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The role of the French–Italian glossary of complications in the outcome evaluation of cervical cancer treatment: an Italian multicentric study

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Contents

Abstract

The optimal treatment for cervical cancer is still a controversial matter: in the last two decades a lot of different modalities combining surgery, radiotherapy (RT) and chemotherapy (CHT) have been suggested and analysed in clinical trials. Nevertheless, analysis of treatment in cancer patients should be directed not only to survival, but also to the cost of complications and quality of life. In June 1988, a French–Italian co-operative group set up a glossary in which the complications of the treatment of cervical cancer are described and ranked. Nowadays, this is the only international system based upon an accurate description of symptoms and signs of complications following multidisciplinary treatment. The glossary was based on our previous experience in treating patients by surgery alone, RT or their combinations. Recently multimodality treatment includes also CHT. The aim of the present study was to verify whether the glossary is still a useful clinical instrument in outcome evaluation of cervical cancer treatment. *Materials and methods:* The analysis has been done on a retrospective consecutive series of 579 patients affected by cervical cancer, treated in five Italian institutions. A minimum of 12 months follow up was required. All medical records of the patients enrolled, were examined by two independent reviewers in order to classify the complications according to the glossary. *Results:* Out of 579 patients 319 (55.1%) were free of complications and 260 (44.9%) experienced at least one complication. We found 436 complications. The distribution by Grade was: G1 58.9%, G2 27.5%, G3 13.5%. We had no fatal complication (G4). The glossary included

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all observed complications, except for pulmonary fibrosis. *Conclusion:* The glossary is still a useful instrument in evaluating the outcome of cervical cancer treatment, whatever the therapy, and should be considered in quality of life assessment.

Keywords: Cervical cancer; Glossary; Complication

1. Introduction

The optimal treatment for cervical cancer is still a controversial matter: in the last two decades a lot of different modalities combining surgery, radiotherapy (RT) and chemotherapy (CHT) have been suggested and analysed in clinical trials. Nevertheless, analysis of treatment results in cancer patients should be directed not only to survival rate, but also to the cost of complications and quality of life [1]. Additional factors influencing the choice between different treatment modalities at equal survival, include the age and general condition of the patient, the need to preserve a functional vagina and the complication rate for each treatment [5].

In June 1988, a French–Italian co-operative group set up a glossary in which the complications of the treatment of cervical cancer are described and ranked (Table 1) [7–9]. Nowadays, this is the only international system based upon an accurate description of symptoms and signs of complications following multidisciplinary treatments [4]. In recent years, several authors have confirmed the reproducibility of the glossary [1–6,12–15].

The aim of this study is to verify if the glossary is still a useful clinical instrument in global outcome evaluation of cervical cancer treatment [6].

Table 1
The glossary (summarised): complications by organ system and grade

Gastrointestinal			
Rectum	G1: a–d	G2: a–d	G3: a–c
Sigmoid colon	G1: a–c	G2: a–c	G3: a–c
Small bowel	G1: a–b	G2: a–c	G3: a–c
Stomach and duodenum	G1: a–b	G2: a–c	G3
Non-specific abdominal symptoms and/or signs	G1: a–b	G2	
Urinary			
Bladder	G1: a–f	G2: a–d	G3: a–d
Ureter	G1: a–b	G2: a–b	G3: a–b
Vascular	G1: a–d	G2: a–d	G3: a–d
Cutaneous	G1: a–d	G2: a–d	G3: a–b
Uterus, vagina, vulva	G1: a–f	G2: a–d	G3: a–c
Pelvic soft tissue	G1: a–b	G2: a–b	G3: a–b
Bone	G1	G2	G3
Peripheral nerves	G1	G2	G3
Haemopoietic tissue	G1	G2	G3

a–f indicate the type of complication (fistula, stress incontinence...). General grading system: G0: no complications, G1: mild complication, G2: moderate complication, G3: severe complications, G4: death.

2. Materials and methods

The analysis was conducted on a retrospective consecutive series of 579 patients treated for cervical cancer (FIGO stage IA/IVB) in five Italian Institutions, from 1 January 1985 to 31 December 1999. A follow up time of 12 months, at least, was required. The mean age of the patients was 50.7 years. Every centre treated patients according to the treatment protocols of that particular Institution: the different protocols for each stage varied from RT alone, to RT plus surgery, surgery plus RT, surgery alone, CHT plus surgery, CHT plus RT, CHT plus surgery plus RT or CHT alone (Tables 2 and 3).

All centres adopted the World Health Organisation (WHO) histological classification for cervical cancer (83.5% squamous, 13.2% adenocarcinoma, 3.2% adenosquamous, 0.2% clear cell) and FIGO classification for cervical cancer staging (Table 4).

A specific clinical record sheet was adopted for surgery, RT, CHT, pathology and follow up, and an extensive description of treatment complications was required. All medical records of the patients enrolled were examined by two independent reviewers in order to classify the complications according to the glossary. The onset, persistence or resolution of complications were registered at every follow up meeting.

Statistical analysis of survival was conducted with actuarial curves and Kaplan–Meier estimator; we analysed complications using frequencies tablets and crosstablets.

3. Results

We analysed the 5-year clinical outcome: the recurrence free survival at 5 years was similar to that reported in literature [6]. A figure showing actuarial survival by stage (Fig. 2) is given.

Complications were classified as follows:

1) By NUMBER: we found 436 complications in 260 patients; 319/579 (55.1%) patients were complications free, 260/579 (44.9%) had one or more complication: 143 (27.4%) had one complication, 77 (13.3%) two complications, 26 (4.49%) three complications, ten (1.7%) four complications, three (0.52%) five complications and only one patient had six complications.
2) By DEGREE of SEVERITY: the great majority of complications observed (58.9%) were mild (G1), 27.5% moderate (G2) and 13.5% were severe complications (G3).

Table 2
Treatments

RT	RT+surg	Surg+RT	Surg	CHT+surg	CHT+RT	CHT+surg+RT	CHT
2.7%	4.2%	30.4%	24.2%	15.2%	9.7%	12.9%	0.5%

Table 3
Treatments for stage

	IB (%)	IIA (%)	IIB (%)	III (%)	IV (%)
RT	1.3	4.2	5.7	3.7	15.4
RT+surg	3.5	5.2	11.3	/	/
Surg+RT	34	36.5	13.2	3.7	7.7
Surg	32.7	11.5	3.8	3.7	/
CHT+surg	16	13.5	17	11.1	7.7
CHT+RT	4	8.3	24.5	51.9	38.5
CHT+surg+RT	8.5	20.8	24.5	25.9	7.7
CHT	/	/	/	/	23.1
	100	100	100	100	100

Table 5
Total number of complications by organ site and grade

	G1	G2	G3	Total
G.I.	55	26	12	93
Urinary	61	48	32	141
Vascular	60	13	5	78
Cutaneous	20	8	1	29
Uterus–vagina–vulva	40	13	4	57
Pelvic soft tissue	7	4	/	11
Peripheral nerves	9	7	2	18
Bone	/	/	/	/
Haemopoietic tissue	5	1	1	7
Total	257	120	59	436

We had no fatal complication (G4). Almost 2/3 of complications were mild (G1).

3) By ORGAN SYSTEM and DEGREE (tab. *): G1 reached 59.1% in gastrointestinal (G.I.) and 43.3% in urological sites, 63.6% in pelvic soft tissue, 69% in the skin, 70% in genital sites and 76.9% in vascular sites. 28% of the G.I., 34% of the urinary, 36.4% of the pelvic soft tissues, 27.6% of the cutaneous and 38.9% of the nervous complications were G2. G3 occurred in 12.9% of the G.I., 22.7% of the urinary and 11.1% of the nervous complications. We observed two pulmonary G3 complications too (pulmonary fibrosis), not described in the glossary. No complications were found in this series involving bone.
4) The urinary tract is the dominant site of complications of any grade and, particularly, 1/3 G2 and half G3 complications are located in this system. The second most frequent site of complications is G.I. Urinary and G.I. systems account, together, for 45.2% of all G1, 61.7% of all G2 and 74.6% of all G3 complications (Table 5).
5) By TIME of ONSET and DEGREE: the median delay between the end of the treatment and the onset of mild complications (G1) was 8 months, 12 months for moderate (G2) and 10 months for severe (G3). We observed that 95% of complications appeared within 36 months, but 18 G1, 5 G2 and 2 G3 appeared between 3 and 5 years after the end of treatment and 33 complications more later than 5 years (G1:16, G2:14, G3:3) (Fig. 1).
6) By TIME of ONSET and ORGAN: G.I., urinary and vascular complications appeared in almost all the intervals of 6 months, the maximum number of events being concentrated at 6/12 months from the end of the treatment. An inferior number of complications tend to appear between 18 and 34 months in G.I., urinary, vascular and uterus–vagina–vulva. As well we observed onset of 10 G.I., seven uterus–vagina–vulva, nine urinary and six vascular complications after 60 months from the end of the treatment (Fig. 1).
7) By ORGAN SITES: out of 93 complications concerning G.I. sites, 42 involved the rectum (45.2%), 21 (22.6%) were a specific abdominal signs or symptoms, and 18 (19.4%) involved colon. 103/132 urinary complications involved bladder and urethra (only 9.9% G3), 29/132 complications involved ureters. Out of 18 complications concerning nervous system, 16 (88.9%) involved peripheral nerves and only two (11.1%) G2 involved CNS.
8) By TREATMENT: the major complication rate by treatment modality was found in patients treated with

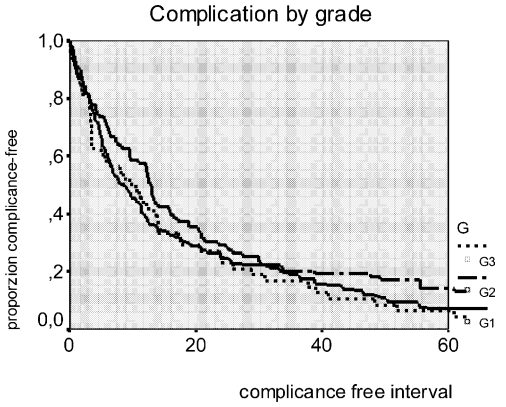

Fig. 1.

Table 4
Distribution for stage

FIGO stage	IA	IB	IIA	IIB	IIIA	IIIB	IVA	IVB
Number of patients (%)	11 (1.9%)	378 (65.3%)	97 (16.8%)	53 (9.2%)	10 (1.7%)	17 (2.9%)	10 (1.7%)	3 (0.5%)

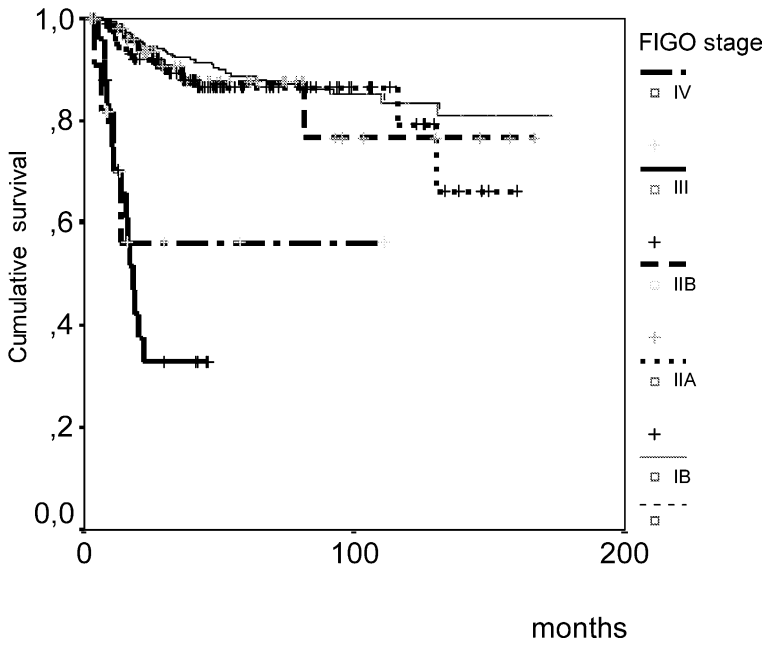

Fig. 2. Disease-free survival by FIGO stage.

RT alone (19/15-1.27), followed by RT plus surgery (22/24-0.91) and neoadjuvant CHT plus surgery plus RT (66/73-0.9). The less complicated treatment modality was CHT plus RT (16/55-0.29), but not by concurrent approach, and neoadjuvant CHT plus surgery (30/86-0.35). The major incidence of urinary complications was found in patients treated by surgery alone, almost 45% of all complications onset in this treatment group, followed by surgery plus RT and CHT plus surgery plus RT (33–35%). The major incidence of G.I. complications was found in chemo-radiotherapy (44%) and in RT alone subgroup (37%). The major incidence of genital and pelvis complications was found in RT (32%) and RT plus surgery subgroup (27%). Pulmonary complications were found in patients CHT-treated.

4. Discussion and conclusions

In modern oncology, survival rate is the primary endpoint in treatment evaluation, but quality of life and analysis of treatment complications are equally of crucial importance. The use of a common instrument for objective observation criteria and commonly accepted definitions in the classification of complications is required for a correct analysis of each treatment modality.

In this series, we found complications in 44.9% of patients analysed: this value is at the upper limit of the range reported in literature (22–50%) [1–6,12–15], but we reported all complications, even if mild or showing for a short time.

As reported in the literature, the most affected organ systems by complications are urinary and G.I., followed by vascular and uterus–vagina–vulva. In this subgroup, the most affected organs were bladder and rectum, according to the major damage of locoregional treatment [1,6,10].

The glossary allows classification and quantification of events sometimes subject to different interpretation by different researchers: in our series, two independent reviewers had complete agreement in classifying complications by analysing medical records where complications were extensively described. The only complication not codified by the glossary was pulmonary fibrosis in two bleomicin-treated patients. On the other hand, we had no complication regarding bone system.

Furthermore, the glossary is suitable in following the persistence, worsening or resolution (spontaneous or after treatment) of the complications, allowing to evaluate the evolution of the complication in relation to time from treatment [1].

Pedersen wrote that is necessary to avoid underestimation of morbidity, with any classification system, to register each symptom, its time of appearance and its grade [11]. This is necessary to allow reporting of the real risk of organ damage, rescoring of complication grade, separation of early and late morbidity and reporting of actuarial estimates [1,11]. The French–Italian glossary answers to all these requirements. This instrument suggests a common language for the outcome evaluation of cervical cancer treatment not only in terms of survival and recurrence, but of observed toxicity too [1].

The glossary is still a useful instrument in evaluating the outcome of cervical cancer treatment, independently from therapy, and it should be considered in quality of life assessment.

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Biography

Paolo Zola was born in Turin on 14 August 1952. Graduated in Medicine at the University of Turin in 1970, discussing a thesis on the conservative treatment in breast cancer. Got a postgraduate school diploma in Obstetrics and Gynaecology in 1980. Got a postgraduate school diploma in Oncology in 1983. Since 1979 he has been working as assistant and researcher at the Obstetrics and Gynaecology Institute, "A", University of Turin. Since 1996 he has been working as clinical researcher at the Department of Gynaecological Oncology, University of Turin. Since October 2001 he is Professor in Obstetrics and Gynaecology at the University of Turin. He is now directing the Pelvic Oncology Unit, Department of Gynaecological Oncology, University of Turin, Mauriziano Umberto I Hospital.