

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Lag time for retinoblastoma in the UK revisited: a retrospective analysis
AUTHORS	Posner, Marcus; Jaulim, Adil; Vasalaki, Marina; Rantell, Khadija; Sagoo, Mandeep; Reddy, Ashwin

VERSION 1 - REVIEW

REVIEWER	Carlos Rodriguez-Galindo, MD St. Jude Children's Research Hospital, USA
REVIEW RETURNED	30-Jan-2017

GENERAL COMMENTS	<p>In this report the authors have conducted a retrospective analysis of time to diagnosis of 93 children with a new diagnosis of sporadic retinoblastoma referred to a specialist unit in London over an 8-year period. The time from first signs to evaluation by primary contact and time from primary contact to referral to RB unit were analyzed and compared to a prior similar study conducted in the 1990s. Correlation between time to diagnosis and intraocular disease group was investigated. No correlation was found between lag time and intraocular disease. The authors conclude that tumor biology may be a more important determinant than delayed diagnosis.</p> <p>The manuscript is well written and referenced, and tables are appropriate for the information provided. However, there are several ways in which this manuscript could be improved.</p> <ol style="list-style-type: none">1. In 79.6% of cases leukocoria was the presenting sign. Could the authors please indicate what other presenting signs were included in the assessment? (strabismus, buphthalmos, other). If data on those other presenting signs are available, the authors should consider analyzing potential correlations between presenting sign and lag time.2. The use of digital photographs (particularly as this technology was incorporated into smart phones) dramatically increased during the study period. Did they authors analyze the impact of these new technologies on lag time or patterns of referral?3. Lag time, particularly to first point of care could be influenced by other socioeconomic factors (rural vs, urban residence, poverty level, paternal education, immigrant status, primary language, etc). I would encourage the authors to include those factors in the analysis. Some references of interest: a. Green et al. Correlation of Insurance, Race, and Ethnicity with Pathologic Risk in a Controlled Retinoblastoma Cohort: A Children's Oncology Group Study. <i>Ophthalmology</i> 2016 Aug;123(8):1817-23 b. Truong et al. Ethnic, Racial, and Socioeconomic Disparities in Retinoblastoma. <i>JAMA Pediatr.</i> 2015 Dec;169(12):1096-1044. Please include a separate analysis for unilateral vs bilateral
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	<p>patients</p> <p>5. For patients with advanced intraocular disease (groups D and E), use of adjuvant chemotherapy was used as surrogate marker for risk pathology. However, since criteria for use of chemotherapy could have changed over the study period, the authors should consider analyzing primary pathology data.</p> <p>6. The authors refer to 'high-risk' retinoblastoma throughout the manuscript. This term should be defined properly for clarity.</p> <p>7. The authors conclude that based on the results of their study, there is no longer a correlation between high-risk retinoblastoma and lengthy delay. This is strong statement that I would not advice including since it is not fully supported by the data presented. The association between delayed diagnosis and disease progression is beyond doubt and should not be questioned; while biology may play a role, we should not minimize the impact of an early diagnosis on ocular and patient outcomes (just consider the data from countries with limited resources, where access to primary and specialized care is limited). Lack of correlation between time to referral and intraocular grouping or use of adjuvant chemotherapy, when most patients were diagnosed within a 4-6 week period from first signs would be expected.</p> <p>8. The authors don't touch on screening by primary pediatricians. Most patients were diagnosed with overt leukocoria, thus suggesting that primary screening of light reflex during routine visits had not been properly done (as it is usually the case). This is where early diagnosis and referral could impact outcomes, not when the patient presents with leukocoria and thus the tumor occupies most of the globe</p>
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REVIEWER	Petra Temming Klinik für Kinderheilkunde 3, University Hospital, Essen
REVIEW RETURNED	31-Jan-2017

GENERAL COMMENTS	<p>The authors present a well written study on lag time for retinoblastoma in the UK. The patient numbers with 93 Patients in 9 years is small and does only allow to detect large differences between the groups. This is discussed by the authors as a limitation. Please provide information whether all patients diagnosed between 2006-2014 are included and please present a flowchart how many patients were excluded from the analysis and please provide the reason for exclusion.</p> <p>It is well-known that hereditary and non-hereditary RB have different age at diagnosis. The authors use laterality as a proxy for heritability. To detect differences in lag time, both groups need to be analysed separately or a multivariant analysis is recommended. This is complicated by the small number of patients. Please provide information of laterality for each group in Table 3. Please add " in months" to the title of column 4 in Table 3 . Page 10 line 50: it is possible that the patients number is not sufficient to test for the relationship between age and Lag 2. Please omit the sentence "we did not find this to be the case" or provide patient size calculation. It would be interesting to compare the number of enucleation and adjuvant chemotherapy with the data with Goddard. Please add this data.</p> <p>Add the lack of RB1 genetic analysis and determination of germline mutation to the limitations paragraph.</p>
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REVIEWER	Jesse L. Berry, MD USC Roski Eye Institute and Children's Hospital Los Angeles, University of Southern California.
REVIEW RETURNED	21-Mar-2017

GENERAL COMMENTS	<p>In <i>Lag time for retinoblastoma in the UK revisited: implications of delay in diagnosis</i>, Posner et al. demonstrate that in the UK there is no longer a significant lag time in attaining care for Retinoblastoma patients. In a previous manuscript in the 90s an extended lag time was shown to exist in the UK which predisposes to advanced grouping and greater need to adjuvant chemotherapy after enucleation in this group.</p> <p>The authors classified Lag time in 3 ways</p> <p>Lag time 1: time from parents noting symptoms to first primary health care visit</p> <p>Lag time 2: time from primary health care to first consultation with ophthalmology</p> <p>Lag time 3: time from consultation with ophthalmology to referral to the retinoblastoma unit</p> <p>A total of 93 children between 2006 to 2014 were included in analysis. Ninety percent of these children were diagnosed with a Group D or E as the most advanced eye. There was a noted increase in the recognition of leukocoria by the parents to 79.6% as compared to 52% in the last study period from 1993 to 1996.</p> <p>In terms of lag time, Lag time 1 increased from 2.5 weeks to 4 weeks in the current study period. The overall median lag time 2 decreased in the current study period from 14 days to 3 days however there was a wide range and the majority of this improved time to referral comes from the emergency department and not other general practitioners, some of which fell outside the '2 week rule' of recommended referral for cancer concerns. Lag 3, which was not previously recorded, was 6 days. Most children were expediently referred from an ophthalmologist to a retinoblastoma center. Nearly ¾ of patients were seen within 2 weeks of first presentation to a health care professional and then appropriately referred to a retinoblastoma specialist.</p> <p>The authors conclude that there was no statistical difference between lag times and stage of disease, need for enucleation or</p>
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	<p>need for adjuvant chemotherapy. It appears that this conclusion is being drawn by comparing Group E eyes (48 eyes, lag time 53.3 days) to Group D (35 eyes, 34 days) AND Group C eyes (8 eyes, 46.5 days).</p> <p>Line 13 page 26 suggests that the overall delay to an ophthalmologist is 38 days which does not seem consistent with table 2, Lag time 2 and also seems inconsistent with the statement that nearly $\frac{3}{4}$ of patients were seen by an ophthalmologist within 2 weeks of first presentation to a health care professional. Additionally, it appears that the conclusion regarding lag time is drawn by comparing Group E eyes to the combined Group D + C eyes. I would like to see this comparison between D and E, eyes that have large enough tumors to routinely cause leukocoria. The issue with retinoblastoma screening has always been that it is a rare disease and the first sign comes with large, advanced tumors, thus children are not generally diagnosed with A or B eyes unless there is a family history (or it is the less affected contralateral eye). Further, the authors state that they cannot directly compare Group E eyes, however 90% of the eyes in this study are Group D or E. I would like similarly to know whether or not 90% of eyes in the earlier study period were Group Vb. Sadly, this study seems to suggest what other studies have: that there remains a high initial lag time between parents noticing the first sign of retinoblastoma and attaining health care, despite national parental awareness campaigns. Further, that many of these children are coming into the retinoblastoma center via emergency rooms. I would like to know how many of those children were</p> <p>imaged in the ER suggesting not that general practitioners are now more aware of the signs of retinoblastoma but rather that imaging done in the ER can make a diagnosis of an ocular cancer faster, and more accurately, that red reflex exam.</p> <p>Overall, this is an important paper and an issue many ocular oncologists, patient advocacy groups and parents struggle with. However, currently the conclusions need to be more directly compared between D and E eyes, and compared to advanced eyes in the previous study period. Without the data, I would surmise that nearly 90% of eyes in the last study period were similarly advanced Reese-Ellsworth grouping suggesting that these small changes in lag time (an increase in 1.5 weeks in Lag time 1, and a decrease in 11 days in Lag time 2) have not been sufficiently good or bad to effect outcomes in this disease.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Carlos Rodriguez-Galindo, MD

Institution and Country: St. Jude Children's Research Hospital, USA

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

In this report the authors have conducted a retrospective analysis of time to diagnosis of 93 children with a new diagnosis of sporadic retinoblastoma referred to a specialist unit in London over an 8-year period. The time from first signs to evaluation by primary contact and time from primary contact to referral to RB unit were analyzed and compared to a prior similar study conducted in the 1990s. Correlation between time to diagnosis and intraocular disease group was investigated. No correlation was found between lag time and intraocular disease. The authors conclude that tumor biology may be a more important determinant than delayed diagnosis.

The manuscript is well written and referenced, and tables are appropriate for the information provided. However, there are several ways in which this manuscript could be improved.

1. In 79.6% of cases leukocoria was the presenting sign. Could the authors please indicate what other presenting signs were included in the assessment? (strabismus, buphthalmos, other). If data on those other presenting signs are available, the authors should consider analyzing potential correlations between presenting sign and lag time.

This is a very interesting point and I thank the reviewer for bringing this to our attention. We agree that presenting signs may be relevant. The second most common sign is squint or strabismus. In order to determine if strabismus is present or not an assessment by an orthoptist at presentation to the retinoblastoma unit is essential. We are aware in paediatric ophthalmology clinics that parents note strabismus in infants yet when assessed by an orthoptist, many patients (over 90%) do not in fact have strabismus. As a result, an orthoptist assessment is essential for meaningful results. Due to these concerns, we concentrated on the white reflex and we were interested if the awareness campaigns which are directed primarily for this presenting feature was having an effect. This is mentioned in the limitations below.

'We were interested in leukocoria as a presenting sign as health education programmes have been directed towards this feature. We felt that squint would require an assessment by an orthoptist at presentation and we did not have this robust evaluation for all our patients.'

We would like to address the reviewer's concerns in a separate paper.

2. The use of digital photographs (particularly as this technology was incorporated into smart phones) dramatically increased during the study period. Did they authors analyze the impact of these new technologies on lag time or patterns of referral?

During the recruitment period, smart phones were in use compared with the earlier study in the 1990s. We have published on the high false positive rate that can occur with assessments of children for the white reflex (Muen et al 2010). We did not specifically analyse a white reflex on photography versus naked eye but we have emphasised this in the limitations section.

3. Lag time, particularly to first point of care could be influenced by other socioeconomic factors (rural vs, urban residence, poverty level, paternal education, immigrant status, primary language, etc). I would encourage the authors to include those factors in the analysis. Some references of interest:

a. Green et al. Correlation of Insurance, Race, and Ethnicity with Pathologic Risk in a Controlled Retinoblastoma Cohort: A Children's Oncology Group Study. *Ophthalmology* 2016 Aug;123(8):1817-23

b. Truong et al. Ethnic, Racial, and Socioeconomic Disparities in Retinoblastoma. *JAMA Pediatr.* 2015

We thank the reviewer for pointing this out as we have unpublished work in this area. We originally examined a cohort of patients for SES and ethnicity in 2009 and presented this as a poster at the American Academy of Ophthalmology in 2010. The results showed that of 119 patients from both centres in the UK (median age 15.9 months), 32 were from group B & C(27%), 44 from group D (37%) and 43 from group E (36%). After adjustment for ethnicity and laterality, we could not find a strong association between low SES and advanced Groups. Ethnicity was not found to be associated with severity of RB, but the numbers in the minority ethnic groups were small. This poster won the poster prize at the Academy in 2010.

Like Green et al and Truong et al we used postcodes (ZIP codes in US) as a crude measure of SES. We feel that an individual family based questionnaire may give a more accurate understanding of this complex issue.

Green et al 2016 used tumor invasiveness on histopathology as a proxy for measuring the lag time to diagnosis. Kalliki et al 2015 demonstrated that 7% of patients are seen over 6 months from symptom onset and yet still do not show tumor invasiveness. Of 10 patients who presented over 6 months, only 1 required adjuvant chemotherapy and 5 had Group D eyes. Our study adds to the understanding that retinoblastoma is complex and there is no linear correlation between lag time and advanced disease (Group E and high Rb) in countries where the majority of patients present within 6 months.

We have added a paragraph in limitations and mentioned our unpublished work.

4. Please include a separate analysis for unilateral vs bilateral patients

Thank you. We have addressed this in a separate paragraph (Results) and analysed the results.

5. For patients with advanced intraocular disease (groups D and E), use of adjuvant chemotherapy was used as surrogate marker for risk pathology. However, since criteria for use of chemotherapy could have changed over the study period, the authors should consider analyzing primary pathology data.

The pathological risk factors are the same as the 1990s and we have added the criteria to the methods to make this explicit. The Goddard paper used anterior chamber seeds, scleral invasion, massive choroidal or retrolaminar optic nerve invasion for adjuvant therapy and we used the same.

6. The authors refer to 'high-risk' retinoblastoma throughout the manuscript. This term should be defined properly for clarity.

We thank the reviewer and have made this explicit in the methods section.

7. The authors conclude that based on the results of their study, there is no longer a correlation between high-risk retinoblastoma and lengthy delay. This is strong statement that I would not advice including since it is not fully supported by the data presented. The association between delayed diagnosis and disease progression is beyond doubt and should not be questioned; while biology may play a role, we should not minimize the impact of an early diagnosis on ocular and patient outcomes (just consider the data from countries with limited resources, where access to primary and specialized care is limited). Lack of correlation between time to referral and intraocular grouping or use of adjuvant chemotherapy, when most patients were diagnosed within a 4-6 week period from first signs would be expected.

We agree with the reviewer. We have already emphasised that in resource poor countries delay in diagnosis can be associated with mortality in the introduction and discussion. Kalliki et al 2015 has shown that a greater than 6 months duration of symptoms is associated with high risk Rb.

Surprisingly, only 21% of patients with high risk Rb had a duration of over 6 months which suggests other factors are at play.

We did not find an association with lag time and this may be related to the fact that very few of our patients had lag times of greater than 6 months. This is in keeping with current knowledge and emphasises the current situation in the UK.

We have emphasised that the work is specific to the UK (rather than other countries) in the conclusion of the abstract:

'Lag time no longer correlates with high risk retinoblastoma in the UK.'

In the conclusion we also have stated,

'It has been shown that in countries with high mortality from Rb, an increased lag time is associated with death.'

8. The authors don't touch on screening by primary pediatricians. Most patients were diagnosed with overt leukocoria, thus suggesting that primary screening of light reflex during routine visits had not been properly done (as it is usually the case). This is where early diagnosis and referral could impact outcomes, not when the patient presents with leukocoria and thus the tumor occupies most of the globe

The reviewer works in the US and does not understand the nature of screening by paediatricians in the UK. In the UK, screening takes place at birth (paediatricians) and 6 weeks (GPs) only as previously mentioned in limitations. This is primarily to detect cataracts. In order to see a paediatrician, the child needs to be referred by a GP (Family Practitioner). The vast majority of patients are not referred for RB to their paediatrician (only 2 of our patients were seen by a paediatrician as described in results). As a result, screening does not take place beyond the newborns by paediatricians in the UK.

Reviewer: 2

Reviewer Name: Petra Temming

Institution and Country: Klinik für Kinderheilkunde 3, University Hospital, Essen

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

The authors present a well written study on lag time for retinoblastoma in the UK. The patient numbers with 93 Patients in 9 years is small and does only allow to detect large differences between the groups. This is discussed by the authors as a limitation. Please provide information whether all patients diagnosed between 2006-2014 are included and please present a flowchart how many patients were excluded from the analysis and please provide the reason for exclusion.

We thank the reviewer for her comments. We have added to the methods that 213 patients presented between 2006 and 2014 and 120 were excluded due to screening of tumours due to family history and lack of data regarding Lag 1 or Lag 2.

It is well-known that hereditary and non-hereditary RB have different age at diagnosis. The authors use laterality as a proxy for heritability. To detect differences in lag time, both groups need to be analysed separately or a multivariate analysis is recommended. This is complicated by the small number of patients. Please provide information of laterality for each group in Table

We have included unilateral and bilateral cases in our analysis (Table 3) and added a paragraph to show the results of the analysis.

3. Please add " in months" to the title of column 4 in Table 3 .

We have changed from days to months

Page 10 line 50: it is possible that the patients number is not sufficient to test for the relationship between age and Lag 2. Please omit the sentence "we did not find this to be the case" or provide patient size calculation.

We have detailed the statistical analysis in the sentence 'There was no correlation between age and lag 2 in our sample population (spearman rank coefficient 0.06, $p=0.64$).' We have removed 'we did not find this to be the case'

It would be interesting to compare the number of enucleation and adjuvant chemotherapy with the data with Goddard. Please add this data.

This is a very important point that we thank the Reviewer for bringing to our attention. We have added the following paragraph in our discussion to address this.

'A gradual shift away from primary enucleation is also recognized in this comparison with the 1990s. We present figures showing that there has been a statistically significant reduction of primary enucleation in patients presenting with sporadic disease compared with a decade earlier. Although less primary enucleations are performed, a higher proportion have high risk Rb (29% vs 15%). This suggests that the service is avoiding enucleation in patients that the examining ophthalmologists (MAR and MSS) consider low risk for metastasis without increasing mortality¹⁰.'

Add the lack of RB1 genetic analysis and determination of germline mutation to the limitations paragraph.

We have added to the limitations

'Another limitation is the lack of RB1 genetic data for each patient. Heritable Rb has an earlier age of onset compared to non-heritable RB and it may be relevant to the lag time of sporadic cases.'

Reviewer: 3

Reviewer Name: Jesse L. Berry, MD

Institution and Country: USC Roski Eye Institute and Children's Hospital Los Angeles, University of Southern California.

Please state any competing interests or state 'None declared': none

In Lag time for retinoblastoma in the UK revisited: implications of delay in diagnosis, Posner et al. demonstrate that in the UK there is no longer a significant lag time in attaining care for Retinoblastoma patients. In a previous manuscript in the 90s an extended lag time was shown to exist in the UK which predisposes to advanced grouping and greater need to adjuvant chemotherapy after enucleation in this group.

The authors classified Lag time in 3 ways

Lag time 1: time from parents noting symptoms to first primary health care visit

Lag time 2: time from primary health care to first consultation with ophthalmology

Lag time 3: time from consultation with ophthalmology to referral to the retinoblastoma unit

A total of 93 children between 2006 to 2014 were included in analysis. Ninety percent of these children were diagnosed with a Group D or E as the most advanced eye. There was a noted increase in the recognition of leukocoria by the parents to 79.6% as compared to 52% in the last study period from 1993 to 1996.

In terms of lag time, Lag time 1 increased from 2.5 weeks to 4 weeks in the current study period. The overall median lag time 2 decreased in the current study period from 14 days to 3 days however there was a wide range and the majority of this improved time to referral comes from the emergency department and not other general practitioners, some of which fell outside the '2 week rule' of recommended referral for cancer concerns. Lag 3, which was not previously recorded, was 6 days. Most children were expediently referred from an ophthalmologist to a retinoblastoma center. Nearly 3/4 of patients were seen within 2 weeks of first presentation to a health care professional and then appropriately referred to a retinoblastoma specialist.

The authors conclude that there was no statistical difference between lag times and

stage of disease, need for enucleation or need for adjuvant chemotherapy. It appears that this conclusion is being drawn by comparing Group E eyes (48 eyes, lag time 53.3 days) to Group D (35 eyes, 34 days) AND Group C eyes (8 eyes, 46.5 days).

Line 13 page 26 suggests that the overall delay to an ophthalmologist is 38 days which does not seem consistent with table 2, Lag time 2 and also seems inconsistent with the statement that nearly 3/4 of patients were seen by an ophthalmologist within 2 weeks of first presentation to a health care professional.

The figure of 38 days is from first symptoms to diagnosis by an RB specialist. This incorporates lag 1 (parental delay – median time 28 days), lag 2 (practitioner delay) and referral from ophthalmologist to RB specialist, lag 3.

Additionally, it appears that the conclusion regarding lag time is drawn by comparing Group E eyes to the combined Group D + C eyes. I would like to see this comparison between D and E, eyes that have large enough tumors to routinely cause leukocoria. The issue with retinoblastoma screening has always been that it is a rare disease and the first sign comes with large, advanced tumors, thus children are not generally diagnosed with A or B eyes unless there is a family history (or it is the less affected contralateral eye).

We agree that D eyes are advanced yet many units including ourselves are salvaging D eyes (63% Fabian et al BJO 2017) with 50% having better than 20/200 vision (Fabian et al AJO 2017 accepted). Of interest, there was no difference between lag time for enucleation compared to primary chemotherapy.

This is in comparison with E eyes that have primary enucleation more often.

We emphasised E eyes as the current literature (Wallach et al 2006) stated that greater than 6 months delay is associated with an increased risk. As 52% of our children had group E eyes, we felt concentrating on E eyes was valid. Unfortunately, we had very few Group C eyes in this study so comparing Groups D+E (83) with Group C (8) was difficult and we acknowledge this in the Results and Discussion.

We have added

‘There were too few C eyes to provide accurate comparison between large tumours (Groups D and E) and Group C.’

Further, the authors state that they cannot directly compare

Group E eyes, however 90% of the eyes in this study are Group D or E. I would like similarly to know whether or not 90% of eyes in the earlier study period were Group Vb.

Unfortunately, the grouping was not described in Goddard et al 1999 so it is difficult to compare the original study with ours in this respect. We have emphasised this limitation. Wallach et al emphasised Group E eyes and for this reason we concentrated on this group.

Sadly, this study seems to suggest what other studies have: that there remains a high initial lag time between parents noticing the first sign of retinoblastoma and attaining health care, despite national parental awareness campaigns. Further, that many of these children are coming into the retinoblastoma center via emergency rooms. I would like to know how many of those children were imaged in the ER suggesting not that general practitioners are now more aware of the signs of retinoblastoma but rather that imaging done in the ER can make a diagnosis of an ocular cancer faster, and more accurately, than red reflex exam.

The US and UK are different in this respect. In the UK as soon as a child enters ER the ER doctor contacts the on-call ophthalmology team who will then see the child either then or in the next ophthalmology clinic. Ultrasounds and MRI scans will not be performed in ER. Ultrasounds are sometimes performed by local ophthalmologists but a MRI scan is never organised.

Overall, this is an important paper and an issue many ocular oncologists, patient advocacy groups and parents struggle with. However, currently the conclusions need to be more directly compared between D and E eyes, and compared to advanced eyes in the previous study period. Without the data, I would surmise that nearly 90% of eyes in the last study period were similarly advanced Reese-Ellsworth grouping suggesting that these small changes in lag time (an increase in 1.5 weeks in Lag time 1, and a decrease in 11 days in Lag time 2) have not been sufficiently good or bad to effect outcomes in this disease.

We agree that the changes have been small and emphasise this in the conclusion, but this study adds to the body of evidence that high risk Rb can still occur despite delays in diagnosis of less than 6 months.

In the UK, we have very few patients with a lag time more than 6 months. This reduces the chance of E eyes (Wallach et al 2006) and high risk Rb (Kalliki et al 2015) yet these conditions are still present. In the 1990s, the median age for high risk Rb was at least 27 weeks (no Lag 3 recorded) for 12 patients who received adjuvant chemotherapy and we can state that the high risk Rb we are seeing is probably attributable to ocular biology rather than delay in diagnosis. Although we had only 10 patients with a lag time greater than 6 months, only 1 required adjuvant chemotherapy and 5 had group D eyes. These numbers are small but adds to the body of evidence stating that there is not a linear relationship between lag time and advanced RB in countries where the majority of patients are seen within 6 months of signs.

We would like the scientific community to be aware that disease progression is not always linear and we may have reached in the UK a plateau where tumour biology is the more important determinant.

VERSION 2 – REVIEW

REVIEWER	Carlos Rodriguez-Galindo St. Jude Children's Research Hospital Memphis, TN (US)
REVIEW RETURNED	14-May-2017

GENERAL COMMENTS	Thanks for addressing the comments raised in my first review. There is one minor comment that the authors could consider addressing. As i understand from the response to my comments, the UK system does not seek to reinforce ocular health screening during the first 2 years of life. Since most patients presented with leukocoria, meaning that the disease is occupying > 50% of the ocular chamber, and the authors conclude that within the 6 month lag time there are no correlations between diagnosis time and outcome, i wonder if a next step to improving ocular outcomes (vision and ocular survival) would be lowering intraocular stage (group) through dedicated screening. Please consider commenting this in the discussion.
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REVIEWER	Petra Temming Pediatric oncology, University Hospital Essen, Germany
REVIEW RETURNED	26-May-2017

GENERAL COMMENTS	The authors present a retrospective analysis of the lag time in 93 patients presenting with sporadic retinoblastoma in the UK between 2006 -2014. The manuscript is well written and appropriately referenced. The results are presented clearly and statistical
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	analyses are completely described and appropriate for the study question. The tables summarize the results adequately. All comments of the reviewers have been addressed. I have no further recommendations to improve the manuscript.
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REVIEWER	Jesse L. Berry, MD USC and CHLA, Los Angeles California
REVIEW RETURNED	09-May-2017

GENERAL COMMENTS	I had requested a review of D v E (instead of D+C v E) and not D+E v C -- that being said the authors have satisfactorily answered by reviews.
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VERSION 2 – AUTHOR RESPONSE

We would like to thank all 3 reviewers for their constructive comments. This has certainly improved the paper.

Reviewer 3. In the previous version: results, subsection Stage, it is stated: 'There was no statistically significant difference between lag 1 in patients presenting with stage D and stage E disease (p=0.56).'

Reviewer 1. We have addressed universal screening in the UK in the previous version. We have added a sentence about universal screening after 6 weeks and referenced 2 papers that show that lowering intraocular stage can only be performed by an ophthalmologist under general anaesthetic. This is not cost effective in a socialised health service. We have added 'Detecting early stage Rb (eg Groups A, B and early Group C) can only be performed by ophthalmologists(14, 15) with children under anaesthesia (as for screening for children with genetic mutations) which is why universal screening after 6 weeks is not cost effective and not performed in the UK.'

VERSION 3 – REVIEW

REVIEWER	Carlos Rodriguez-Galindo St. Jude Children's Research Hospital
REVIEW RETURNED	05-Jun-2017

GENERAL COMMENTS	No further comments
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