Determinants of Small Bowel Toxicity in Postoperative Pelvic Irradiation for Gynaecological Malignancies

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Abstract. *Background: Patients treated with postoperative radiotherapy for endometrial and cervical carcinomas from 1981 to 2000 were retrospectively analysed in order to assess the rate of late small bowel toxicity. Patients and Methods: Eight hundred and six patients had received pelvic irradiation, with total doses of 40-55 Gy. The mean age was 57 years. Three hundred and eighteen patients had been treated for cervical and 488 for endometrial cancer; 46 had diabetes and 22 vascular diseases; 141 had a history of smoking and 367 were previously submitted to surgery for benign diseases. A CT treatment plan had been applied in 285 patients; 256 had been treated by arc moving therapy, 232 with 2 opposed beams (AP-PA) and 318 with 3 or 4 coplanar beams. Three hundred and forty-six were treated with X photons of 10 MV or more, 202 with 4-5 MV and 258 with cobalt gamma rays. Personalized blocks had been used in 389. Thirty-four women had received chemotherapy. Five hundred and eighty-four had been treated with dose fractions of 180 cGy or more and 56 had received a boost with brachytherapy or external beams. Eighty-one had needed treatment discontinuation due to acute small bowel toxicity. Results: The median follow-up was 70 months. Thirty five patients had bowel obstructions, after a median time of 31 months. The 5- and 10-year toxicity rates were 4 and 7%. Uni- and multivariate comparisons identified age, acute toxicity and dose fraction as predictors for complications. Conclusion: Postoperative pelvic irradiation with standard techniques for gynaecological carcinomas results in tolerable rates of clinically significant late bowel damage, while older patients suffering from significant acute toxicity seem to be at higher risk.*

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Postoperative radiation therapy, alone or associated with chemotherapy (CHT), is a powerful modality for the treatment of tumours and, nowadays is widely applied in gynaecological carcinomas. Unfortunately, surgery followed by pelvic irradiation at standard doses (45-50 Gy in 25-28 daily fractions) is associated with morbid consequences, either during or after the completion of treatment, due to exposure of the small bowel. The small intestine is the most vulnerable organ in the pelvis and small bowel damage is the most important toxicity in postoperative pelvic irradiation, both as frequency and as clinical consequences. Late radiation injury to this organ, although relatively rare, is a serious side-effect entailing significant morbidity and mortality. According to the literature, the exact rate of severe late small bowel toxicity remains controversial, with a wide range (1-25%) and an accepted average of 5% (1-7). Several risk factors emerged from historical data, although a clear provisional model has not yet been defined (1, 5-14).

Individual variations (previous laparotomies, vascular diseases, history of diabetes, inflammatory pelvic disease, age), surgical parameters (development of adhesions, unsuccessful reperitonealisation) and radiation-related factors (total dose, volume of bowel included, fractionation schedule, irradiation technique, association with chemotherapy) contribute to the toxicity pathway. The variety of involved primaries and treatments creates much confusion over the risk factors; the diffuse habit of accumulating small and large bowel toxicity and the use of different scoring systems add to the problem. Moreover, the analysis of radiation side-effects, in particular late effects, in published papers seems to suffer from statistical underpower and from differences in scoring systems. Bowel damage analysis usually included both small bowel and rectal toxicity, so that comparison between results is difficult. The aim of this work was to determine the frequency of severe late damage, limited to the small bowel, in a mono-institutional population of patients treated with postoperative pelvic radiotherapy after radical hysterectomy and to try to highlight patient, primary disease and treatment factors that can predispose to radiation injury.

Patients and Methods

Patients treated postoperatively from 1981 to 2000 were retrospectively reviewed. The data were collected from hospital records. Inclusion criteria were: no evidence of macroscopic residual disease after surgery; postoperative pelvic irradiation, including nodal areas, for cervical and endometrial carcinomas and total radiation doses between 40 and 55 Gy. Patients with synchronous or previous malignancies were excluded as well as those receiving less than 40 Gy and whole abdomen or para-aortic irradiation and complete absence of follow-up were exclusion criteria too.

Eight hundred and six patients met the criteria for this study, and the patients characteristics are shown in Table I.

The patient's age ranged from 25 to 93 years, with a median value of 58 years. The majority of patients had good performance status (PS≥80 following Karnofsky index).The body mass index (BMI) could be calculated in only 586 patients and ranged from 15 to 48, with a median value of 27. Forty-five percent of patients had previously been submitted to surgery for other benign diseases.

Planned target volumes had been defined on CT slices (1 to 7) in 35% cases; in all the other patients standard irradiation fields had been defined using radiological anatomical boundaries. In these cases, the dose distribution had been manually calculated. Thirty-two percent of patients had been treated by arc moving therapy, 29% with opposed antero-posterior and postero-anterior fields (AP-PA) and 40% with a 3 or 4 beam arrangement. Cobalt gamma rays had been used in 32% of the patients, 4-6 MV photons in 25% and 10 MV in the remaining 43%. Personalized shielding blocks had been used in 48% of cases.

The daily and total doses reported were referred to ICRU point; to standardize the results, the cases in which the dose was prescribed at the minimal isodose encompassing the target volumes were retrospectively recalculated.

The dose fractions ranged from 1.5 to 2 Gy (median value 1.8), total doses from 40.5 to 55 Gy (median 46). Fifty-six patients (10%) had received a small volume boost either on the primary site or limited nodal areas or the vaginal cuff; 19 had received a maximum of 10 Gy by external beams and 37 by endocavitary brachytherapy (mainly 8 Gy with high dose rate prescribed at 1 cm from the applicator surface).

The median time from surgery to beginning of radiotherapy was 44 days; irradiation lasted a median of 39 days. CHT, concomitant or sequential, had been administered in 34 patients (4%). Ten percent of patients needed a temporary interruption of treatment because of severe acute bowel toxicity.

According to the literature, only complications occurring after 3 months from the end of irradiation were scored as late. Events included small bowel obstructions or fistulae requiring hospitalisation for medical or surgical care. The complication grade reported represented the highest observed during follow-up. If no complications were reported observations were censored at the date of death or disease recurrence. The actuarial probability of being late complication-free was assessed through the Kaplan-Meier method. The influence of patient and treatment factors was tested by the Cox regression model. The analysed variables included age, sex, BMI, PS scored following the Karnofsky index, prior abdominal surgery, DM, vascular co-morbidity as defined in Charlson index (12), site of primary, CHT, acute toxicity requiring treatment interruption, use of CT in treatment planning, extension of irradiation fields, irradiation techniques, beam energy, use of shielding blocks, boost delivery, daily and total doses, irradiation delay and overall treatment time.

Table I. *Population characteristics*.

	Patient characteristics		
Factors	Group	n	%
Age (mean 57 years)	<60 years	432	54
	≥60 years	374	46
Tumour site	Cervix	318	39
	Endometrium	488	61
Performance status	<70	49	6
(Karnofsky index)	≥80	757	94
Diabetes	Yes	46	6
	No	760	94
Vascular co-morbidity	Yes	22	3
	No	784	97
Smoker	Yes	141	17
	No	665	83
Prior surgery	Yes	367	45
	No	439	55
CT treatment plan	Yes	285	35
	No	521	65
Radiotherapy technique	Box 4 fields	318	39
	Double arc	256	32
	AP-PA	232	29
Upper field limit	L4-L5	757	94
	L5-S1	49	6
Energy	60Cobalt	258	32
	X 4-6 MV	202	25
	X 10-18 MV	346	43
Blocks	Yes	389	48
	No	417	52
Daily dose	<180 cGy	222	27
	≥180 cGy	584	73
Boost	Yes	56	7
	No	750	93
Chemotherapy	Yes	34	4
	No	772	96

L/S: Lumbar/sacral vertebra; AP-PA: opposed antero-posterior and postero-anterior fields.

Results

The median follow-up for the whole population was 5.8 years; for surviving patients (604), it was 6.5 years.

Late severe small bowel toxicity (obstruction or fistula) was reported in 35 patients (4%). The 5- and 10-year toxicity rates were respectively 4% ±0.008 and 7% ±0.011 (Figure 1). Eleven patients (1.4% of the whole group) underwent surgery for small bowel complications and 24 (3%) had to be hospitalized for medical care. The surgical patients were managed by lisis of adherences in eight cases and by ileal

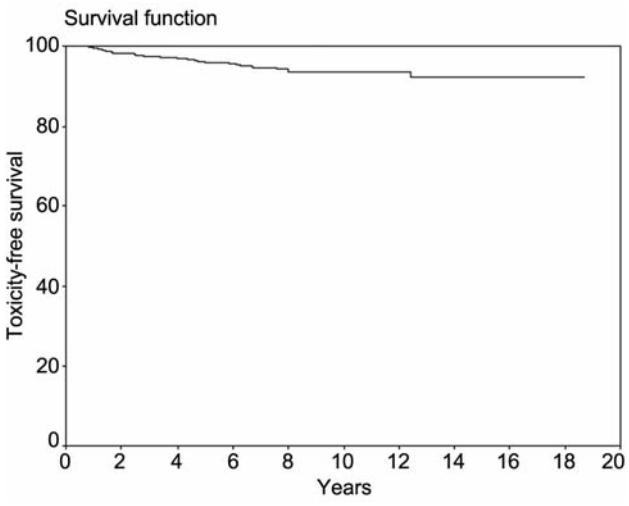

Figure 1. *Probability of being free from small bowel complications.*

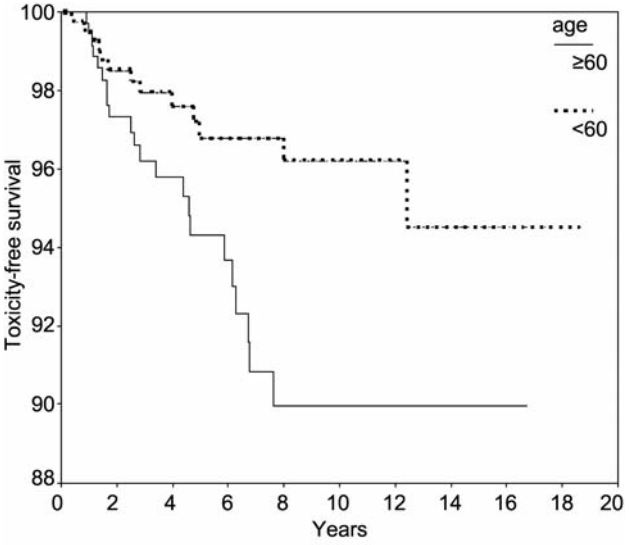

Figure 2. *Probability of being free from small bowel complications according to age.*

resection in the other three. Twenty-five patients experienced only one event, while 10 had repeated hospitalization. No association between repeated events and toxicity treatment (medical, surgical lisis of adherences or small bowel resection) was found. Toxicity occurred after a median time of 31 months (range 5-151), more than half of the events (57%) after 2 years.

The patient age at the time of irradiation significantly affected the probability of developing bowel damage (Figure 2): patients older than 60 had, in fact, a more than doubled

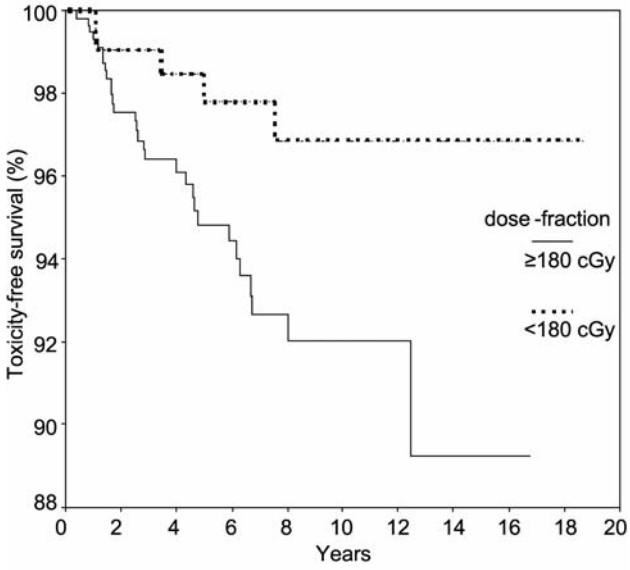

Figure 3. *Probability of being free from small bowel complications according to dose fraction.*

risk of developing severe radiation injuries (HR 2.2) None of the other patient characteristics had any impact on outcome: BMI, PS, smoking, diabetes or vascular co-morbidity did not modify the toxicity rates.

Prior abdominal surgery and nodal dissection did not have significance, but the low quality of anamnestic data could be responsible.

The total pelvic dose and the overall treatment time had no effect on the end-point. Daily doses of less than 180 cGy determined, as expected, a significant reduction of bowel damage risk (Figure 3). In contrast, although not significantly, the probability of late injuries seemed to be higher in patients submitted to a CT based treatment plan with personalized shaping of fields. A statistical correlation between CT plan, blocks and higher dose fraction emerged from the analysis, explaining the results. More favourable outcomes for the patients treated with 3-4 fields or arc therapy was also found but the difference was not significant. Also irrelevant for outcome were the cranial extension of irradiation fields (up to L5 or L4), beam energy, boost delivery, and CHT. Severe acute bowel toxicity had a clear effect on late damage, the patients requiring treatment discontinuation for acute side-effects had a significant increase of late damage risk (Figure 4). The actuarial toxicity details for the most important factors are reported in Table II.

The Cox regression model confirmed the aforementioned factors as being independently associated with severe small bowel damage. Older patients treated with daily doses of 180-200 cGy or suffering from higher grade of acute toxicity were more likely to develop severe late small bowel injury (Table III).

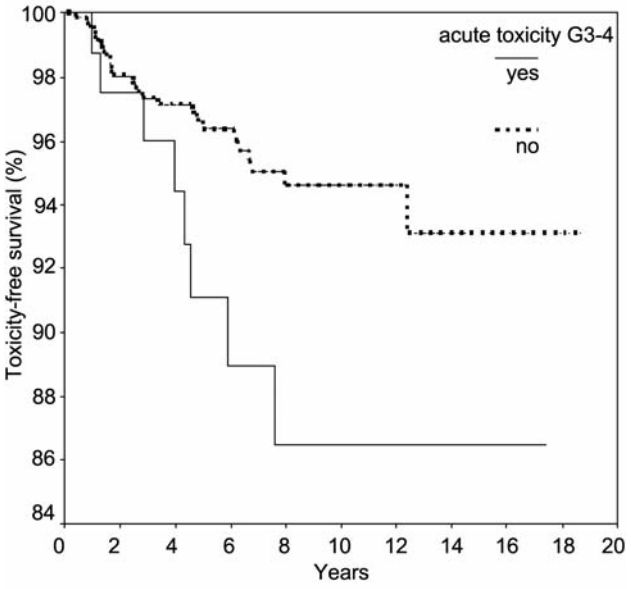

Figure 4. *Probability of being free from small bowel complications according to acute toxicity requiring temporary treatment interruption.*

Table II. *Univariate analysis of late small bowel toxicity.*

		Small bowel complication - Actuarial rates		
Factor	Group	5-Year	10-Year	*p*-Value
Age	≤60 years	3%	4%	0.0149
	>60 years	6%	10%	
CT plan	Yes	4%	9%	
	No	4%	5%	ns
Blocks	Yes	5%	10%	
	No	4%	5%	ns
Radiotherapy technique	Box 4 fields	4%	8%	
	AP-PA	6%	9%	
	Arc therapy	3%	4%	ns
Energy	X>10 MV	5%	8%	
	X 4-6 MV	4%	8%	
	60 Co	3%	4%	ns
Daily dose	<180 cGy	2%	3%	
	≥180cGy	5%	8%	0.0232
Cranial field limit	L5-S1	0%	0%	
	L4-L5	5%	7%	ns
Chemotherapy	Yes	9%	9%	
	No	4%	6%	ns
Severe acute toxicity	Yes	9%	13%	
	No	4%	5%	0.0299

Discussion

Although limited by a retrospective approach, our work showed a probability of severe small bowel damage of 4% at 5 and 7% at 10 years, consistent with other institutional experiences and certainly tolerable for a complementary treatment (13, 14, 7). In particular, Iraha *et al*. in a recent paper reported the same toxicity rate in a similar population (7).

Stratification for risk factors suggested that patient, disease and treatment factors contributed to morbidity and indicated a relationship between acute and late bowel toxicity. In the present patients three factors contributed to determining late small bowel effects: age, dose fraction and high grade of acute small bowel toxicity (requiring treatment discontinuation). Regarding age, Yeh (18) and Chen *et al*. (19) reported similar results after adjuvant radiotherapy for cervical cancer treated with radical hysterectomy. However other authors drew the opposite conclusion (17, 20). The present findings suggest that older patients could be more vulnerable to small bowel damage. This could be related to impaired normal tissue recovery from radiation damage, as already described for other tissues (8). Age and smoking can predispose injury in a similar way, however in this series smoking did not emerge as significant factor. The importance of smoking was identified by Eifel analysing more than 3400 patients with about 150 events (21). Limitations of sample size and, subsequently, number of events could explain the present results.

Table III. *Late small bowel toxicity: final Cox regression model.*

Factor	Group	*p*-Value	RR
Acute toxicity	G3-4 G0-2	0.0070	3.01
Dose fraction	≥180 cGy <180 cGy	0.0371	2.81
Age*		0.0128	1.02°

RR: Relative risk; *continous variable, °per year.

The role of dose fraction in determining late side-effects is well known in radiation practice (22). In the present sample, patients treated with daily doses of less than 180 cGy showed a clearly reduced risk of developing late damage. Higher daily doses could be responsible for vascular damage, causing reduced blood supply to small bowel walls with subsequent ischemia and fibrosis.

More recently, however, investigators have focused on other toxicity pathways such as mucosal stem cell depletion, clinically represented by acute toxicity. From the present analysis, an independent link between acute and late radiation damage, specifically with reference to small bowel clearly emerged. Single pathology populations analysis related to different tissues (23-26) has already indicated such a relationship, therefore this result was far from being unexpected.

In patients submitted to pelvic irradiation, other authors reported higher late injuries in those suffering from acute toxicity (17, 23, 26). In recent work on this argument, Jereczec-Fossa *et al*. demonstrated a relative risk for late bowel damage (all sites included) of 4.5 in patients experiencing a severe grade acute toxicity (27). The present findings limited to small bowel damage drew similar conclusions: a higher grade of acute toxicity determined a doubled risk of severe late damage. The way in which acute influenced late toxicity is not clear. Again, the hypothesis of excessive depletion of mucosal stem cells and the consequent reduced tissue rescue could explain the phoenomena, in the so-called consequential late effect, as already described for the rectum (28, 29). Due to the limitation of retrospective analysis, the persistency of acute reactions and their possible evolution into late effects could not be determined; therefore, based on the present results, the consequential effect for the small bowel can only be hypothesized. However the results supported the increasing evidence that late reactions in the small bowel may occur both as genuine late or as a continuation of severe acute reactions. In fact 43% of the toxicity events occurred within 2 years after irradiation, with a timing suggesting the existence of consequential toxicity, while the other 57% may be ascribed purely to late damage.

Although most events may be detected in the first 5 years, a lifelong risk of developing severe late complications seems to remain. More than 20% of severe toxicity developed after 5 years, confirming other literature data (30).

Retrospective evaluation did not allow any direct analysis of small bowel irradiated volume. Although the opposed AP-PA fields, presumed to include a larger volume of small bowel, resulted in an increase of complications compared to the box techniques or arc therapy, the difference was not significant. Other authors however reported similar results (1, 8, 10, 17, 28). The presence of confounding factors, such as differences in dose fraction or optimization over the years, could probably explain these findings.

Therapy of small bowel injuries frequently requires a surgical intervention, from which morbidity and mortality may be substantial (31). The emerging evidence of a possible link between acute and late complications being influenced in addition by all other known factors has strong implications both for the prediction and prevention of late injuries. More recent irradiation techniques such as intensity modulated radiotherapy (IMRT) allows a better sparing of the bowel in pelvic irradiation, but they are quite time and cost consuming and anyway not avalaible in all radiotherapy centers. Therefore, in cases of standard pelvic irradiation in particular subgroups of patients with known risk factors, expressing severe acute side-effects, personalized follow-up might reduce the necessity for major interventions.

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