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Prostate Cancer

Metastatic Prostate Cancer Incidence and Prostate-specific Antigen Testing: New Insights from the European Randomized Study of Screening for Prostate Cancer

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Article info

Article history:
Accepted February 27, 2015

Keywords:
Prostate screening
PSA
Metastatic cancer incidence
Mortality reduction

Abstract

Background: The European Randomized Study of Screening for Prostate Cancer (ERSPC) has shown a 21% reduction in prostate cancer (PCa) mortality and a 1.6-fold increase in PCa incidence with prostate-specific antigen (PSA)-based screening (at 13 yr of follow-up). We evaluated PCa incidence by risk category at diagnosis across the study arms to assess the potential impact on PCa mortality.
Design, setting, and participants: Information on arm, centre, T and M stage, Gleason score, serum PSA at diagnosis, age at randomisation, follow-up time, and vital status were extracted from the ERSPC database. Four risk categories at diagnosis were defined: 1, low; 2, intermediate; 3, high; 4, metastatic disease. PSA ($\leq$100 or $>$100 ng/ml) was used as the indicator of metastasis.
Outcome measurements and statistical analysis: Incidence rate ratios (IRRs) for screening versus control arm by risk category at diagnosis and follow-up time were calculated using Poisson regression analysis for seven centres. Follow-up was truncated at 13 yr. Missing data were imputed using chained equations. The analyses were carried out on an intention-to-treat basis.
Results and limitations: In the screening arm, 7408 PCa cases were diagnosed and 6107 in the control arm. The proportion of missing stage, Gleason score, or PSA value was comparable in the two arms (8% vs 10%), but differed among centres. The IRRs were elevated in the screening arm for the low-risk (IRR: 2.14; 95% CI, 2.03–2.25) and intermediate-risk (IRR: 1.24; 95% CI, 1.16–1.34) categories at diagnosis, equal to unity for the high-risk category at diagnosis (IRR: 1.00; 95% CI, 0.89–1.13), and reduced for

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http://dx.doi.org/10.1016/j.eururo.2015.02.042
0302-2838/

metastatic disease at diagnosis (IRR: 0.60; 95% CI, 0.52–0.70). The IRR of metastatic disease had temporal pattern similar to mortality, shifted forwards an average of almost 3 yr, although the mortality reduction was smaller.
Conclusions: The results confirm a reduction in metastatic disease at diagnosis in the screening arm, preceding mortality reduction by almost 3 yr.
Patient summary: The findings of this study indicate that the decrease in metastatic disease at diagnosis is the major determinant of the prostate cancer mortality reduction in the European Randomized study of Screening for Prostate Cancer.

1. Introduction

An update to the European Randomized Study of Screening for Prostate Cancer (ERSPC) has recently confirmed the reduction in prostate cancer (PCa) mortality within the ERSPC screening arm invited to prostate-specific antigen (PSA) testing [1]. The validity of the result has been questioned [2,3] based mainly on the differences in treatment between the arms, ignoring the difference in disease characteristics at presentation [4]. Previous evaluations of treatment and different methods of mortality analysis [5–8], however, have shown that differences in treatment are unlikely to explain the impact of screening on mortality. Nevertheless, detailed analysis of key prognostic features of PCa across the study arms is worthwhile to better understand how the mortality difference has emerged.

In principle [9], assuming that the cancer staging system is consistent for the compared groups, the requirements for an effective screening programme are an ability to produce a stage migration (downstaging) in the screening arm, a stage migration accompanied by a decrease in the incidence of advanced cancers, and a decrease in advanced-stage incidence occurring before a mortality reduction in the screening arm.

Meeting these requirements would not mean that early diagnosis had been the cause (or the only cause) of any observed reduction in mortality; however, if these requirements were not met, it would be unlikely that screening could explain any observed mortality reduction.

A reduction in the risk of diagnosis of metastatic disease in the screening arm of four ERSPC centres was shown in a previous work [10]. That paper addressed the occurrence of metastatic disease both at diagnosis and in the post-treatment follow-up.

In the current study, we present updated results on the stage distribution by arm in seven ERSPC centres. We evaluated whether the aforementioned requirements were met and explored the association of the decrease of advanced-cancer incidence rates (if any) with the reduction in PCa mortality.

2. Materials and methods

The ERSPC is a multicentre, randomised screening trial comparing an intervention arm of men to whom regular PSA screening is offered with those in a control arm to whom such screening is not offered. The trial started in Belgium, The Netherlands, Finland, Sweden, Spain, Italy, Switzerland, and France during the period 1993–1998 [11]. The study methodology has been described in detail previously [12]. Data were obtained by linkage to local cancer registries for PCa incidence and national registries for overall mortality. PCa deaths were ascertained by local, independent, cause-of-death committees [13].

Data on trial arm, centre, T and M stage [14], Gleason score, serum PSA at diagnosis, age at randomisation, follow-up time (until 31 December 2010), and vital status were extracted from the trial database.

We selected men aged 55–69 yr (the core age group), excluding those who died, who were diagnosed with PCa, or who emigrated between randomisation and screening invitation (n = 145). The median follow-up for the two French centres, Herault and Tarn, was 6–7 yr and thus too short for their data to be included in this analysis.

The risk classification adopted in the last ERSPC analysis [1] was used. Four risk categories at diagnosis were defined using information available at diagnosis: low risk (category 1) indicated clinical stage T1–2 and Gleason score $\leq$6; intermediate risk (category 2) indicated T1–2 and Gleason score 7 or T3 and Gleason score $\leq$7; high risk (category 3) indicated T1–3 and Gleason score 8–10 or T4 and any Gleason score; and metastatic disease (category 4) indicated M1 or PSA $>$100 ng/ml. Data on disease progression and metastasis status during the entire period of postdiagnosis follow-up have already been published for those centres for which information was available [10]. In the present analysis, only information on risk category at diagnosis, available for all centres, was considered.

The accuracy of risk category definition was evaluated by a sensitivity analysis, restricting the evaluation of metastasis to M1 cases only.

We imputed missing data for the variables used in defining the risk categories at diagnosis, using multiple imputations by the technique of chained equations (MICE) [15]. Briefly, MICE uses the distribution of observed data to identify a set of plausible values for the missing data by incorporating a random component to reflect the uncertainty of the estimate. Several data sets are generated, and the same analysis is conducted on each data set with the aim of obtaining a set of parameter estimates that are combined in a single overall estimate (computed as the average of the estimates in each simulated data set) with relative standard errors (computed including the between- and within-imputation variance) and confidence intervals (CIs) [16].

For the incomplete variables (T and M stage, Gleason score, and PSA level), we derived imputation models that included the complete variables: arm, centre, vital status, follow-up time, age at randomisation, and interactions between each variable and trial arm. The interactions between each variable and trial arm were included to incorporate potential differences among centres in the mechanism causing the missing data. Ten final data sets were generated after the algorithm converged. In the literature on multiple imputation, three to five imputed data sets are considered adequate [17]. The estimates were combined using Rubin's rules [18]. We conducted a sensitivity analysis

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by imputing directly the risk categories at diagnosis. We used version 12 of the Stata software (StataCorp, College Station, TX, USA).

PCa incidence rate ratios (IRRs) by centre and risk categories at diagnosis were calculated for the screening versus control arms using Poisson regression analysis. Person-years were calculated as time from randomisation to PCa diagnosis, death, or end of follow-up, whichever came first. We adjusted all analyses for the randomisation ratio 1:1.5 for the screening versus control arms in Finland.

Primary analyses were carried out on an intention-to-treat (intention-to-screen) basis (ie, men were included in the analysis in the arm to which they were randomly assigned, regardless of compliance). Moreover, to provide a sensitivity analysis, we split the cumulative occurrence within the screening arm according to screening status, defining subjects who underwent at least the first screening after first invitation, as *attendees*.

Complete case analysis (before missing data imputation) and all-case analysis (after data imputation) are presented.

3. Results

In the core age group, 162 338 men were randomised. The median age at randomisation was 60.2 yr.

With data truncated at 13.0 yr of follow-up, 7408 and 6107 PCa cases were diagnosed in the screening and control arms, respectively. The distribution of missing values was similar in the two arms (8% in the screening and 10% in the control arm); however, for some centres (Belgium, Italy, and Spain), data were missing for between 38% and 77% of cases, and there was an imbalance between the arms of at least 10 percentage points (Table 1).

Imputation did not materially affect the results (Table 2); therefore, the results based on imputed data are shown henceforth.

The IRRs (screening vs control arm) for the low- and intermediate-risk categories at diagnosis were significantly elevated (IRR: 2.14 [95% CI, 2.03–2.25]; and 1.24 [95% CI, 1·16–1·34], respectively); the high-risk category had unity (IRR: 1.00; 95% CI, 0.89–1.13). The IRR was significantly reduced by 40% for the metastatic disease category (IRR: 0.60; 95% CI, 0.52–0.70).

The reduction was even greater when restricting the evaluation to M1 cases only (IRR: 0.50; 95% CI, 0.43–0.57).

The absolute excess in the low-risk category was larger than the deficit of advanced disease: The incidence rate difference (IRD) per 1000 randomised men for the low-risk category was 34.26 (95% CI, 31.99–36.52). The IRD for the intermediate-, high-, and metastatic-risk categories at diagnosis were 4.26 (95% CI, 2.74–5.79), 0.47 (95% CI, −1.09–0.74), and −3.14 (95% CI, −3.93 to −2.35), respectively.

The IRRs (screening vs control arm) for the low- and intermediate-risk categories dropped strongly and consistently with follow-up. The high IRRs in the first 3 yr were associated with the prevalence round and overdiagnosis. There was a sharp decrease of IRR in the high-risk category within the first 6 yr, and a further reduction thereafter as the risk converged with the control arm. A slight decrease of IRR was evident until the ninth year for the metastatic disease category, but afterwards it remained constant (Table 3).

Table 1 – Numbers of randomised subjects and prostate cancer cases (total and by risk category) by centre and arm

Centre	Screening arm							Control arm						
	Randomised men, no.	PCa cases, *n* (%)	Risk category, *n* (%) *					Randomised men	PCa cases, *n* (%)	Risk category, *n* (%) *				
			1	2	3	4	Missing			1	2	3	4	Missing
Netherlands	17 443	2180 (100)	1447 (66)	472 (22)	126 (6)	39 (2)	96 (4)	17 390	1070 (100)	481 (45)	290 (27)	143 (13)	125 (12)	31 (3)
Belgium	4307	417 (100)	85 (20)	28 (7)	10 (2)	14 (3)	280 (67)	4255	321 (100)	25 (8)	5 (2)	8 (2)	11 (3)	272 (85)
Sweden	5901	738 (100)	525 (71)	139 (19)	27 (4)	32 (4)	15 (2)	5951	469 (100)	208 (44)	132 (28)	35 (7)	59 (13)	35 (7)
Finland	31 970	3018 (100)	1822 (60)	761 (25)	269 (9)	149 (5)	17 (1)	48 409	3609 (100)	1619 (45)	1165 (32)	419 (12)	361 (10)	45 (1)
Italy	7266	396 (100)	142 (36)	77 (19)	42 (11)	10 (3)	125 (32)	7251	289 (100)	41 (14)	32 (11)	27 (9)	12 (4)	177 (61)
Spain	1056	87 (100)	40 (46)	15 (17)	4 (5)	2 (2)	26 (30)	1141	52 (100)	9 (17)	9 (17)	3 (6)	3 (6)	28 (54)
Switzerland	4948	572 (100)	381 (67)	133 (23)	41 (7)	6 (1)	11 (2)	4955	297 (100)	160 (54)	78 (26)	32 (11)	15 (5)	12 (4)
Herault **	28 793	1196 (100)	433 (36)	269 (22)	40 (3)	51 (4)	403 (34)	28 869	1094 (100)	377 (34)	241 (22)	33 (3)	47 (4)	396 (36)
Tarn **	10 879	559 (100)	248 (44)	192 (34)	74 (13)	21 (4)	24 (4)	10 470	506 (100)	207 (41)	193 (38)	71 (14)	14 (3)	21 (4)
Total	112 563	9163 (100)	5126 (56)	2086 (23)	633 (7)	324 (4)	997 (11)	128 691	7707 (100)	3127 (41)	2145 (28)	771 (10)	647 (8)	1017 (13)
Total with Herault and Tarn excluded **	72 891	7408 (100)	4442 (60)	1625 (22)	519 (7)	252 (3)	570 (8)	89 352	6107 (100)	2543 (42)	1711 (28)	667 (11)	586 (10)	600 (10)

PCa = prostate cancer.
* 1 = low; 2 = intermediate; 3 = high; 4 = metastatic.
** Herault and Tarn are the centres in France.

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Table 2 – Cumulative incidence rate ratio and 95% confidence intervals by risk category for the original data and after data imputation

Risk Category	Original data					After data imputation		
	Screening		Control		IRR (95% CI)	Screening	Control	IRR (95% CI)
	n	%	*n*	%		%	%	
1: Low risk	4442	60	2543	42	2.29 (2.18–2.42)	65	47	2.14 (2.03–2.25)
2: Intermediate risk	1625	22	1711	28	1.27 (1.18–1.37)	24	30	1.24 (1.16–1.34)
3: High risk	519	7	667	11	1.02 (0.90–1.15)	8	12	1.00 (0.89–1.13)
4: M1 and/or PSA >100 ng/ml risk	252	3	586	10	0.56 (0.48–0.65)	4	11	0.60 (0.52–0.70)
Missing values	570	8	600	10	1.01 (0.90–1.13)	–	–	
Total	7408	100	6107	100	1.56 (1.50–1.62)	100	100	1.56 (1.51–1.62)

CI = confidence interval; PSA = prostate-specific antigen; IRR = rate ratio.

Table 3 – Cumulative incidence rate ratios and 95% confidence intervals by risk category and periods from randomisation after data imputation

Risk category	Time since randomisation, yr, IRR (95% CI)					Time since randomisation, 0–13 yr, IRD (95% CI)
	0–3	0–6	0–9	0–11	0–13	
1: Low risk	3.82 (3.37–4.33)	3.09 (2.86–3.34)	2.56 (2.4–2.72)	2.22 (2.10–2.34)	2.14 (2.03–2.25)	34.26 (31.99–36.52)
2: Intermediate risk	3.15 (2.57–3.87)	2.02 (1.79–2.28)	1.55 (1.42–1.69)	1.35 (1.25–1.47)	1.24 (1.16–1.34)	4.26 (2.74–5.79)
3: High risk	1.74 (1.3–2.34)	1.36 (1.12–1.65)	1.19 (1.02–1.38)	1.07 (0.93–1.22)	1.00 (0.89–1.13)	0.47 (−1.09 to 0.74)
4: M1 and/or PSA >100 ng/ml	0.94 (0.70–1.27)	0.74 (0.60–0.9)	0.63 (0.53–0.74)	0.61 (0.52–0.71)	0.60 (0.52–0.70)	−3.14 (−3.93 to −2.35)
Total	3.07 (2.83–3.34)	2.36 (2.23–2.49)	1.91 (1.83–1.99)	1.66 (1.60–1.72)	1.56 (1.51–1.62)	3.44 (3.16–3.72)

CI = confidence interval; PSA = prostate-specific antigen; IRD = incidence rate difference; IRR = incidence rate ratio.
IRD and 95% CIs per 1000 randomised men.

A sharper contrast was seen between the arms for the entire 13-yr period when only the attendees were used to calculate the IRRs: 2.45 (95% CI, 2.32–2.58) for low-risk, 1.32 (95% CI, 1.23–1.43) for intermediate-risk, 1.00 (95% CI, 0.88–1.14) for high-risk, and 0.45 (95% CI, 0.38–0.53) for metastatic disease at diagnosis.

The reduction in cumulative (0–13 yr) IRRs (screening vs control arm) for metastatic disease at diagnosis (IRR: 0.60) was clear and evident within the first 6 yr of follow-up, whereas the reduction in mortality was smaller (IRR: 0.79) and emerged roughly 3 yr later (Fig. 1).

4. Discussion

In the present study, we examined the incidence rates of PCa by risk category at diagnosis between the two arms of the ERSPC trial.

The net effect in the screening arm was a marked increase of the cumulative incidence of low-risk PCa, along with a significant reduction of cumulative incidence of metastatic disease at diagnosis. A slight increase in the intermediate-risk category and no difference in the high-risk category (with an early excess disappearing by year 10)

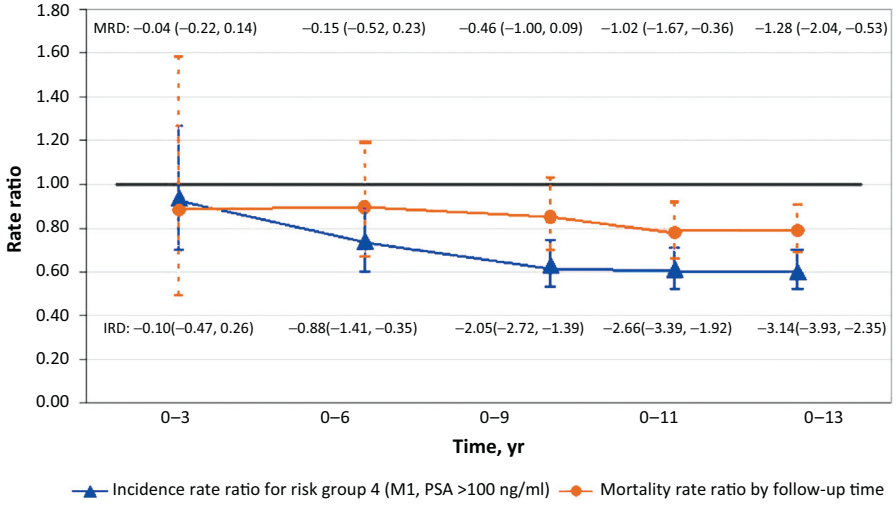

Fig. 1 – Cumulative incidence rate ratios for risk category 4 (after data imputation) and cumulative prostate cancer mortality rate ratio by time since randomisation (95% confidence intervals given in parentheses).
IRD = incidence rate difference per 1000 randomised men; MRD = mortality rate difference per 1000 randomised men.

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were observed. When interpreting these results, we must keep in mind that early detection resulting in a stage migration is expected to increase early disease, with corresponding decreases in advanced disease.

In this study, the reduction found for metastatic disease at diagnosis was not reflected as an excess in the high-risk category, but increased risk was found only in the intermediate- and, above all, the low-risk categories. The absolute excess in the low-risk category was substantially larger than the deficit of advanced disease: The difference reflects the excess of incidence in the screening arm, which was reported in the aforementioned update to the ERSPC trial along with the conclusion that one PCa death is averted for 27 excess cases detected in 13 yr of follow-up [1].

To avoid potential biases due to the imbalance of the proportions of missing data in the two arms and among centres, we used multiple imputation. As the results did not change considerably with imputation, results with imputed data are shown because they are more comprehensive and precise.

The IRRs for the screening versus control arms decreased with follow-up time both overall and for each risk category at diagnosis, though not in a similar fashion. Cumulative incidence for low-risk PCa was three times higher in the screening arm than in the control arm during the first 3 yr of follow-up, and then fell off steadily to an incidence twice as high in the screening arm in the overall period of 13 years. The IRRs for intermediate- and high-risk categories also decreased over time. In contrast, a decrease in the cumulative incidence for the metastatic disease category was not evident in the first 3 yr of follow-up (IRR: 0.94), but thereafter it decreased until the ninth year (IRR: 0.63) and then remained stable.

This pattern was reinforced for those who were attendees (ie, subjects who underwent at least the first screening after first invitation), for example, the IRR (screening vs control arm) for metastatic disease at diagnosis was 0.45. A comparison of attendees with the entire control arm could be biased because of a difference in underlying risk due to selection bias. Nevertheless, such a comparison confirms that PSA-based early diagnosis determined a decrease of metastatic disease at diagnosis.

The current result is consistent with an earlier analysis [10] in showing a reduction in metastatic disease at diagnosis, although the magnitude of effect is slightly smaller in the current analysis, with data from a larger number of centres and longer follow-up and data imputation. In the previous paper, a relative reduction of 50% of metastatic disease at diagnosis was reported (IRR: 0.50; 95% CI, 0.40–0.62).

In the present study, we had no information on disease progression after diagnosis. It is not sufficient for screening to increase detection of early disease; it should affect the course of the disease so that deaths are averted or postponed by early treatment. This requires that there is no compensatory increase in disease progression after diagnosis. In the earlier paper [10], no differences were reported in metastatic disease emerging during the follow-up period (after diagnosis), although a slight but statistically nonsignificant increase was seen in the post-diagnosis incidence of metastasis in the screening arm (IRR: 1.16; 95% CI, 0.9–1.47). The lack of further reduction in development of metastatic disease after diagnosis is not surprising given the higher incidence of low- and intermediate-risk PCa in the screening arm and the lack of any difference in high-risk PCa between the two arms. Hence, a similar occurrence of metastatic disease after diagnosis seems plausible, likely indicating that early diagnosis and treatment could not stop disease progression in all cases. The lack of reduction in incidence of metastasis after diagnosis is in agreement with the smaller reduction of mortality (IRR: 0.79) than in incidence of metastatic PCa (IRR: 0.60).

4.1. Limitations

Two potential limitations regarding the risk categories at diagnosis adopted in the present analysis should be considered. First, we used a rather crude classification, based only on Gleason score and clinical stage, including PSA >100 ng/ml just as a criterion for metastasis. The choice was driven by a need to use the classification used in the last ERSPC analyses [1,19]. Moreover, PSA data for the control arm were incomplete and thus unusable for more precise group definitions. The accuracy of such a definition was evaluated by a sensitivity analysis, and when restricting the evaluation to M1 cases only, the reduction was even higher. The lower value is probably associated with the more complete PSA information in the screening arm. The assumption of consistency in the cancer staging system across the compared groups is plausible in a randomised trial because a similar distribution by stages in the two arms would be expected in the absence of screening. We used the staging assigned by population-based cancer registries. Further information on staging and treatment was recovered from medical records in a nondifferential way for all cases in both arms.

Second, consistency in cancer staging presumably changed over time. Modifications are due to trends in pathology reporting, but we have assumed that this phenomenon did not affect the comparability between arms because there is no reason to suspect it would be differential by study assignment.

5. Conclusions

The present results confirm a stage migration in the screening arm with a 40% reduction in metastatic disease at diagnosis, which preceded a mortality reduction by almost 3 yr. These results strongly suggest that a decrease of metastatic disease at diagnosis is a major determinant of the reduction of PCa mortality in the ERSPC trial, although we cannot exclude additional contributions from other factors.

Author contributions: Marco Zappa had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Buzzoni, Zappa.
Acquisition of data: Auvinen, Roobol, Carlsson, Moss, Puliti, de Koning, Bangma, Denis, Kwiatkowski, Lujan, Nelen, Paez, Randazzo, Rebillard, Tammela, Villers, Hugosson, Schröder.

Analysis and interpretation of data: Buzzoni, Zappa, Auvinen.
Drafting of the manuscript: Buzzoni, Zappa.
Critical revision of the manuscript for important intellectual content: Auvinen, Roobol, Carlsson, Moss, Puliti, de Koning, Bangma, Denis, Kwiatkowski, Lujan, Nelen, Paez, Randazzo, Rebillard, Tammela, Villers, Hugosson, Schröder.
Statistical analysis: Buzzoni, Zappa.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: None.
Other (specify): None.

Financial disclosures: Marco Zappa certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: European Randomized Study of Screening for Prostate Cancer.

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Please cite this article in press as: Buzzoni C, et al. Metastatic Prostate Cancer Incidence and Prostate-specific Antigen Testing: New Insights from the European Randomized Study of Screening for Prostate Cancer. Eur Urol (2015), http://dx.doi.org/10.1016/j.eururo.2015.02.042