DVA→DDP→BLM→MMC	11	–	
BEM	DVA→BLM→MMC	11	–	
MEP	DVA→MMC→DDP	7	4	MMC→DVA→DDP (2) DVA→DDP→MMC (2)

DVA, vindesine.

Table 4
Ranges of dose percentages[a] given in 11 different centres

Centre code	*n* of pts	No. of cycles	Combinations: BEMP, MEP or BEM				Single agent DDP
			DVA	DDP	BLM	MMC	
551	7	40	90–107	92–98	100–100	94–195	94–101
552	6	19	92–101	97–100	22–100	91–97	97–98
553	7	42	95–120	96–106	100–100	0–105	98–103
554	6	24	95–103	100–103	100–100	98–103	97–103
555	5	17	54–114	98–101	100–100	76–101	85–99
556	5	19	96–117	98–103	100–100	96–117	96–102
557	3	15	103–112	103–112	87–100	103–112	97–105
558	3	5	95–100	95–100	100–160	96–102	100–100
559	4	18	84–97	90–101	100–100	89–113	100–101
560	4	25	49–106	94–105	100–100	80–103	94–101
561	5	26	92–110	94–102	100–100	93–105	99–102
All	55	250	49–120	92–112	22–160	0–195	85–105
Median % dose			98	100	100	99	100

[a] Deviations from 100% ideal dose, recalculated on the basis of changes in body surface area and toxicity variables. For abbreviations see Fig. 1 and Table 3.

In two institutions a declaration, used for all kinds of treatments, was signed by the patient. However, this information could not be found in the medical records during the site visits. In three centres (554, 558, 559), the outline of the study was explained and in two of them notes in the medical record could indeed be retrieved. Only in one centre (561) was written informed consent available for each patient in the trial.

In the different institutions chemotherapy-induced toxicity was reported in the hospital file (5), on working sheets (2), on the CRFs only (2) or on specially designed toxicity forms (3). Reports were descriptive only (6) or descriptive and coded (4) or coded only (2).

Professional data managers were present in only 3 of the 11 centres (27%). In one centre (558) the data manager was not supervised by the responsible physician before sending the CRF's to the Data Center. In the other eight centres, data management was done either by the responsible physician, by junior doctors or by secretaries and the data were always reviewed before they were sent to the Data Center.

The data quality review consisted of an item by item comparison of the CRF's sent to the Data Center with the corresponding items (all key data of the protocol) on the medical record at the visited centre (Table 6). A total of 4424 items from 59 patients were checked in 11 centres; a mean of 402 per centre (range: 151–579). The mean overall percentage of incorrect data was 7% (median: 6.5%). However, this percentage varied widely from institution to institution (Table 6) and to a large extent incorrect transcription of data was the cause of this (95.6%). The same was true for information that was missing on the CRFs (92.8%). Ambiguity of the protocol and/or the CRFs accounted only for 3.3% of

Table 5
Incidence and causes of changes in treatment intervals[a]

Centre code	*n* of pts	Evaluated intervals	Interval too short	Delay of treatment cycles				
				Total	Toxicity	P.R.	I.D.	AD
551	7	27	–	8	6	–	–	2
552	6	13	–	1	–	–	1	–
553	7	32	2	7	1	5	–	1
554	6	16	2	–	–	–	–	–
555	5	11	–	4	3	1	–	–
556	5	17	–	4	4	–	–	–
557	3	8	–	7	–	–	3	4
558	3	2	–	–	–	–	–	–
559	4	10	–	3	1	–	–	2
560	4	16	2	6	1	2	–	3
561	5	24	–	8	3	2	2	1
All	55	176	6	48	19	10	6	13

[a] PR, patient's request; I.D., intercurrent disease; AD, avoidable delay.

Table 6
Quality of data

Centre code	Numbers of items checked	Correct (%)	Incorrect (%)	Missing on form (%)	On form NIF[b] (%)
551	579	65.6	8.0	9.0	17.5
552	327	82.0	6.0	1.0	11.0
553	543	81.5	3.0	1.0	14.5
554[a]	477	97.0	2.3	–	0.7
555	354	80.0	8.0	4.0	8.0
556	398	86.0	6.0	1.0	7.0
557	276	74.5	14.5	6.5	4.5
558[a]	151	82.0	12.0	2.5	3.5
559[a]	360	87.5	6.5	3.0	3.0
560	449	73.0	8.0	12.0	7.0
561	510	91.0	2.5	–	6.5
All ($n=11$)	4424	81.8[c]	7.0[c]	3.6[c]	7.6[c]

[a] Professional data manager employed.
[b] NIF, not in file.
[c] Mean.

the incorrect data and were overall only in 1.1% the cause of errors. Overall, 81.8% of data items could be matched in CRFs and the medical record. Only two of the visited centres had >90% correct data (554 and 561). The poor results in some institutions was primarily because source information in the medical file could not be found to verify CRF data items. This was often because the CRF itself was considered part of the medical record. In general, this was not a problem in centres with a professional data manager (554, 558, 559) where the data on CRFs was almost always to be found in the medical record. Interestingly, in the single centre in which data managers were not supervised the percentage of incorrect data was nevertheless one of the highest (12%).

A review was done on the presence or absence and/or severity of side-effects reported on the chemotherapy forms in five centres. Each chemotherapy form contained 17 boxes which were to be coded for specific non-haematological side-effects. In a total of 125 cycles, 19 drug effects were missing and 59 were incorrectly graded. Errors were most frequently made with respect to nausea and vomiting (10 of 19 (53%) in missing data, 43 of 59 (73%) in wrongly graded data). In part, this was due to shortcomings in the WHO toxicity scoring recommendations. Indeed, when prophylactic antiemetics were given, most centres graded 'transient vomiting' as grade 2 instead of 3. Nausea and/or vomiting was not reported in 10 forms (8%), drug fever in 4 (3%), diarrhoea in 2 (2%), and neuropathy and infection in 1 (1% each). Moreover, alopecia, lung toxicity, cardiac toxicity, peripheral neuropathy, diarrhoea and changes in blood pressure were wrongly graded in 4, 4, 2, 2, 1 and 1%, respectively. The percentage of requested laboratory tests actually performed was low: only in 55 of 179 (31%) induction cycles had weekly counts been obtained as per protocol.

4. Discussion

Scientific quality in multicentre trials is the result of different variables. In this respect, the clinical trials infrastructure (physicians, disciplines, nurses, pharmacists, types of institution, local facilities, etc.) may play an important role. Moreover, accurate data collection is of extreme importance.

Even though the question of data quality and cooperative group reliability is often raised when MCT are evaluated, literature data is scarce on this, in particular when it concerns chemotherapy [9,13,15,19,20]. To date, it has not been well documented whether protocol compliance and treatment administrations are different in community versus university hospitals. However, others have noted that the presence of a professional data manager provides greater data accuracy on CRFs [9]. The experience within the EORTC-GCCG is useful additional information since unlike the members of the Soft Tissue and Bone Sarcoma Group (STBSG) of the EORTC, who have published their results, treatment in the GCCG is given not only by medical oncologists, but also by gynaecologists or gynaecological oncologists and (rarely) by radiotherapists with a training in giving chemotherapy. This report represents the second largest systematic investigation performed after the STBSG experience [9] and the Southwest Oncology Group (SWOG) contribution — albeit in abstract form — reported in 1990 [19].

The 11 centres visited for this purpose were all major participants in the protocol specifically reviewed, but also in all clinical trials conducted within the GCCG. Therefore, they provided a general overview of the main characteristics of the centres participating in the group.

Site visits are time and resource consuming; the final calculated cost per site visit was US$1500 and did not include the salaries lost through time taken from regular duties. This figure, even though it was modified by the contribution of some other sponsors besides the European Economic Community (EEC), is higher than that reported by the SGDM — US$800 [15] — and by the STBSG, US$797 [13].

Interesting observations were obtained during the site visits whilst discussing the protocol management with the various responsible physicians and data managers. In general, the entire protocol schema (Fig. 1) was judged as fairly complicated and difficult to follow. Not surprisingly, therefore, this led to protocol violations at different points in the study. Moreover, pitfalls were found in the protocol itself such as the lack of a clear description of 'date of diagnosis' and 'date the treatment stopped'. Pitfalls were also found in the CRFs; e.g. vagueness about whether palliative radiotherapy for vaginal bleeding was part of the exclusion criterion of 'previous radiotherapy'. Importantly, there was considerable controversy about toxicity grading. The lack of a useful classification of gastrointestinal side-effects had a negative impact on the reported toxicites, since WHO criteria do not address this adequately. Finally, different policies with respect to toxicity data recording, i.e. whether or not a special toxicity checklist was used, had an impact on the overall evaluation of treatment-related side effects. It has to be noted that at the time of site visits (1990–1991) the 'systemic therapy checklist' — implemented by the EORTC in 1992 [15] — was not available. Indeed, the use of this checklist within one collaborative group has been proven to be of value in data acquisition and recording in MCT [13].

As shown in Tables 2 and 3 a certain 'heterogeneity' was found in chemotherapy prescription, preparation and administration procedures at different centres. Whether or not this might have had an impact on drug efficacy is still unknown. Indeed, in this respect, the only

available experience published [9] stresses the importance of specialist oncology-trained nurses as a factor in treatment delivery.

In terms of data quality the results were more positive (Table 6). Overall 81.8% of data items on CRFs were verified as correct in the medical record. This seems to be acceptable. Two centres — 554 and 561 — showed more than 90% correct data and 4/11 of centres showed more than 85%. The overall accuracy as determined at the site visits was influenced by many factors, but mainly by failure to find information in the medical records. Indeed, if those data (7.6% 'on form but not in file' and 3.6% 'missing on CRF's') would have been available the overall percentage of correct data would be about 90%. In any case, 7.0% of incorrect data is still within the range (0.5–7.0%) of other 20 EORTC centres visited in the pilot study of SGDM [7] which was based on three different and rather less complicated protocols. It is also in the same range (1.0–7.5%) of inaccuracy reported by the STBSG [9] and by the SWOG (overall 5%) [19].

The observed range of inaccuracy between centres (2.3–14.5%) is certainly a matter of concern with respect to the reliability of, in particular, two centres who showed more than 10% of data was incorrect. The centre with the highest accuracy in this survey was an institution with professional data managers working in close cooperation with clinical trial oriented physicians. In contrast, the weakest centre was an institution without professional data managers and whose CRFs were used as part of medical files.

As far as the 'informed consent' procedure is concerned, it must be remembered that at the time of the site visits, there was no EORTC standard requirement in place and the protocol in fact requested that the informed consent was to be 'obtained according to regulations followed in individual participating institutions'. Therefore, the observations obtained at the site visits were in complete accordance with the actual policy in Europe at that time, although clearly the results show deficiencies if assessed by 1999 standards.

With respect to the overview of protocol treatment adherence, it has been mentioned already that protocol number 55863 was a rather complicated chemotherapy protocol. Nevertheless, overall dosages given — expressed as median per cent dose delivered — ranged from 98–100% with combination chemotherapy and was 100% with single agent cisplatin. Important deviations, however, were seen more often with some of the components of the combinations (e.g. 22–100% for bleomycin and 0–105% for mitomycin C in some of the institutions). Mistakes in dose calculation might have been avoided by providing an adequate protocol-treatment flow-sheet to the physicians.

Intervals between cycles and phases were properly followed in most instances (Table 5). Nevertheless, an excessive number of treatments (23/48) were delayed due to reasons other than intercurrent disease or toxicity; either 'planning mistakes' — mostly on patient's request — or 'local organisational problems' that could have been avoided by requiring strict adherence to oncology protocols within the centres and by motivating both patients and physicians to follow the exact time schedule.

In conclusion, the overall picture of the EORTC-GCCG in terms of data management and trial handling of this complicated chemotherapy protocol is acceptable with an overall accuracy of data of 81.8%. However, further improvement is required in order to reach 90% correctness in all centres participating in the group. True data inaccuracy was low (7.0%) and the amount of missing data on CRFs (3.6%) and inassessable data (7.6%) could be reduced with better data management.

Based on our experiences the following suggestions are made:

1. Protocols dealing with MCT must be simple and should contain precise statements of treatment and patient management to avoid misinterpretations.
2. Case report forms should be as simple as possible and should not be part of the medical file.
3. The highest 'homogeneity' in treatment administration should be pursued amongst centres participating in the MCT. Whether or not the discipline involved in giving chemotherapy may have an impact on trial results is not known but should be investigated.
4. Data managers should be present in all institutions, should be fully trained and work in close cooperation with the responsible physician.
5. The use of a standard systemic therapy checklist for toxicity recording should be used in all centres participating in the MCT.
6. Quality control activities should be mandatory within all groups running MCT and should be encouraged by the scientific review boards, on a global basis.

Further activity of the EORTC-SGDM, the EORTC Quality Assurance Unit and the EORTC-GCCG has included a repeat visit to the centres included in the present report following introduction of the toxicity-reporting checklist. The results of this second evaluation will be reported separately.

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