

Shortened irradiation scheme, continuous infusion of 5-fluorouracil and fractionation of mitomycin C in locally advanced anal carcinomas. Results of a phase II study of the European Organization for Research and Treatment of Cancer. Radiotherapy and Gastrointestinal Cooperative Groups[☆]

J.F. Bosset^{a,*}, F. Roelofsen^b, D.A.L. Morgan^c, V. Budach^d, P. Coucke^e, J.J. Jager^f, E. Van der Steen-Banasik^g, N. Trivi  re^h, G. St  benⁱ, M. Puyraveau^a, M. Mercier^a

^aRadiotherapy Department, Besan  on University Hospital, Besan  on, France

^bKlinik f  r Allgemein und Visceralchirurgie, Universit  tsklinikum, Essen, Germany

^cDepartment of Clinical Oncology, City Hospital, Nottingham, UK

^dKlinik f  r Strahlentherapie, Charit   Hospital, Berlin, Germany

^eD  partement de Radioth  rapie-Oncologie, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

^fRadiotherapeutisch Instituut Limburg, Heerlen, The Netherlands

^gRadiotherapy Department, Arnhem Radiotherapy Instituut, The Netherlands

^hRadiotherapy Department, Institut Jules Bordet, Brussels, Belgium

ⁱStrahlenklinik, Universit  tsklinikum, Essen, Germany

Abstract

The European Organization for Research and Treatment of Cancer (EORTC) 22861 randomised trial established that combined radiochemotherapy is the standard treatment for locally advanced anal cancer. This EORTC phase II study (#22953) tests the feasibility of reducing the gap between sequences to 2 weeks, to deliver Mitomycin C (MMC) in each radiotherapy sequence and 5-FU continuously during the treatment. The first sequence consisted of 36 Gy over 4 weeks. 5-FU 200 mg/m²/days 1–26, MMC 10 mg/m²/day 1 gap 16 days. Then a second sequence of 23.4 Gy over 17 days, 5-FU 200 mg/m²/days 1–17 and, MMC 10 mg/m²/day 1 was given. 43 patients with a World Health Organization (WHO) status of 0 (*n* = 27) or 1 (*n* = 16) and with T2–T4, N0–3 tumours were included. Compliance with the planned treatment, doses and duration was 93%. The complete response rate was 90.7%. Grade 3 toxicities of 28, 12 and 2% were observed for skin, diarrhoea and haematological toxicities, respectively. The 3-year estimated rates for trials 22861 and 22953 are: 68 and 88% for local control; 72 and 81% for colostomy-free interval, 62 and 84% for severe late toxicity-free interval, and 70 and 81% for survival, respectively. The 22953 scheme is feasible and the results are promising. This is now considered as the new standard scheme by the EORTC.

Keywords: Chemoradiotherapy; Anal cancer; Accelerated treatment; Phase II clinical trial

1. Introduction

Two similar randomised clinical trials conducted in Europe compared radiotherapy alone with radiotherapy

combined with chemotherapy as treatment for anal cancers [1,2].

The United Kingdom (UK) trial [1] was opened to patients with early and locally advanced stages while the trial conducted by European Organization for Research and Treatment of Cancer (EORTC) was restricted to advanced stages only [2].

In both trials, patients received initially either radiotherapy of 45 Gy over 5 weeks or the same regimen combined with 5-fluorouracil (5-FU) by continuous

[☆] Presented in part at the 11th European Cancer Conference—Lisbon 21–25 October 2001.

* Corresponding author. Tel.: +33-3-8166-8310; fax: +33-3-8166-8551.

E-mail address: jean-francois.bosset@ufc-chu.univ-fcomte.fr (J.F. Bosset).

infusion during the first and last week of radiotherapy and mitomycin C (MMC) on day 1 of the first chemotherapy course. Six weeks after the end of treatment, patients with a partial or complete response had a boost dose of 15–20 Gy by external fields or brachytherapy. Poor or non-responders had salvage surgery. Both trials demonstrated significantly better local control and colostomy-free interval for patients treated with the combined modality treatment (CMT). There was no difference in overall survival, but a reduction in cancer-related deaths was observed in the UK trial.

An Intergroup United States (US) randomised trial compared two CMT regimens [3]. In one arm, 5-FU by continuous infusion was given during the first and last week of radiotherapy, in the other arm, MMC was added on day 1 of each 5-FU course. The radiotherapy dose was limited to 45–50 Gy over 5 weeks with field reductions at 30.6 and 36 Gy. The addition of MMC significantly increased the disease-free and colostomy-free intervals, mainly in patients with large tumours. However, MMC induced more World Health Organization (WHO) grade 4 and 5 toxicities.

Presently, CMT with 5-FU and MMC is considered standard treatment, at least for locally advanced anal carcinomas [4]. However, the loco-regional recurrence rate remains as high as 30–40%, representing 60–70% of all failures. These figures clearly indicate that there is a need for improvement and that further increasing the local control remains a major goal.

Taking our previous EORTC scheme as a reference, we could have tried to optimise each treatment parameter separately (i.e. the radiation scheme, chemotherapy scheme, chemotherapy delivery). However, we would likely not have observed a relevant effect. Therefore, we decided to change all of the parameters at once.

This multicentric EORTC phase II trial aimed to test the feasibility of a modified and intensified treatment, reducing the gap between whole pelvis and boost radiotherapy to 2 weeks only, delivering the 5-FU and MMC chemotherapy during the two radiotherapy sequences and a protracted infusion of 5-FU over the whole treatment time. The main endpoints were compliance to treatment, acute toxicity and tumour response.

2. Patients and methods

2.1. Eligibility criteria

Eligible patients had invasive squamous-cell carcinoma of the anal canal or of the anal margin with anal infiltration; WHO status of 0 or 1; age up to and including 75 years; a granulocyte count above 2×10^9 cells/l; a platelet count above 100×10^9 cells/l; a serum creatinine level less than 120 $\mu\text{mol/l}$.

The extent of the tumour was evaluated by clinical examination, proctoscopy, computed tomography (CT) of the pelvis, ultrasonography of the liver and chest X-ray. Cytology for enlarged nodes was recommended. Tumours were staged according to the International Union Against Cancer (UICC) 1997 classification [5]. We included patients with T2–N0 equal or greater than 4 cm, T3, 4–N0 and N1–N3 whatever the T classification.

Patients with other histologies, or who had been previously treated, or had other primary cancers, angina pectoris and distal arteritis were excluded. Written informed consent was required.

2.2. Treatment

2.2.1. First sequence

Radiotherapy was directed to a target including the anal margin, the perineum, the anal canal, the perirectal nodes up to the top of the second sacral vertebra, the posterior pelvis, anteriorly a 3-cm margin beyond the macroscopical extension of the tumour; laterally the internal iliac nodes and 3 cm of tissues beyond the macroscopical extension of the tumour. This volume was extended to the inguinal region when the distal primary was located less than 1 cm from the anal margin, or when the inguinal and/or the pelvic nodes were clinically positive. Treatment was delivered using a 2- or 4-field technique, depending upon inguinal node involvement. The inguinal nodes were included in the anterior photons portal and received additional anterior-electron beam complements.

This large initial volume was given 36 Gy in 20 fractions over 26 days. 5-FU was delivered continuously at the dose of 200 $\text{mg/m}^2/\text{day}$ from day 1 to day 26. MMC was given at the dose of 10 mg/m^2 on day 1.

During treatment, patients were examined once a week to determine acute toxicities and their biological profile. In cases of grade 3 diarrhoea, 5-FU was permanently stopped while radiotherapy was delayed until diarrhoea improved to the grade 2 level. The 5-FU dose was lowered by 25 or 50% in cases of haematological toxicity grades 1 or 2, respectively. It was permanently stopped in cases of grade 3 or more.

2.3. Gap

At the end of the first sequence, a 16-day gap was planned. Then, patients with tumour progression were offered a salvage surgery while responders had a second CMT sequence.

2.4. Second sequence

Radiotherapy was directed to a target including the anal canal, anal margin, primary tumour and involved nodes, with a 1 cm margin. For involved inguinal nodes, the recommendation was to exclude them from the second

radiotherapy sequence and to perform a simple excision after treatment completion.

This reduced volume was treated with a 3- or 4-field technique up to 23.4 Gy in 13 fractions over 17 days by external beams or the same dose by brachytherapy (total dose 59.4 Gy in 33 fractions and 59 days).

5-FU was delivered continuously at the dose of 200 mg/m²/day from day 1 to day 17, MMC at the dose of 10 mg/m² on day 1.

The second sequence was given with full-dose chemotherapy when there was no haematological toxicity or grade 3 diarrhoea. If these occurred, the gap duration was extended to 3 weeks. In cases of persistent grades 1 or 2 haematological toxicity, the 5-FU dose was reduced by 25 or 50%, respectively, while MMC was not reintroduced. Acute grade 3 skin or mucosal reactions were not supposed to delay the start of the second sequence.

2.5. Follow-up

After the end of treatment, patients were followed up once a week until acute toxicities disappeared.

Six weeks after the end of treatment, clinical examination, biological profile, pelvic CT scan and liver ultrasonography were planned. These examinations were repeated 10 weeks later and every 6 months thereafter.

In cases of suspected local recurrence, confirmation should have been obtained by biopsy before a salvage surgery was performed.

2.6. Evaluation of toxicity and responses

Acute toxicities and tumour responses were recorded following the WHO acute morbidity scoring system and WHO recommendations for measurable and non-measurable disease [6]. Late toxicities were recorded following the subjective, objective, management, analytic (SOMA) scale recommendations [7].

2.7. Statistical considerations

The main endpoint was compliance to treatment. A compliant case was considered as those able to receive the treatment with a gap equal or shorter than 3 weeks, and for whom no dose reduction of more than 50% was needed. It was estimated that the proportion of compliant patients would be 80%.

Taking a 95% confidence interval (CI) varying from $(P-0.2 \times P)$ to $(P+0.2 \times P)$, 40 patients were required.

3. Results

3.1. Patients

From June 1996 to May 1999, 44 patients were enrolled. One patient was lost to follow-up before

treatment and was thus ineligible. The characteristics of the 43 patients are reported in Table 1.

3.2. Compliance to treatment

The median duration of the first sequence was 26 days (25–31 days) and 26 days (17–30 days) for radiation and 5-FU delivery, respectively. The median dose for radiotherapy was 36 Gy (36–36.7 Gy). The median daily doses of 5-FU and MMC were 197 mg/m² (165–230 mg/m²) and 10 mg/m² (6–15 mg/m²), respectively.

The median gap duration was 18 days (14–30 days). 6 patients had an increased gap duration: 3 for grade 3 toxicity, 2 for deep venous thrombosis, 1 unknown. One patient only had a gap lasting for more than 3 weeks.

All patients underwent the second treatment sequence, and 5 had a brachytherapy boost instead of an external radiotherapy boost.

The median duration of the second sequence was 17 days (16–26 days) and 17 days (8–20 days) for radiation and 5-FU delivery, respectively. The median dose for radiotherapy was 23.4 Gy (23.4–23.4 Gy). The median daily doses of 5-FU and MMC were 199 mg/m² (82–223 mg/m²) and 10 mg/m² (6–11.5 mg/m²), respectively. 2 patients had a definitive interruption of 5-FU due to acute pneumonia and deep venous thrombosis. Treatment compliance for both radiation and chemotherapy doses, treatment duration and gap duration was 93%.

3.3. Acute toxicity

No grade 4 or 5 toxicity was observed. Only 5 patients had a grade 3 diarrhoea. Haematological toxicities were uncommon and minimal (Table 2).

Acute grades 2 and 3 perineal skin reaction and diarrhoea appeared during the second or third week of the

Table 1
Patient/tumour characteristics ($n=43$)

Male/female	16/27
Median age (range) (years)	59.2 (37–75)
WHO status	
0	27 (63%)
1	16 (37%)
T stage	
2	10 (23%)
3	23 (53%)
4	10 (23%)
N stage	
0	21 (49%)
1	14 (33%)
2	4 (9%)

WHO, World Health Organization.

Table 2
Maximum score of acute side-effects ($n=43$)

	Grade	No. pts
Diarrhoea	3	5 (12%)
	2	19 (44%)
Perineal	3	12 (28%)
	2	26 (60%)
WBC	3	1 (2%)
	2	2 (5%)
Platelets	3	1 (2%)
	2	3 (7%)

WBC, white blood cells; pts, patients; pts, patients.

first sequence, peaked at its end and resolved rapidly during the second sequence (Figs. 1 and 2).

3.4. Tumour response

At the end of the gap, 6 patients already had a complete response, 26 a partial response, 2 had no change and 9 were not evaluated. Six weeks after treatment completion, 36 patients had a CR, 5 a PR, 3 of those had a delayed CR 1–4 months later, 2 had a tumour progression.

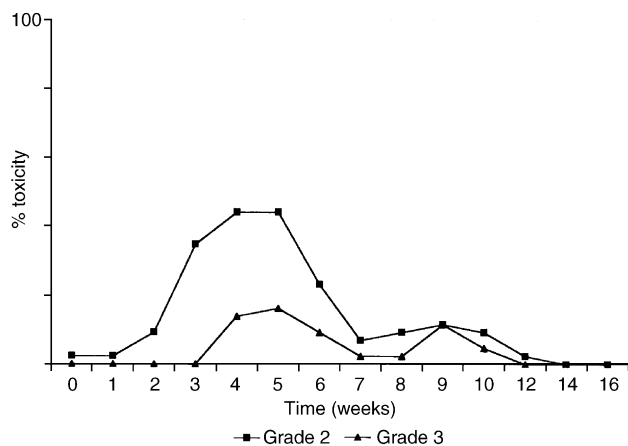


Fig. 1. Time course of acute grades 2–3 perineal skin reactions.

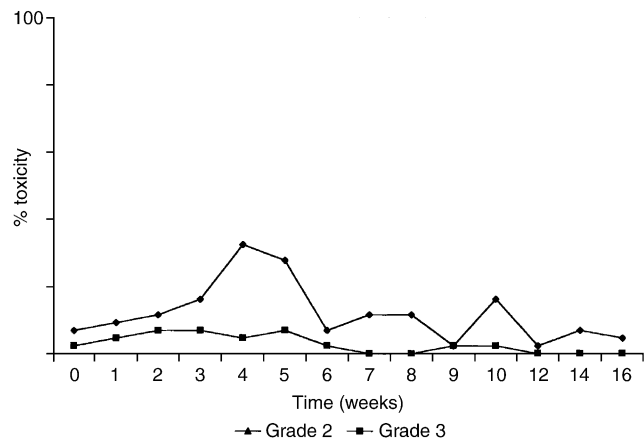


Fig. 2. Time course of acute grades 2–3 diarrhoea.

3.5. Recurrences

Among the 39 patients in CR after CMT, 2 presented later with a local failure and 2 with distant metastasis. After salvage surgery, 1 patient is living at 6 months, 1 died from local progression at 8 months.

Among the 4 patients with progression or PR after CMT, 1 had no further treatment, and 3 had salvage surgery. 2 died from local recurrences 12 and 19 months later; 1 is alive without disease 10 months after surgery. After salvage of the failures, the overall 3 year loco-regional control rate was 88% (Fig. 3).

3.6. Colostomies

8 patients had a permanent colostomy. In 3 patients with suspected local recurrence, the pathological specimen did not show residual disease. No postoperative deaths were observed. The 3-year colostomy-free interval rate was 81% (Fig. 4).

3.7. Severe late toxicities

4 patients had a transient anal ulcer, one of which necessitated a temporary colostomy. Another 1 had a

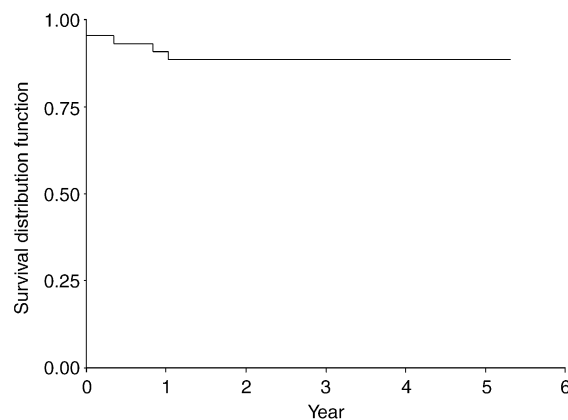


Fig. 3. Local-free interval.

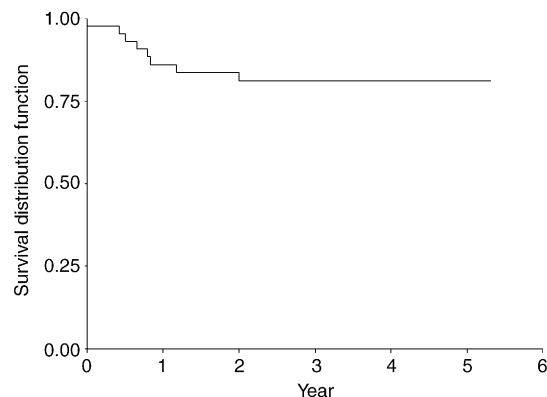


Fig. 4. Colostomy-free interval.

bowel occlusion which resolved spontaneously. The 3-year severe toxicity-free interval rate was 84% (Fig. 5).

3.8. Survival

After a median follow-up of 30 months (10–64 months), 4 patients died, all from cancer. The 3-year survival rate was 81%.

3.9. Comparison of 22861 and 22953 EORTC trials

Patient selection for the previous EORTC study (#22861) and the 22953 trial was very similar. The two CMT schemes differed mainly by the chemotherapy scheme, the gap duration (6 weeks versus 2 weeks) and the dose of radiation delivered during the first sequence (45 Gy versus 36 Gy). Comparing the main results of both studies is not completely irrelevant, keeping in mind the limitations of historical comparisons (Table 3).

At 3 years, this attempted comparison suggests there is an improved local control with a lower late toxicity following treatment with the most recent 22953 scheme.

4. Discussion

Pioneered by Papillon [8,9], radiation alone became the standard treatment for anal cancer in the 1970s [10–13]. Originally, it was delivered in two sequences. The

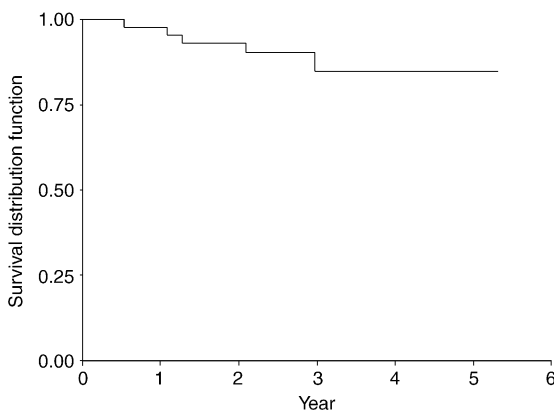


Fig. 5. Severe toxicity-free interval.

Table 3
Comparison of the 22861 and 22953 main results: 3-year estimated rates (%)^a

	22861	22953
No. patients	51	43
Locoregional control (months)	68 (54–82)	88 (73–100)
Colostomy-free interval (months)	72 (60–86)	81 (63–98)
Overall survival (months)	70 (58–86)	81 (67–95)
Severe toxicity-free interval (months)	62 (47–76)	84 (70–98)

^a 95% Confidence Interval given in parentheses.

first consisted of a 45–50 Gy external beam radiation dose given over 5 weeks or an equivalent dose (30 Gy in 18 days and 10 fractions in Papillon's scheme) to the primary tumour and subclinical locoregional disease. Then a 6-week gap was planned. This long period was intended to allow an optimal regression of the tumour and the healing of acute reactions. Then a second sequence of either surgery for non- or partial responders or a radiotherapy boost dose of 15–20 Gy with either external fields or brachytherapy for good responders was given.

The treatment schemes of the two European randomised trials that tested CMT were designed to fit this schedule, with chemotherapy being delivered only during the first sequence.

The current phase II study demonstrates that it is possible to reduce the gap from 6 to 2 weeks, to deliver chemotherapy during both sequences and 5-FU continuously. This scheme has permitted to an increase in the 5-FU dose from 615 mg/m²/week in the previous EORTC trial to 1400 mg/m²/week in this trial and the MMC dose from 1.1 to 2.3 mg/m²/week.

Acute toxicity was moderate and healed rapidly. Haematological toxicity was low, despite MMC being given twice. Among the 34 patients who were evaluated at the end of the gap, 32 (94%) were considered good responders, indicating that anal cancer is a tumour that rapidly responds to radiochemotherapy and that a 36 Gy dose seems sufficient to select responders from non-responders in CMT.

The complete response rate was 90.7%. Of interest, 3 patients had a complete response 10–22 weeks after treatment completion.

The 3-year local control rate was 88%, better than that observed in the two European studies (61 and 68% in the UK and EORTC studies, respectively) [1,2], and in the same range as that observed in the 5-FU-MMC arm of the American study that included both early and locally advanced diseases [3]. Late toxicity was substantially lower in the present study than that observed in the previous EORTC study [2]. There is no clear explanation for this. One reason could be the lower radiotherapy dose given in the first sequence (36 Gy versus 45 Gy), another could be the modality of the 5-FU administration.

The absence of mortality observed after surgery performed after full radiochemotherapy treatment indicates that this should be considered in cases of local recurrence. It may give a curative chance to approximately 50% of patients [14–16]. However, because the local aspect of the disease may mimic a recurrence, confirmation should be obtained before making the decision to operate.

Lengthening the overall treatment time has been shown to decrease the efficacy of radiation in many cancers and this has been attributed to tumour cell

repopulation [17]. In anal cancer, Peiffert and colleagues [18] observed a loss of local control when the gap duration was over 63 days before the boost by brachytherapy. Allal and colleagues [19] made a similar observation when it was over 75 days before the boost by external radiation. In an attempt to further increase the local control of CMT, the Radiation Therapy Oncology Group conducted a phase II study to test the feasibility of CMT while increasing the radiotherapy dose up to 59.4 Gy (Radiation Therapy Oncology Group (RTOG) #92.08). A 2-week gap was planned after 30.6 Gy. Two courses of 5-FU-MMC were delivered during the radiation. 47 patients were entered into the study, 28% had a grade 3 and over acute toxicities and there was one toxic death. After 2 years, the colostomy rate was 30% compared with 7% in the intergroup study that used a 45 Gy dose without gap. It was concluded that introducing a 2-week gap was responsible for this deterioration in the results, despite an increased radiotherapy dose [20]. The radiation scheme used in the RTOG 92.08 and in the EORTC 22953 are very similar, but the chemotherapy doses and delivery differ and this likely explains differences in toxicity. However, the time course of acute toxicity observed in our study, especially the perineal skin reactions, indicates it is unlikely that the gap can be further reduced or omitted.

Rich and colleagues tested 5-FU given as a continuous infusion for CMT for anal cancer. The tolerance was acceptable when infusion was given at 250–300 mg/day, 5 days/week, a dose intensity similar to ours. When given with a 50–55 Gy radiotherapy dose, they observed a 73% rate of local control, while the addition of daily cisplatin increased this rate to 89% [21]. Whether 5-FU–cisplatin is more efficient or less toxic than 5-FU–MMC is currently under investigation in a large US phase III trial (RTOG #98-11).

Because the 22953 scheme appears to increase local control and to decrease the late side-effects compared with our previous study, the RT and Gastrointestinal (GI) EORTC Groups have decided to use this new scheme as a reference and to study MMC–5-FU versus MMC–cisplatin chemotherapies in a future randomised CMT study.

Acknowledgements

This work was supported by grants from La Ligue Nationale Française de Lutte contre le Cancer. We thank J.J. Pavy MD, for his help in the preparation of the study.

Appendix

Other EORTC participants in the study were: Dr G. Poulin Hospital, Belfort, France; Pr P. Maingon Centre

Georges-François Leclerc, Dijon, France; Dr R. Orecchia European Institute of Oncology, Milan, Italy; Pr W. Budach University Hospital, Tübingen, Germany; Dr P. Rodrigus Bernard Verbeeten Institut, Tilburg, The Netherlands.

References

1. UKCCCR Anal Cancer Trial Working Party. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. *Lancet* 1996, **348**, 1049–1054.
2. Bartelink H, Roelofsen F, Eschwege F, *et al.* Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *J Clin Oncol* 1997, **15**, 2040–2049.
3. Flam M, John M, Pajak TF, *et al.* Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal cancer: results of a phase III Randomized Intergroup Study. *J Clin Oncol* 1996, **14**, 2527–2539.
4. Bosset JF, Pavy JJ, Roelofsen F, Bartelink H, for the EORTC Radiotherapy Gastrointestinal Cooperative Groups. Combined radiotherapy and chemotherapy for anal cancer. *Lancet* 1997, **349**, 205–206.
5. Sobin LH, Wittekind C. *TNM Classification of Malignant Tumours*, 5th edn. New York, Wiley-Liss, 1997.
6. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 107–214.
7. Pavy JJ, Denekamp J, Letschert J, *et al.* EORTC late effects working group. Late effects toxicity scoring: the SOMA scale. *Radiation Oncol* 1995, **35**, 11–15.
8. Papillon J. *Rectal and Anal Cancers. Conservative Treatment by Irradiation—An Alternative to Radical Surgery*. Berlin, Heidelberg, New York, Springer-Verlag, 1982.
9. Papillon J, Montbarbon J. Epidermoid carcinoma of the anal canal: a series of 276 cases. *Dis Colon Rectum* 1987, **30**, 324–333.
10. Cummings B. The place of radiation therapy in the treatment of carcinoma of the anal canal. *Cancer Treat Rev* 1982, **9**, 125–147.
11. Eschwege F, Lasser P, Chavy A, *et al.* Squamous cell carcinoma of the anal canal: treatment by external beam irradiation. *Radiat Oncol* 1985, **3**, 145–150.
12. Doggett SW, Green JP, Cantril ST. Efficacy of radiation therapy alone for limited squamous cell carcinoma of the anal canal. *Int J Radiat Oncol Biol Phys* 1988, **15**, 1069–1072.
13. Schlienger M, Krzisch C, Pene F, *et al.* Epidermoid carcinoma of the anal canal treatment results and prognostic variables in a series of 242 cases. *Int J Radiat Oncol Biol Phys* 1989, **17**, 1141–1151.
14. Zelnick RS, Haas PA, Aljouni M, Szilagyi E, Fox TA. Results of abdominoperineal resections for failures after combination chemotherapy and radiation therapy for anal cancers. *Dis Colon Rectum* 1992, **35**, 574–578.
15. Grabenbauer GG, Matzel KE, Schneider IHF, *et al.* Sphincter preservation with chemoradiation in anal canal carcinoma. *Dis Colon Rectum* 1998, **41**, 441–450.
16. Allal AS, Laurencet FM, Reymond MA, Kurtz JM, Marti MC. Effectiveness of surgical salvage therapy for patients with locally uncontrolled anal carcinoma after sphincter-conserving treatment. *Cancer* 1999, **86**, 405–409.
17. Fowler JF, Lindstrom MJ. Loss of local control with prolongation in radiotherapy. *Int J Radiat Oncol Biol Phys* 1992, **23**, 457–467.
18. Peiffert D, Bey P, Pernot M, *et al.* Conservative treatment by

- irradiation of epidermoid cancers of the anal canal: prognostic factors of tumoral control and complications. *Int J Radiat Oncol Biol Phys* 1997, **37**, 313–324.
19. Allal AS, Mermillod B, Roth AD, Marti MC, Kurtz JM. The impact of treatment factors of local control in T2-T3 anal carcinomas treated by radiotherapy with or without chemotherapy. *Cancer* 1997, **79**, 2329–2335.
 20. John M, Pajak T, Flam M, *et al.* Dose escalation in chemoradiation for anal cancer: preliminary results of RTOG 92–08. *Cancer J Sci Am* 1996, **2**, 205.
 21. Rich TA, Ajani JA, Morrison WH, Ota D, Levin B. Chemoradiation therapy for anal cancer: radiation plus continuous infusion of 5-fluorouracil with or without cisplatin. *Radiother Oncol* 1993, **27**, 209–215.