The Influence of Cyst Emptying, Lymph Node Resection and Chemotherapy on Survival in Stage IA and IC1 Epithelial Ovarian Cancer

MIKKEL ROSENDAHL, BERIT JUL MOSGAARD and CLAUS HØGDALL

Copenhagen University Hospital, Rigshospitalet, Department of Obstetrics and Gynaecology, Copenhagen, Denmark

Abstract. *Aim: To determine if survival in stage I ovarian cancer is influenced by cyst emptying, lymph node resection and chemotherapy. Patients and Methods: A survival analysis of 607 patients with ovarian cancer in stage IA, IA with cyst emptying (IAempty) and IC1 was performed. Results: There was no difference in five-year survival between IA (87%) and IC1 (87%) ($p=0.899$), between IA and IAempty (86%) ($p=0.500$) nor between IA+IAempty (87%) and IC1 without IAempty (84%) ($p=0.527$). Five-year survival rate (5YSR) was significantly higher after lymph node resection in stage IA (94% vs. 85%; $p=0.01$) and IA+IC1 (93% vs. 85%; $p=0.004$). In multivariate analysis, lymph node resection improved prognosis significantly for all sub-stages, whereas stage and chemotherapy did not affect survival. Conclusion: In stage IA ovarian cancer, controlled cyst emptying without spill does not worsen prognosis. Lymph node resection is associated with improved survival in stage IA and IC1. Chemotherapy should only be offered where randomized controlled studies have shown a benefit.*

Adjuvant chemotherapy in stage I ovarian cancer (tumor confined to ovaries or fallopian tube(s)) is recommended for stage IA and IB grade 2-3, all stage IC and all clear cell carcinomas (1, 2). In 2013, the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) staging system for ovarian, fallopian tube and primary peritoneal cancer was revised with introduction of new sub-stages (3). One important alteration was a sub-division of stage IC in stages IC1, IC2 and IC3.

Correspondence to: Mikkel Rosendahl, MD, Ph.D., Copenhagen University Hospital, Rigshospitalet, Department of Obstetrics and Gynaecology, Blegdamsvej 9, DK-2100 Kbh Ø, Denmark. Tel: +45 35459676, e-mail: Mikkel.rosendahl.03@regionh.dk

Key Words: Ovarian cancer, staging, cyst spill, cyst rupture, survival, lymph node, stage I.

Stage IC1 confines tumor limited to one or both ovaries or fallopian tubes, with surgical spill. Hence, an apparent stage IA is upstaged to stage IC1 in case of surgical spill.

Surgical spill has been shown to worsen prognosis (2, 4) and the consequence of surgical spill in the former FIGO classification would be upstaging to stage IC, that previously included tumor limited to the ovaries with ruptured capsule and/or tumor on ovarian surface and/or positive washings. In most cases, these patients are recommended for adjuvant chemotherapy.

In a recent publication, we examined the consequence of the revised FIGO staging and found similar five-year survival rates (5YSR) and hazard ratios (HRs) for stages IA and IC1(5). We discussed that the similar survival rates in stage IA and IC1 could be due to administration of adjuvant chemotherapy in the stage IC1 patients (former stage IC) who then would obtain the same good prognosis as stage IA. On the other hand, it is plausible that some cases of surgical spill –now staged IC1– were considered as stage IA and not given chemotherapy. However, at that time, we did not have the patients' specific information about chemotherapy and, therefore, could not confirm this hypothesis. We have now obtained the patients' specific information about adjuvant chemotherapy and lymph node resection and the aim of the present study was to analyze the impact of adjuvant chemotherapy and lymph node resection on stage IA and IC1 epithelial ovarian cancer (EOC) and evaluate the importance of perioperative cyst emptying without apparent spill.

In a former study (5), we coded stage IA with controlled cyst emptying without spill into the peritoneal cavity (in this study called stage IAempty) as stage IC1, but also discussed whether it would be more appropriate to code it as stage IA. Therefore, one of the questions we seek to answer in the present study is whether IAempty should belong to IA or IC1?

For this purpose, we made comparisons of five-year and overall survival between the following stages: 1. Stage IA vs. Stage IC1 (controlled cyst emptying + cystic spill) 2. Stage IA vs. Stage IAempty (IA with controlled cyst

emptying). 3. Stage IA + IAempty (IA with controlled cyst emptying) vs. Stage IC1 without IAempty (only uncontrolled cystic spill).

Patients and Methods

In Denmark, with a population of 5.4 million, all surgery for ovarian, fallopian tube and peritoneal cancer is performed in three highly specialized centers. For optimal data storage and reliability, all patient data are collected and stored in The Danish Gynecologic Cancer Database (DGCD). After each outpatient visit and after surgery, all the details of the surgery are prospectively collected in a database, thus assuring high data quality.

All Danish citizens are issued with a personal and unique ID-number in the Danish Civil Registration System (DCRS), which automatizes survival registration and is also linked to The Danish National Pathology Registry (PATOBANK). The National Patient Register (NPR) provided information about whether patients had received chemotherapy. This provides a unique platform for epidemiological studies.

Data were obtained from DGCD, PATOBANK, NPR and the DCRS. Chemotherapy was recorded as yes/no but specific information about the choice of chemotherapy was unavailable. However, standard treatment during the recorded period was three-six courses of paclitaxel and carboplatin or carboplatin alone for stage IA and IB grade 2-3 patients and all stage IC patients.

According to national guidelines at the time of the beginning of the study, systematic lymphadenectomy was not performed in all cases. From 2003-2009, suspect pelvic and paraaortal lymph nodes were removed in presumed stage I-II disease. From 2009, pelvic lymphadenectomy was performed in presumed stage I disease. In advanced stages, only macroscopically suspicious nodes were removed.

Data on size of the lymph node metastasis was not available. Death is registered as death from any cause. Specific and detailed data about the surgery, in particular cyst rupture/emptying, was available from the DGCD. However, the exact method of emptying in individual cases was not available (bag, internal, external, etc.). Pre- and post-emptying peritoneal lavage and biopsies were not performed routinely in the beginning of the study period. However, data are prospectively recorded and are, therefore, more reliable than retrospectively screened medical journals. Lymph node resection was recorded as yes/no but information about the anatomic localization was unavailable.

Women diagnosed with an ovarian, fallopian tube or primary peritoneal cancers in 2005-2013 were included. Patients with borderline tumors were excluded.

The study was approved by the DGCD and the Danish Data Protection Agency (file no: 2007-58-0014).

Statistical analysis. Data analysis was performed using IBM SPSS version 22.0. software (IBM Corp., Armonk, NY, USA). Kaplan-Meier curves, including life tables and log-rank test (Mantel-Cox), were used for analysis of 5YSR. 5YSR is shown as the cumulative proportion (%) surviving until 60 months with 95% confidence interval (CI). HRs are shown with 95% CI.

Cox regression was used for analysis of differences in survival between groups. Chi2 are calculated using log-rank test for 5YSR and in Tables according to Pearson's Chi-squared test. All p-values were two-sided and <0.05 was considered significant.

Results

According to the 2013 FIGO staging (3), there were 464 patients in stage IA and 143 patients in stage IC1.

In 39 cases, controlled cyst emptying without notable spill had resulted in upstaging to IC1. In the following, these patients are referred to as IAempty. If there was bilateral tumor (stage IB) and controlled cyst-emptying, the patient remained in IC1. Histology, tumor grade and demographics are listed in Table I.

Stage IA vs. IC1. The 5YSR in stage IA was 87% (95%CI=83-91%). The 5YSR of stage IC1 was 87% (95%CI=80-94%). This was not different from stage IA (Chi²=0.016; *p*=0.899).

In stage IA, 35% had lymph node resection vs. only 30% in stage IC1 (not significant (NS)). However, in stage IA, among patients who had lymph node resection, only 38% of patients received chemotherapy versus 62% among the patients in stage IC1 who had lymph node resection (Chi²=12.560; *p*=0.002).

In the Cox-regression, we included age, American Society of Anesthesiologist (ASA) score, performance status (6) (PS), histology, tumor grade, adjuvant chemotherapy, omentectomy, lymph node resection and stage (IA vs. IC1).

Age (HR=1.046 (95%CI=1.026-1.066); *p*<0.0001) and PS (HR=1.815 (95%CI=1.388-2.372); *p*<0.0001) were significantly associated with a poorer prognosis.

Stage (IA vs. IC1) did not affect prognosis (HR=0.926 (95%CI=0.521-1.645), *p*=0.79) and neither did administration of chemotherapy (HR=0.708 (95%CI=0.416-1.215); *p*=0.21).

Failure to perform lymph node resection (LNR) significantly deteriorated prognoses (HR=1.926 (95%CI=1.032-3.596); *p*=0.04).

Stage IA vs. IAempty. The 5YSR of IA empty was 93% (95%CI=84-102%). However, in the entire group (N=39) there were only four deaths and the latest event in the five-year period was after 37 months. If 5YSR was defined by the third event occurring just after 60 months, 5YSR was 86% (95%CI=69-103%). There was no significant difference between the 5YSR in stage IA and IA empty (log-rank: Chi²=455; *p*=0.500).

In stage IA, 29% had received chemotherapy; in stage IAempty, 28% had received chemotherapy (Chi²=0.008; *p*=0.929). In stage IA, 35% had lymph node dissection versus 23% in stage IA empty (Chi²=0.270; *p*=0.259).

In case of lymph node resection, 38% in stage IA and 33% in IAempty received chemotherapy (NS).

In the Cox-regression, we adjusted for age, ASA score, PS, histology, tumor grade, adjuvant chemotherapy, omentectomy, lymph node resection and stage (IA vs. IAempty). Stage (IA

Table I. Summary of included patients.

	IA		IAempty		IC1		IC1 (without IAempty)	
	N=464		N=39		N=143		N=104	
Age (years)	Median 59	(Range) (13-93)	Median 61	(Range) (35-95)	Median 60	(Range) (17-95)	Median 60	(Range) (17-85)
Follow-up (months)	Median 46	(Range) (0.4-103)	Median 47	(Range) (2-99)	Median 45	(Range) (2-99)	Median 44	(Range) (4-99)
5-year survival rate% (SE)	% 87	95% CI 83-91	% 93	95% CI 84-102	% 87	95% CI 80-94	% 84	95% CI 76-92
Lymph node resection	N ^c 163	(%) (35%)	N 9	(%) (23%)	N ^c 42	(%) (30%)	N 33	(%) (32%)
Omentectomy	N 391	(%) (85%)	N 33	(%) (85%)	N 126	(%) (89%)	N 93	(%) (90%)
Adjuvant chemotherapy	N ^{*,b} 134	(%) (29%)	N ^{a,b} 11	(%) (28%)	N 71	(%) (50%)	N ^{*,a} 60	(%) (58%)
Histology	N ^{a, c}	(%)	N ^a	(%)	N ^c	(%)	N ^{a, a}	(%)
Serous	108	(23%)	9	(9%)	36	(25%)	27	26%
Mucinous	105	(23%)	18	(46%)	33	(23%)	15	14%
Clear cell	40	(9%)	2	(5%)	23	(16%)	21	20%
Endometrioid	85	(18%)	4	(10%)	24	(17%)	20	19%
Miscellaneous and unknown	126	(27%)	6	(15%)	27	(19%)	21	20%
Grade	N ^{a,c}	(%)	N	(%)	N ^c	(%)	N ^a	(%)
1	206	(44%)	21	(54%)	52	(36%)	31	30%
2	101	(22%)	7	(18%)	35	(25%)	26	27%
3	55	(12%)	4	(10%)	24	(17%)	20	19%
Unknown	102	(22%)	7	(18%)	32	(22%)	25	24%

95%CI, 95% Confidence interval. b: IA vs. IA with controlled emptying. Chi² between collums; $p < 0.05$. *IA vs. IC1 without controlled emptying. Chi² between collums; $p < 0.0001$. ^aChi² between collums; $p < 0.05$. ^aIA with controlled emptying vs. IC1. Chi² between collums; $p < 0.05$. c: IA vs. IC1. Chi² between collums; $p < 0.0001$.

vs. IAempty), tumor grade, histology, ASA and omentectomy were not significantly associated to OS.

Prognosis deteriorated significantly with increasing age, (HR=1.045, 95%CI=1.023-1.067); ($p < 0.0001$), PS (HR=1.946, 95%CI=1.449-2.612); ($p < 0.0001$) and no LNR (HR=1.994, 95%CI=1.019-3.899); ($p = 0.044$).

Patients who did not receive chemotherapy had significantly better prognosis (HR=0.507, 95%CI=0.280-0.918); ($p = 0.025$).

IA plus IAempty vs. IC1 without IAempty. In order to evaluate the impact on survival in stage IC1 by those patients who were upstaged to IC1, only due to emptying of a cyst without obvious spill (IAempty), 39 patients were excluded from IC1 in the analysis and the remaining 104 patients in IC1 were compared to IA, including IAempty.

5YSR for IC1 without IAempty was 84%, 95%CI=76-92%.

The 5YSR for IA + IAempty (87%, 95%CI=83-91%) was unchanged and there was no difference between IA, including IAempty and IC1 without IAempty (Chi²=0.401; $p = 0.527$). The Kaplan-Meier curves for stage IA, IAempty and IC1 are shown in Figure 1.

In a Cox regression adjusting for the same co-factors as above, the re-staging did not have a significant influence on survival (HR=1.191, 95%CI=0.629-2.253); ($p = 0.592$).

Again, increasing age (HR=1.046, 95%CI=1.026-1.066); ($p < 0.0001$), performance status (HR=1.810, 95%CI=1.384-2.366); ($p < 0.0001$) and failure to perform LNR (HR=1.921, 95%CI=1.025-3.601); ($p = 0.042$) remained significantly negatively related to prognosis.

Administration of chemotherapy did not influence the prognosis (HR=0.749, 95%CI=0.431-1.304); ($p = 0.307$).

Survival and lymph node resection. In the above analyses, lymph node resection was significantly associated with improved prognosis in the Cox regression. We, therefore, performed a sub-analysis of stages IA and IC1 with focus on lymph node resection. The Kaplan-Meier curves are shown in Figure 2 and results are summarized in Table II.

Stage IA.

All patients in stage IA were divided according to +/-LNR. Patients who did not have LNR performed had a 5YSR of 85% (95%CI=80-90%). Patients who did have LNR performed had a significantly improved 5YSR of 94% (95%CI=89-99%), $\text{Chi}^2=6.667$; $p=0.010$.

Stage IC1. Patients who did not have LNR performed had a 5YSR of 85% (95%CI=77-93%). With LNR, the 5YSR was 88% (95%CI=72-104%). The difference was not significant ($\text{Chi}^2=1.410$; $p=0.235$). However, among the patients in stage IC1 with LNR, there were only two deaths in 60 months and 11 deaths in the group that did not have LNR performed. The small numbers are prone to reduce statistical accuracy.

Stage IA+IC1. As the 5YSR for stage IA and IC1 were not different, we pooled the two groups. Patients who did not have LNR performed had a 5YSR of 85% (95%CI=81-89%) versus 93% (95%CI=88-98%) among patients with LNR. Again, the difference was highly significant suggesting an important difference between the groups ($\text{Chi}^2=8.123$; $p=0.004$).

+/- Lymph node resection +/- chemotherapy (CT). Next, we analyzed if chemotherapy could compensate for lack of LNR. Again, all patients (Stage IA and IC1) were pooled and we analyzed the 5YSR +/- LNR and +/- CT. Data were available for all but two patients. The results were: (i) +LNR+CT (N=26) (5YSR=93% (95%CI=79-107%)); (ii) -LNR+CT (N=43) (5YSR=90% (95%CI=79-101%)); (iii) -LNR-CT (N=520) (5YSR=87% (95%CI=83-91%)) and (iv) +LNR-CT (N=16) (5YSR=67% (95%CI=62-72%)). In three groups, there were only 1-3 deaths in the 5-year period, making statistical calculations unreliable.

None of the groups were significantly different with p -values for the Kaplan-Meier curves ranging from 0.276-0.844.

Discussion

There were three important findings in the present study: a) Survival in stages IA and IC1 are not different. b) Controlled emptying of a malignant cyst without apparent leaking into the peritoneal cavity does not seem to worsen prognosis. c) Patients who had lymph node resection performed had a significantly better survival. The findings will be discussed in detail below.

Table II. 5YSR in stage IA and IC1 with and without lymph node resection.

Stage +/-LNR	5YSR %	95% CI	p -Value
IA(+LNR)	94	89-99	$\text{Chi}^2=6.667$; $p=0.010$
IA(-LNR)	85	80-90	
IC1(+LNR)	88	72-104	$\text{Chi}^2=1.410$; $p=0.235$
IC1(-LNR)	85	77-93	
IA+IC1(+LNR)	93	88-98	$\text{Chi}^2=8.123$; $p=0.004$
IA+IC1(-LNR)	85	81-89	

5YSR, Five-year survival rate; +/-LNR, with/without lymph node resection; 95% CI, 95% confidence interval; Chi^2 calculated with log-rank-test.

We recently published a study discussing the influence of the 2013-FIGO staging on survival in ovarian cancer. One consequence of the revised staging was introduction of the sub-stages IC1, IC2 and IC3. We found that that IC1 (IA and IB with surgical spill) had a survival similar to stage IA (5). In the present study, we confirmed this observation. However, we also had the possibility to adjust for the possible bias that the high survival in stage IC1 could be due to administration of chemotherapy. Chemotherapy, however, did not have a positive influence on survival. As a matter of fact, in the analysis of Stage IA and IAempty, adjuvant chemotherapy was significantly negatively associated with survival. This may be a statistical random phenomenon and, as this was a retrospective analysis, the results should be interpreted with caution. Nevertheless, they support that adjuvant chemotherapy should only be given in stage IA when randomized controlled trials have shown a benefit.

Whether completely controlled emptying of a cyst without any spillage should be assigned to stage IA or IC1, is a matter of opinion. Some may argue that the emptying is never completely controlled and that contamination of the peritoneum is inevitable. Others may argue that if the consequence is adjuvant chemotherapy, they would rather downstage the patient to IA. In this analysis, we re-staged all those patients who had been assigned to stage IC1 due to controlled cyst emptying without apparent spill and re-named them IAempty.

The 5YSR of IA and IAempty were not different and, in the Cox-regression analysis, stage was not a significant predictor of survival. However, there were only 39 patients in IAempty and very few deaths. This makes the analysis unreliable. It does, nevertheless, indicate that controlled cyst emptying without obvious spill does not dramatically worsen prognosis. Vergote *et al.* (2) and later Paulsen *et al.* (4) showed that cyst rupture in stage I ovarian cancer was correlated to a poorer prognosis. However, rupture is different from controlled emptying due to the -if any- limited volume

Figure 1. 5YSR in stage IA, IAempty and IC1. (a) Kaplan-Meier plot for stage IA vs. IAempty. ($\chi^2=455$; $p=0.500$). (b) Kaplan-Meier plot for stage IA vs. IC1. ($\chi^2=0.016$; $p=0.899$). (c) Kaplan-Meier plot for stage IA with IAempty vs. stage IC1 without IAempty. ($\chi^2=0.401$; $p=0.527$).

of cystic fluid compared to cyst rupture. Thus, we still strongly suggest that all suspicious cysts are removed *in toto*.

This group advocates that any rupture of the cyst surface should be considered as possible leak and, therefore, as IC1. Even though there is no survival difference, a uniform classification is mandatory for comparison of results and benchmarking between centers.

Even when the stage IAempty patients were removed from IC1 and pooled with IA, the 5YSRs did not differ. This shows that stage IC1 (IA and IB with surgical spill) is not measurably worse than stage IA regardless of administration of adjuvant chemotherapy.

Throughout the Cox-regressions described above, we repetitively found LNR to be an independent factor of

improved survival. We, therefore, performed a sub-analysis of stages IA and IC1 concentrating on LNR. For both stages IA and IA+IC1, there was a considerable and significantly improved 5YSR of 9% and 8%, respectively, if the patient had lymph node resection performed. This confirms the 10-year median follow-up data of the ACTION trial, a randomized trial designed to evaluate the benefit of adjuvant chemotherapy in early stage ovarian cancer. In the original trial, complete staging was related to better recurrence-free and overall survival. This was confirmed in the long term follow-up, even in the case of adjuvant chemotherapy (7).

There are three possible explanations for this survival benefit. One is stage migration: Lymph node metastases occur in 14% of cases of presumed stage I-II ovarian cancer

Figure 2. The influence of lymph node resection on 5YSR in stage IA and IC1. (a) The influence of lymph node resection on five-year survival in stage IA. IA+LNR (5YSR=94% (95%CI=89-99%); IA-LNR (5YSR=85% (95%CI=80-90%)), $\chi^2=6.667$; $p=0.010$. (b) The influence of lymph node resection on five-year survival in stage IC1. IC1+LN (5YSR=88% (95%CI=72-104%); IC1-LN (5YSR=85% (95%CI=77-93%)), $\chi^2=1.410$; $p=0.235$. (c) The influence of lymph node resection on five-year survival in stage IA+IC1. IA+IC1+LN (5YSR=93% (95%CI=88-98%); IA+IC1-LN (5YSR=85% (95%CI=81-89%)), $\chi^2=8.123$; $p=0.004$.

(where LNR has been performed) (8) and, obviously, LNR will unveil potential concealed stage IIIA1 patients and, thereby, remove patients with a poorer prognosis to other groups. Indeed, the survival rates for stage IIIA1 patients are significantly worse than for stage IA and IC1. We recently published the effect of the revised FIGO staging of ovarian, peritoneal and fallopian tube cancers on survival (5). Only 16 out of 4,036 patients were re-coded as IIIA1 (previous IIIC only due to lymph node metastases). Follow-up was only available for 49 months and 5YSR could not be calculated. Three-year survival rate was 59% (95%CI=22-96%) and compared to stage IA; HR was 3.57 (95%CI=1.29-9.89), $p=0.014$). This underlines the severity of lymph node metastases and the importance of proper staging.

A second plausible explanation for the effect of LNR is removal of micrometastases in otherwise histologically normal lymph nodes. In one study, micrometastases were detected in 61% of histologically normal lymph nodes from patients in stage I and II ovarian cancer where the presence of micrometastases was correlated with a significantly worsened prognosis. (9)

Finally, it could be assumed that omitting LNR is predominantly done in patients with poor PS and, therefore, an already increased risk of death. However, since LNR at the time of the data collection rarely included full paraaortic LNR and since both PS and LNR were individual factors leading to poor survival, this is unlikely.

Despite that chemotherapy was not associated with improved survival, we analyzed if lack of LNR could be

compensated by chemotherapy. We found no survival effect probably due to quite few patients in each sub-group; thus, no conclusion can be made based on these findings. However, in a recent Dutch study, it was shown that chemotherapy does not compensate for the lack of LNR. The authors analyzed survival in 3,658 patients with stage I-IIA and IIIA1 ovarian cancer in the Netherlands. In 1,813 (50%) of the cases, LNR was performed and these patients had significantly improved outcome, while patients without LNR, who received adjuvant chemotherapy, had a poorer survival compared to patients with LNR without adjuvant chemotherapy (10).

Even though this study is based on prospectively gathered data, there are limitations: The number of patients with cyst emptying is small and a potential harmful effect may not reach significance. Also, 65% of the patients did not undergo lymphadenectomy. Nor did we have any information about the level of the lymphadenectomy. Consequently, the impact of LNR may be even more pronounced on low stages than shown here, as some patients with presumed stage I disease may have occult lymph node metastases resulting in a lower overall survival in the stage I patients. The data are, nevertheless, in that regard comparable to the ICON I study (11) where LNR was not a requirement but on the basis of which adjuvant chemotherapy was initiated in many institutions for early stage ovarian cancer.

Secondly, the procedure for cyst emptying was neither uniform nor recorded -only that no spill occurred- and finally, chemotherapy was recorded as Y/N but the number of series and the administered substances and doses were not available.

Nevertheless, we are able to conclude that stage IA patients with cyst emptying without contamination do not have a poor prognosis compared to stage IA patients. Prognosis is influenced by age, PS and lymph node resection, but not by controlled cyst emptying or adjuvant chemotherapy. Controlled cyst emptying should be avoided due to risk of contamination. However, in case of an unexpected malignancy and positively no contamination, our data do not support administration of chemotherapy to this group of patients. Adjuvant chemotherapy should be administered only to those patients who, in randomized controlled trials, have been shown to benefit from it or in protocolled clinical studies.

Lymph node resection should be performed in early-stage ovarian cancer. Our data show that five-year survival is improved by 9% and 8%, respectively, in case of LNR in stage IA and IC1. Optimal staging is of paramount importance as a significant percentage of the patients may harbor lymph node metastases and, thereby, be occult stage IIIA. Finally, un-sampled lymph nodes may contain otherwise undetected micrometastases that may proliferate and cause progression.

Acknowledgements

The Authors wish to commend all the clinicians who again and again reported these very important prospective data to the database.

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Received August 26, 2016

Revised September 9, 2016

Accepted September 12, 2016