Annals of Oncology 23: 695–700, 2012
doi:10.1093/annonc/mdr354
Published online 22 August 2011

Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial

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Received 13 February 2011; revised 2 May 2011; revised 3 June 2011; accepted 20 June 2011

Background: The purpose of the study was to evaluate the benefit of adjuvant chemotherapy (AC) versus surgery alone in patients with muscle-invasive bladder cancer (MIBC).

Patients and methods: One hundred and ninety-four patients with pT2G3, pT3–4, N0–2 transitional cell bladder carcinoma were randomly allocated to control (92 patients) or to four courses of AC (102 patients). These latter patients were further randomly assigned to receive gemcitabine 1000 mg/m^2 days 1, 8 and 15 and cisplatin 70 mg/m^2 day 2 or gemcitabine as above plus cisplatin 70 mg/m^2 day 15, every 28 days.

Results: At a median follow-up of 35 months, the 5-year overall survival (OS) was 48.5%, with no difference between the two arms [P = 0.24, hazard ratio (HR) 1.29, 95% confidence interval (CI) 0.84–1.99]. Mortality hazard was significantly correlated with Nodes (N) and Tumor (T) stage. The control and AC arms had comparable disease-free survival (42.3% and 37.2%, respectively; P = 0.70, HR 1.08, 95% CI 0.73–1.59). Only 62% of patients received the planned cycles. A significant higher incidence of thrombocytopenia was observed in patients receiving cisplatin on day 2 (P = 0.006). A similar global quality of life was observed in the two arms.

Conclusion: The study was underpowered to demonstrate that AC with cisplatin and gemcitabine improves OS and disease-free survival in patients with MIBC.

Key words: bladder cancer, adjuvant chemotherapy, phase III trial

introduction

Bladder cancer represents the fifth most common cancer in Europe [1], and ∼60% of patients with bladder cancer will develop a muscle-invasive disease.

Until recently, radical cystectomy was considered the gold standard of the treatment of muscle-invasive bladder cancer (MIBC), and although new surgical techniques [2, 3] reduced the morbidity and mortality related to this procedure, the 5-year survival rates for all stages still range from 48% to 66% [4, 5]. Recently, two meta-analyses showed a significant overall survival (OS) benefit in favor of neoadjuvant cisplatin-based chemotherapy, thus making it the new standard of care for these patients [6, 7]. In respect to neoadjuvant chemotherapy, adjuvant chemotherapy (AC) has several putative advantages, namely, it is administered to patients properly selected on the basis of factors predicting for relapse and it does not imply any delay of definitive treatment.

Several randomized trials have been done to investigate the use of AC in MIBC [8–14]. Almost all these studies provide insufficient evidence to support the routine use of AC, due to small sample sizes, early stopping of patient entry, confusing analyses and terminology and the reporting of questionable conclusions [15, 16]. Two meta-analyses [17, 18] provided statistically significant evidence in favor of AC relative to OS and disease-free survival. However, both meta-analyses' results should be carefully evaluated before considering AC as a current standard for these patients because of both the small number of trials and the patients included and should be rather

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regarded as a first step toward generating new hypotheses to be tested in larger randomized trials [19, 20].

In advanced bladder cancer, the combination of cisplatin (C; day 2) and gemcitabine (G; days 1, 8, 15) has been demonstrated to be as effective as M-VAC (combination chemotherapy with methotrexate, vinblastine, doxorubicin and cisplatin) but with less myelotoxicity [21]. On the other hand, the schedule of cisplatin (day 15) plus gemcitabine, which has proven to further reduce the bone marrow toxicity in non-small-cell lung cancer patients [22, 23], has not been tested in adjuvant bladder cancer.

This phase III, Italian, multicenter randomized clinical trial aimed to demonstrate the efficacy of chemotherapy administered immediately after radical cystectomy versus the same chemotherapy administered at the time of disease recurrence.

patients and methods

patients

Patients with histologically proven transitional cell carcinoma of the bladder pT2 G3 (N0–2), pT3–4 (N0–2) any G or pN1–2, any Tumor (T), any G were considered eligible. A radical cystectomy with no residual disease and a minimum of 10 lymph nodes dissection was required. Randomization was required within 10 weeks after surgery. Neither prior neoadjuvant chemotherapy nor radiotherapy was allowed, while no restrictions were applied to prior endoluminal therapy. Eligible patients were also required to have an Eastern Cooperative Oncology Group performance status (PS) of two or less, age ≤ 75 years, adequate bone marrow reserve and a good renal (creatinine level ≤ 1.25 μmol/l, measured creatinine clearance ≥ 60 ml/min) and liver function. The trial was conducted according to the guidelines of the Helsinki Declaration and approved by all institutional ethics committees. All patients were required to sign a written informed consent before randomization.

study design and allocated treatments

After cystectomy, patients were randomly assigned (1 : 1) to observation and treatment on relapse (arm A) or AC (arm B). Before randomization, two stratification factors were considered: nodal involvement (N0 versus N1–2) and investigator center. Treatment allocation was established by the two coordinating centers using computer-generated random lists.

Patients in the AC arm were further randomly assigned (1 : 1) to receive two different schedules of the same regimen (arm B2 and arm B15). Patients on the B2 arm received gemcitabine 1000 mg/m^2 i.v. over 30 min, days 1, 8 and 15 plus cisplatin 70 mg/m^2 i.v. on day 2; patients on the B15 arm received the same gemcitabine schedule as for B2 arm, but cisplatin at the same dose was administered on day 15. On both arms, cycles were repeated every 28 days for a total of four cycles. Patients randomly assigned to observation arm were scheduled to be treated at first evidence of recurrence with one of the two cisplatin–gemcitabine regimens, at investigator's discretion.

Hematologic and non-hematologic toxicities were graded according to the World Health Organization (WHO) grading system [24].

Both drugs were omitted for grade 4 toxicity, whereas a 50% dose reduction was planned for grade 3 hematological and non-hematological side-effects. The dose of cisplatin was splitted in 2 days if measured creatinine clearance was 50–59 ml/min and omitted for creatinine clearance <49 ml/min.

trial end points and evaluations

The primary end point of the study was the comparison of the OS, defined as the time from randomization to death for any cause, between control and AC arm. Secondary aims were disease-free survival, defined as the time from randomization to the earliest occurrence of recurrence or death from any cause, toxicity of the two GC schedules, and quality of life (QoL).

All patients were clinically staged before randomization by computed tomography (CT) and bone scan. All patients had clinical and laboratory evaluation at baseline and during treatment. In the control arm and at the end of chemotherapy in the AC arms, patients were examined at 3-month intervals for the first 2 years, then every 6 months for further 3 years and then yearly thereafter. CT scan was carried out every 6 months for the first 3 years and on an annual basis thereafter. QoL tests were compiled at the study entry; at 2, 3 and 4 months and then at 6 and 12 months. Relapse was defined as the detection of at least one lesion that could not be identified as an independent second malignancy.

sample size and statistical analysis

Sample size was determined according to the survival data reported in the literature indicating that the annual risk of death for patients with MIBC following radical cystectomy was ∼35% [8–11], which means a 2-year probability of survival of 50%. The hypothesis was that AC would be able to improve 2-year OS of 10%: assuming an α error of 0.05 and a power of 80%, it was calculated that 610 patients (305 for each arm) should be accrued in 3 years and followed for further 2 years. All analyses were carried out according to the intent-to-treat principle. In order to evaluate the hypothesis of a relative difference of ∼30% in the incidence of thrombocytopenia between arm B2 and arm B15 (relative risk = 0.70), it was estimated that overall 350 patients would be required.

Survival curves were estimated by the Kaplan–Meier method and compared using the log-rank test. Data were reported as 5-year percentages and their standard errors. Additional analyses were done by the Cox proportional hazards model with the aim to adjust estimations for multiple baseline characteristics.

Comparisons of proportions between the two groups were carried out using a two-sided χ^2 test or a two-sided Fisher's exact test, as appropriate.

results

Because of the low accrual rate, the trial was prematurely closed and the final analysis was carried out in July 2009. From September 2001 to July 2007, 194 patients from 45 Italian centers (see Appendix 1) were entered on to the trial, 92 in the control arm and 102 in the AC arm. Eleven patients, six in arm A and five in arm B, were lost after randomization and were not considered assessable for final analysis. Of the 97 assessable patients in the chemotherapy arm, 8 patients refused to start chemotherapy and were not included in the toxicity analysis. Of the remaining 89, 43 patients were randomly assigned to receive cisplatin on day 2 (arm B2) and 46 to receive cisplatin on day 15 (arm B15).

Patient characteristics were balanced between the two arms except for pN2, which were more in the CT group, but the difference was not statistically significant (Table 1). A poorly differentiated tumor grade was predominant in both arms and almost half of the patients had positive regional lymph nodes. Median time to therapy in the adjuvant arm was 8 weeks, ranging from 4 to 12 weeks.

overall survival

At a median follow-up of 35 months (interquartile range 15–57), 84 patients had died (arm A, $N = 38$; arm B, $N = 46$). Tumor was the cause of death in 34 patients in the control arm and in 39

Table 1. Patient characteristics

	Control ($N = 86$), *n* (%)	AC ($N = 97$), *n* (%)
Median age (range), years	63 (36–75)	64 (38–75)
Sex		
Male	75 (87.2)	90 (92.8)
Female	11 (12.8)	7 (7.2)
PS (ECOG)		
0	61 (70.9)	79 (81.4)
1–2	21 (24.4)	16 (16.5)
Missing	4 (4.7)	2 (2.1)
Histology		
Transitional cell carcinoma	85 (98.8)	95 (97.9)
Other	1 (1.2)	2 (2.1)
T grade		
G2	4 (4.7)	3 (3.1)
G3	80 (93.0)	90 (92.8)
Gx or missing	2 (2.3)	4 (4.1)
T stage		
pT1	1 (1.1)	3 (3.1)
pT2	19 (22.1)	29 (29.9)
pT3	49 (57.0)	46 (47.4)
pT4	17 (19.8)	19 (19.6)
Lymph nodal status		
pN0	49 (57.0)	47 (48.5)
pN1	19 (22.1)	20 (20.6)
pN2	18 (20.9)	30 (30.9)

AC, adjuvant chemotherapy; PS, performance status; ECOG, Eastern Cooperative Oncology Group; T, tumor; pT, pathological Tumor; pN, pathological Nodes.

patients in the chemotherapy arm. Eleven patients died in absence of proven tumor progression (five in the control arm and six in the AC arm). The 5-year OS of the whole series was 48.5% (standard error 4.2%), slightly higher than expected, probably due to the consistent percentage of node-negative patients included, with no significant difference between the two arms ($P = 0.24$): 53.7% in the control group and 43.4% in the AC arm. No difference in OS according to GC schedule was evident in the AC arm: 46.6% of patients assigned to the B2 schedule were alive at 5 years compared with 39.9% of those assigned to the B15 schedule ($P = 0.88$). Survival curves are shown in Figure 1.

In patients with lymph node-negative disease, 5-year OS rates were 73.2% in the control arm and 64.5% in the AC arm ($P = 0.65$); whereas in patients with lymph node involvement, OS rates were 27.6% and 25.8% in the control and AC groups, respectively ($P = 0.71$).

The hazard ratio (HR) for mortality from any cause according to treatment (chemotherapy versus control) also failed to reveal any difference in OS between the two arms [HR 1.29; 95% confidence interval (CI) 0.84–1.99; $P = 0.24$]. Mortality analysis confirmed that, independently of treatment arm, mortality hazard was significantly correlated with nodal status (pN1 versus pN0: HR 2.42; 95% CI 1.38–4.26; pN2 versus pN0: HR 4.33; 95% CI 2.60–7.20) and T stage (pT3 versus pT1–2: HR 2.01; 95% CI 1.14–3.56; pT4 versus pT1–2: HR 2.57; 95% CI 1.34–4.92). These results were confirmed also by multivariate analysis (data not shown).

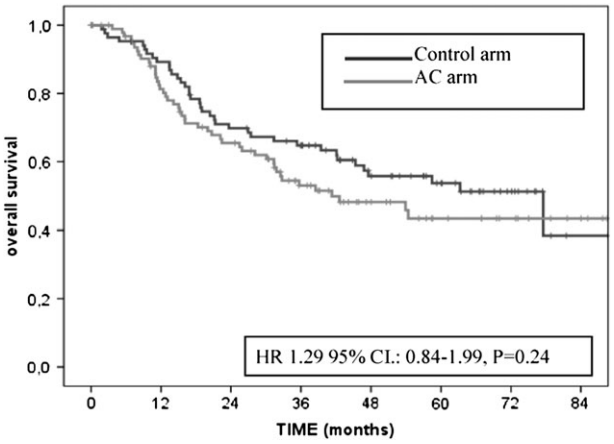

Figure 1. Kaplan–Meier curves for overall survival in patients who underwent chemotherapy or observation. AC, adjuvant chemotherapy; HR, hazard ratio; CI, confidence interval.

disease-free survival

Overall, tumor relapse occurred in 83 patients, 40 in arm A and 43 in arm B. The first site of relapse were the pelvis in 11 patients (6 in arm A and 5 in arm B); the bones in 15 patients (7 in arm A and 8 in arm B); the lungs in 10 patients (5 in arm A and 5 in arm B) and the lymph nodes in 12 patients (8 in arm A and 4 in arm B). Twenty-seven patients relapsed at more than one site (11 in arm A and 16 in arm B). Secondary primary tumors were reported in nine patients.

The 5-year disease-free survival of the whole cohort on study was 39.5% (standard error 3.9%). The control and AC arms were almost comparable relative to disease-free survival: 42.3%, arm A and 37.2%, arm B ($P = 0.70$, HR 1.08; 95% CI 0.73–1.59). Disease-free survival curves are shown in Figure 2.

In the subgroup analysis according to nodal status, the 5-year disease-free survival of the node-negative patients was 59.5% in the control arm and 57.6% in the AC arm ($P = 0.97$). In node-positive patients, 5-year disease-free survival was 19.4% in the control group and 18.9% in the AC group ($P = 0.80$). Treatments received at relapse are listed on Table 2.

toxicity

Patients in the AC arm received in total 297 cycles, 135 in arm B2 and 162 in arm B15. Overall, 92% of patients completed the first cycle, 78% two cycles, 74% three cycles and only 62% of patients received the planned four cycles, mainly due to treatment-related toxic effects. In the B2 arm, 67% required dose adjustment and 39% patients required an early stop treatment. In the B15 arm, a dose reduction and an early stop treatment was required for 72% and 26% patients, respectively. All the WHO hematologic and non-hematologic toxic effects observed in B2 and B15 arms are listed in Table 3. A statistically significant higher incidence of grade 3/4 thrombocytopenia was observed in B2 arm as compared with B15 arm (25.6% versus 4.3%, $P = 0.006$). On the contrary, patients in B15 arm experienced more grade 3/4 leukopenia (15.2% versus 9.3%) and neutropenia (34.8% versus 21%), not reaching statistical significance. The incidence of grade 3 and 4 nausea and vomiting was higher in B2 arm (9.4% versus

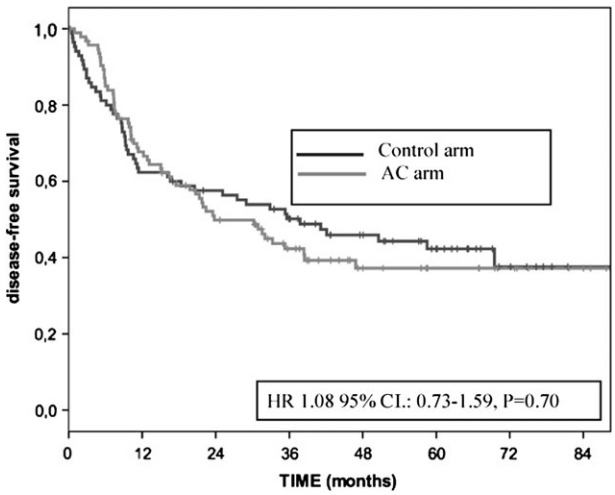

Figure 2. Kaplan–Meier curves for disease-free survival in patients who underwent chemotherapy or observation. AC, adjuvant chemotherapy; HR, hazard ratio; CI, confidence interval.

Table 2. Treatment of relapsed patients

	Control (total PD = 40)	AC (total PD = 43)
CDDP/GEM (B2 schedule)	9	–
CDDP/GEM (B15 schedule)	4	–
CDDP/GEM (other schedules)	5	3
Other chemotherapies[a]	5	18
Surgery	1	3
RT	2	2
Best supportive care	5	11
Missing	9	6

[a]M-VAC and regimens containing carboplatin and/or paclitaxel.
AC, adjuvant chemotherapy; CDDP, cisplatin; GEM, gemcitabine; B2, cisplatin administered on day 2; B15, cisplatin administered on day 15; RT, radiotherapy; M-VAC, combination chemotherapy with methotrexate, vinblastine, doxorubicin and cisplatin; PD, progressive disease.

2.2%, $P = 0.31$). No drug toxicity-related death was observed in either arm.

Global QoL was similar for patients assigned both to control and to AC arm. In this latter group, there was a slight worsening of the general QoL during the last 2 months of chemotherapy, with a subsequent improvement during follow-up so returning comparable with the control group.

discussion

The present study is an Italian, multicenter, randomized phase III trial comparing immediate AC with cisplatin and gemcitabine versus the same chemotherapy at relapse in patients with MIBC who underwent radical cystectomy. Our study was underpowered to demonstrate that AC improves OS and disease-free survival in these patients.

Despite being limited by an accrual much slower than expected and by the small number of patients recruited, much lower than that originally planned, this is the largest phase III trial reported so far exploring the role of AC in patients with MIBC.

Table 3. Summary of treatment-related toxic effects

	CDDP/GEM (B2; $N = 43$), %		CDDP/GEM (B15; $N = 46$), %	
	All	3/4	All	3/4
Leukopenia	65	9	66	15
Neutropenia	68	21	70	35
Anemia	63	5	55	6
Thrombocytopenia	49	26	45	4
Fever	39	–	28	2
Nausea–vomiting	48	9	54	2
Cefalea	7	–	4	–
Diarrhea	19	2	17	–
Stomatitis–mucositis	21	–	11	4
Hypertransaminasemia	–	–	4	2
Hypercreatininemia	14	–	15	–
Decrease creatinine clearance	14	2	9	–
Proteinuria	14	–	4	–
Alopecia	28	2	23	2
Infection	21	5	11	–
Asthenia	65	5	46	2

CDDP, cisplatin; GEM, gemcitabine; B2, cisplatin administered on day 2; B15, cisplatin administered on day 15.

The choice of the cisplatin–gemcitabine regimen was made on the basis of the results of a large phase III trial in the metastatic setting, comparing this regimen versus M-VAC, showing comparable responses but a lower toxicity of the GC regimen [21, 25]. In fact, in our study, both hematological and non-hematological toxicities were acceptable with a low incidence of grade 3–4 side-effects, with the exception of thrombocytopenia, which occurred significantly more frequently in the B2 arm. These data confirm the results obtained in two prior studies [22, 23].

In spite of the quite acceptable incidence and severity of chemoinduced toxic effects, our trial confirmed that the compliance of patients to chemotherapy after radical cystectomy was poor. Only 62% of patients could complete chemotherapy as planned, and more than half of the patients required a dose reduction. These data confirm that the compliance of patients to chemotherapy after radical cystectomy decreases rapidly with a lower tolerance to drugs. The low compliance to AC was previously reported in other studies also [8, 9] and can partly explain the negative results of most previous published randomized trials [10–13]. The putative difficulties in delivering AC to bladder cancer patients should be taken into adequate account in treatment planning.

Despite this data compliance, the QoL of patients who received AC seems to be similar to the one observed in patients treated with surgery alone. This could be probably due to the high number of dose reductions and/or early termination of treatment in that arm.

As shown in Table 2, only 62% of patients were treated for metastatic disease, and 75% of them received the planned gemcitabine–cisplatin regimen. Several patients were not

suitable to receive a first-line chemotherapy or a cisplatin-containing regimen. This result confirms that metastatic bladder cancer can occur in a very aggressive way that does not always allow to submit patients to the same chemotherapy regimen planned in the adjuvant setting.

Seven randomized trials have compared AC with observation after cystectomy [8–14]. All these trials used combination platinum-based chemotherapy except for one that tested the value of cisplatinum monotherapy [10]. Three trials [8, 9, 14] showed an advantage in OS in favor of the patients assigned to adjuvant therapy and the other four studies were negative [10–13]. The lack of advantage from AC observed in these trials was probably due to the small sample size and in some studies due to the suboptimal treatment option. These studies included <100 patients, except for the Paz-Ares trial, and were all stopped prematurely on the basis of an interim analysis, favoring the chemotherapy group.

Beyond their small size, long recruitment period, early stopping on the basis of interim analysis and inadequacy of the chemotherapy employed, most of these studies are also biased by the lack of standardization of treatment on progression. This aspect might be crucial relative to OS estimation. In fact, on one hand, it is well known that patients with metastatic disease can benefit from frontline chemotherapy [26, 27]. On the other hand, no chemotherapy regimen can be regarded yet as the standard to manage the patients who fail adjuvant cisplatin-based chemotherapy. Standardization of treatment on relapse is one of the points of strength of our study, though our findings confirm that only a limited proportion of the recurring patients can actually be managed by full-dose chemotherapy regimens, mainly due to a rapid decline in PS.

In order to better clarify the impact of AC for radically removed bladder cancer, two meta-analyses were carried out, both of them providing a moderate but statistically significant survival benefit in favor of the treated patients, regardless of the chemotherapy regimen employed [17, 18, 28]. In particular, in the individual patient data meta-analysis (6 gathered trials, 491 collected patients), a 25% significant reduction in the risk of death ($P = 0.019$) in favor of the AC was found, with an absolute benefit of 9% at 3 years [17]. Actually, the clinical heterogeneity (i.e. surgical technique, the chemotherapy regimen and drugs, the patient selection with particular regard to the node status at surgery, the trial design) and the overall sample size, which was certainly underpowered to detect that difference (900 events would have been required, with 80% power and 5% significance), did not suggest any definitive recommendation on the use of AC.

Our study enrolled 190 patients, an accrual that was larger than in other intergroup trials, and confirmed the feasibility of the adjuvant approach in patients with MIBC. Unfortunately, the number of patients who entered the study remains the major limit of the present trial, considering that the original plan was to recruit 610 patients. Thus, no meaningful conclusion can be extrapolated from a study with any adequate power. In fact, with less than one-third of the planned patients, our trial has a high chance to be falsely negative. However, our study might give an important contribution to the meta-analysis.

A phase III trial comparing four cycles of adjuvant paclitaxel–gemcitabine–cisplatin regimen with observation was recently presented [14]. The Spanish trial randomly allocated 68 patients to the chemotherapy arm and 74 patients to the observation arm. At median follow-up of 29.8 months, Paz-Ares reported a significant advantage for AC in terms of OS ($P < 0.0009$) and progression-free survival ($P < 0.0001$).

Given the opposite results coming from our study and the Spanish trial, the update of the literature-based meta-analysis previously carried out does confirm the benefit in favor of AC (8 trials, 827 patients, relative risk reduction of 14%, $P = 0.034$, heterogeneity $P = 0.27$, absolute benefit 4.9%, corresponding to 20–21 number of patients needed to treat for one to benefit), with no significant interaction ($P = 0.40$) according to the number of administered drugs (data not shown).

Moreover, it further supports the conclusion that there is insufficient evidence to reliably base any treatment decision. This has to be properly taken into account not only for decision making in the everyday practice but also in trial designing. Due to the present uncertainness relative to the more appropriate way to manage these patients, there is still an urgent need for further research into the use of AC in MIBC. It is necessary that future studies have adequate statistical power or learn more about the biology of this tumor. In fact, few biologic tumor characteristics, such as *ERCC-1* and *BRCA1* expression level, are known to be predictive of chemosensitivity in bladder cancer [29] and are factors to consider, in order to develop more effective strategies with smaller number of patients.

acknowledgements

We thank the patients and the clinicians who participated in this study. We also thank Emilio Bria for the statistical meta-analysis calculations.

funding

Italian Minister of Health (RF 01.130).

disclosure

The authors declare no conflict of interest.

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appendix 1

†Members of the Study Group, which selects, enrolls and/or treats patients, were (number of patients included) as follows: Cantiani R., Istituto Tumori Regina Elena, Roma (56); Aglietta M., IRCC Candiolo, Torino (17); Bertetto O., Ospedale San Giovanni, Torino (9); Cetto G. L., Ospedale Civile Maggiore Borgo Trento, Verona (7); Orlandini P., Azienda Ospdaliera Pisana, Pisa (7); Ferrazzi E., Ospedale Civile, Rovigo (6); Nardi M., Ospedali Riuniti, Reggio Calabria (5); Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo (Bari) (5); Manzione L., Ospedale San Carlo, Potenza (5); Adamo V., Policlinico Universitario G. Martino, Messina (4); Porcile G., Ospedale San Lazzaro, Alba (CN) (4); Lentini M., Ospedale San Camillo-Forlanini, Roma (3); Breda E., Ospedale Fatebenefratelli, Roma (3); Gamucci T., Ospedale S.S. Trinità, Sora (3); Tummarello D., Ospedali Riuniti, Ancona (3); Dogliotti L., Ospedale San Luigi, Orbassano (TO) (3); Tumolo S., Ospedale Civile S.M. degli Angeli, Pordenone (3); Motta M., Ospedale V. Emanuele, Catania (2); Lo Russo V., Istituto Oncologico, Bari (2); De Grande G., Azienda Ospedaliera Umberto I, Siracusa (2); Sacco C., Ospedale Santa Maria della Misericordia, Udine (2); Gaion F., Ospedale Camposanpiero, Citta della Pieve (PD) (2); Lavarello A., Ospedale Civile, Sestri Levante (GE) (2); Nuzzo A., Ospedale Civile Renzetti, Lanciano (CH) (2); Clerico M., Ospedale Infermi, Biella (2); Aragona C., Ospedale Papardo, Messina (1); Gernone A., Policlinico di Bari, Ospedale Giovanni XXIII, Bari (1); Morelli F., Olivito V., Mater Domini, Catanzaro (1); Cupini, Ospedale Umberto I, Frosinone (1); Mattioli R., Ospedale S. Croce, Fano (1); Aiello Istituto San Luigi, Catania (1); Marra A., Ospedale Cardarelli, Napoli (1); Antimi M., Ospedale Sant'Eugenio, Roma (1); Silingardi V., Policlinico Universitario, Modena (1); Labianca R., Ospedali Riuniti, Bergamo (1); Martoni A., Ospedale S. Orsola, Bologna (1); Bortolussi V., Ospedale di Portogruaro, Portogruaro (VE) (1); Luoni M., Ospedale Civile Legnano, Legnano (MI) (1); Rosabian A., Ospedale Civile Boldrini, Thiene (VC) (1); Di Vito F., Ospedale Civile, Aosta (1); Catalano G., Ospedale San Salvatore, Pesaro (1); Gebbia N., Policlinico Universitario, Palermo (1).