Analysis of dose to the macula, optic disc, and lens in relation to vision toxicities – A retrospective study using COMS eye plaques

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ABSTRACT

Purpose: The aim of this study was to relate common toxicity endpoints with dose to the macula, optic disc, and lens for uveal melanoma patients treated with Iodine-125 Collaborative Ocular Melanoma Study (COMS) eye plaque brachytherapy.

Methods: A cohort of 52 patients treated at a single institution between 2005 and 2019 were retrospectively reviewed. Demographics, dosimetry, and clinical outcomes were recorded. Univariate, relative risk, and Kaplan-Meier analyses were performed to relate dose to toxicity endpoints including retinopathy, vision decline, and cataracts.

Results: By the end of follow up (Median = 3.6 years, Range = 0.4 – 13.5 years), 65% of eyes sustained radiation retinopathy, 40% demonstrated moderate vision decline (>5 Snellen lines lost), and 56% developed cataracts. Significant (p < 0.05) risk estimates exist for retinopathy and VA decline for doses >52 Gy to the macula and >42 Gy to the optic disc. Moreover, dose to the lens >16 Gy showed a significant risk for cataract formation. Kaplan-Meier analysis demonstrated significantly different incidence of radiation retinopathy for > 52 Gy to the macula and >42 Gy to the optic disc. In addition, the Kaplan-Meier analysis showed significantly different incidence of cataract formation for patients with lens dose > 16 Gy.

Conclusions: Dose-effect relationships exist for the macula and optic disc with respect to the loss of visual acuity and the development of retinopathy. To better preserve vision after treatment, further research is needed to reduce macula, optic disc, and lens doses while maintaining tumor control.

INTRODUCTION

Uveal melanoma is a rare malignancy with a diagnosis rate of one per 5.1 million worldwide [1,2]. Eye plaque brachytherapy is a common treatment approach, with a variety of plaque manufacturers. Modern plaques utilize low energy photon-emitting seeds such as Iodine-125 (125I), Palladium-103 (103Pd), and Cesium-131 (131Cs) or beta particle-emitting plaques including Ruthenium-106 (106Ru) and Strontium-90 (90Sr) [3]. The COMS group standardized the 125I and 103Pd eye plaque apparatus and technique along with radioactive seed loading. The original studies found no significant difference in survival between eye plaque and enucleation groups for medium-sized tumors [2,4]. While tumor control rates are excellent, high doses may be received by normal tissues including the sclera, lens, optic nerve, and macula.

External beam radiation therapy has established dose recommendations for tissues such as the optic nerve and lens, but these recommendations are not directly transferable to low dose rate (LDR) sources. Some LDR eye plaque studies have identified elevated risk for scleral necrosis and cataract formation likely to occur at 400 Gy to the sclera and 15 Gy to the lens, respectively [5,6]. Currently no recommended maximum dose exists for the macula or optic disc in LDR brachytherapy, and limited dose reduction strategies are available to avoid toxicity. AAPM Task Group 129 stated a need for research to reduce the irradiation of ocular structures and emphasized this gap in information [7]. While developing an intracocular shielding method for patients, the authors found that with no maximum dose recommendation, the extent of necessary shielding is unknown. It is hypothesized to use a high-Z ferromagnetic fluid in the eye, which would strongly attenuate low-

Abbreviations: COMS, Collaborative Ocular Melanoma Study; VA, Visual Acuity; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval; OAR, Organ at Risk; AAPM, American Association of Physicists in Medicine.

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energy $^{125}$I photons ($E_{\text{avg}} = 28$ keV). However, without the necessary dose limit, the amount of fluid required for adequate dose reduction is unknown.

The historical standard of care for treatment had been enucleation prior to introduction of eye plaque brachytherapy in 1980 [4,8,9]. In 1995 the COMS group reported similar survival outcomes in patients treated with eye plaques compared to enucleation, making brachytherapy an appealing option for patients to retain their eye [2,4,10,11]. Enucleation continues to be used for patients with large tumor volumes (>8 mm thickness), and blind or painful eyes. Based on eligibility, affordability, cosmetic appeal, and favorable treatment outcome, plaque brachytherapy is currently the primary treatment method for medium-size uveal melanoma (3.1–8.0 mm thickness), as opposed to external beam therapy [12].

A wide range of reported toxicity and incidence rates for plaque brachytherapy exist across institutional studies with radiation retinopathy rates extending from 20 to 74 %, and cataract rates varying from 15 to 68 % [6,10,13–15]. Multivariate models have indicated that patient age, smoking status, and preexisting medical conditions as well as tumor apex, height, tumor basal diameter, have a statistically significant impact on patient outcome and toxicities [2,4,9]. Based on COMS reports, 49 % of eyes experienced vision loss within three years, and 68 % within 10 years [2,9,10]. In addition, 45 % of patients qualified as blind (20/200 or worse) by three years post-treatment [2].

While incidence of toxicity is commonly described, $^{125}$I plaque treatment for uveal melanoma from 2005 to 2019 were retrospectively reviewed. Patients with more than five months of follow up data were excluded. Demographics recorded include age, body mass index (BMI), sex, smoking status, and eye laterality. Best corrected visual acuity (VA) of the treated eye before therapy was documented as baseline in addition to preexisting conditions (macular degeneration, glaucoma, vitreous detachment, cataracts). Six patients who had previously undergone a lens replacement were not included in the lens dose or cataract data.

Change in VA, as well as the onset of radiation retinopathy, cataracts, glaucoma, macular degeneration, or vitreous detachment, were collected from each follow-up appointment with the ophthalmologist. Change in vision was calculated as the difference between the baseline and follow up VA. ‘Mild VA Decline’ was defined as one to five Snellen lines lost since plaque insertion date, and ‘Moderate VA Decline’ was a loss of six or more Snellen lines to be consistent with previous COMS reporting metrics [2]. In the United States the legal definition of blind is VA of 20/200 or worse [26]. Therefore, in this study, VA better than 20/200 before treatment that fell below 20/200 was considered blind. A single time-to-event was recorded as the time elapsed between the insertion date and the event. In this study we did not distinguish between maculopathy and retinopathy.

The treatment planning process follows recommendations in the COMS Manual of Procedures [27]. The ophthalmologist took fundus photographs and an ultrasound. From the fundus images the following measurements were recorded based on formulas described in the COMS documentation: macula to tumor margin (MT), disc to tumor margin (DT), and base dimension of tumor [27,28]. The ultrasound determines the tumor height. These measurements were used to identify locations of tumor apex, and organs at risk (OAR) including the optic disc, inner sclera, lens center, macula, and opposite retina relative to the origin and seed placement in the plaque coordinate system. The plaque coordinate system used was originally proposed by Kline et al. for the original COMS trials [28].

A Kolmogorov-Smirnov normality test was performed to ensure that dose or short distance to a structure will induce normal tissue toxicity.

### Statistical analysis

To evaluate dose and related toxicities, a sequence of tests were performed including a univariate analysis (t-test), relative risk (RR) analysis, and Kaplan-Meier hazard ratios. Each test was performed hypothesizing that dose or short distance to a structure will induce normal tissue toxicity.

### Univariate analysis

A Kolmogorov-Smirnov normality test was performed to ensure that data is normally distributed, and parametric analyses were appropriate. Toxicity endpoints included radiation retinopathy, moderate VA decline, onset of blindness, and cataract formation. A two-sample t-test was performed among groups experiencing, or not experiencing each toxicity. The analysis was performed for all continuous independent variables (age, BMI, plaque size, tumor height, OAR dose, OAR distance) and their relationship with dependent variables (toxicities). A chi-square test was performed for categorical variables (sex, smoking history, eye laterality) and their relationship with dependent variables. Additionally, incidence rates were provided for doses above and below each structure’s median dose to align with reported QUANTEC dose and incidence rates commonly used in external beam therapy [31].

A p-value ≤ 0.05 was used to determine statistical significance. To correct for confounding variables (preexisting conditions), sensitivity tests were conducted by repeating the analysis minus patients with preexisting conditions. A p-value adjustment was not desirable for this data due to the exploratory nature of the study [32].

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**References**

1. **Subjects & data collection**

Upon receiving IRB approval, patients who received $^{125}$I plaque treatment for uveal melanoma from 2005 to 2019 were retrospectively reviewed. Patients with more than five months of follow up data were excluded. Demographics recorded include age, body mass index (BMI), sex, smoking status, and eye laterality. Best corrected visual acuity (VA) of the treated eye before therapy was documented as baseline in addition to preexisting conditions (macular degeneration, glaucoma, vitreous detachment, cataracts). Six patients who had...
Relative risk

A RR analysis was estimated for each toxicity endpoint based on associated independent variables (dose and distance to the OAR, age, BMI, and tumor size characteristics). Continuous variables were divided into equal groups using the median. For example, the median dose to the macula was 52 Gy, therefore RR was evaluated for groups receiving greater than or less than 52 Gy to the macula. Dichotomous variables were divided into two respective groups. If the resulting RR and 95% CI is > 1.0, a significant (p ≤ 0.05) risk exists. Confounding preexisting conditions were again determined with sensitivity tests.

Kaplan-Meier analysis and hazard ratios

For variables and endpoints with significant RR estimates, Kaplan-Meier cumulative incidence curves were utilized to identify toxicity differences over time between high or low doses to the OAR. A single time point (years since treatment) was used to define the diagnosed event for each patient. The continuous variables were again divided into equal groups using the median. Upon death or lost contact, patients were censored. A log-rank test and hazard ratio (HR) were evaluated for each Kaplan-Meier analysis to evaluate significant difference in survival over time.

Univariate, chi-square, relative risk, and Kaplan-Meier statistical analyses were performed in Microsoft Excel (version 2205) using the Data Analysis toolkit and the StatPlus add on (version 7.6.5.0, AnalystSoft Inc.).

Results

Demographics & treatment outcomes

From 2004 to 2019, 52 patients undergoing 125I eye plaque brachytherapy met selection criteria and were included in the study (Table 1). Patients were excluded due to lack of follow up time, and two patients were excluded as they underwent enucleation. Median, maximum, and minimum dose and distances to OARs in the patient population can be found in Table 2.

The average follow-up time was 4.0 (range 0.4–13.5) years, 85% (44/52) of treated eyes had at least a mild change in vision, 40% (21/52) experienced moderate VA decline, and 31% (16/52) did not have clinically useful vision (blind) at time of the last follow up. Moreover, 65% (34/52) experienced radiation retinopathy, and 65% (29/52) experienced moderate VA decline, and 31% (16/52) did not have clinically useful vision (blind) at time of the last follow up. At 1-, 2-, and 3 years of follow up radiation retinopathy was experienced by 28, 33, and 57% of patients. The median time to development of retinopathy was 2.4 years, and time to moderate VA decline was 4.1 years. Cumulative incidence curves illustrate the increasing rates of radiation retinopathy and moderate VA decline over time (Fig. 1). No eyes experienced scleral necrosis. The vision outcome rates of patients receiving above or below the median dose are reported (Table 4).

Univariate analysis

The presence of radiation retinopathy was significantly related to increasing dose to the macula (Dmacula) and the optic disc (DOD) (Table 5). After adjusting for confounding variables, moderate VA decline was related to DOD. In addition, cataract formation was significantly related to the lens dose (DLens). The proximity of the macula and optic disc to the tumor also predicted radiation retinopathy. Additionally, age was related to incidence of retinopathy. All categorical variables (sex, smoking status, eye laterality) were not significantly related to outcomes including retinopathy, VA decline, onset of blindness, or cataract formation.

Relative risk

Dmacula > 52 Gy and DOD > 42 Gy pose significant RR for retinopathy, VA decline, and blindness (Table 6). DLens > 16 Gy had a RR for cataract formation. Male patients had a significant risk radiation retinopathy and onset of blindness compared to females, while increased BMI showed an increased risk of moderate VA decline.

Kaplan-Meier curves and hazard ratios

Median Dmacula (52 Gy), DOD (42 Gy), and DLens (16 Gy) were again used to differentiate high vs low dose groups for survival curves. The
results showed that over time there was higher incidence of retinopathy with both $D_{\text{macula}} > 52$ Gy and $D_{\text{OD}} > 42$ Gy (Fig. 2). Respective HRs were 2.81 and 2.04 for high vs low dose groups (Fig. 2). High lens dose of $> 16$ Gy had significantly different survival, and a HR of 2.59 compared to low dose.

Discussion

We evaluated relationships between dose to ocular structures and common normal tissue toxicities from $^{125i}$ eye plaque brachytherapy. The cumulative proportion of patients experiencing toxicity increased over time. Increasing dose to the macula and optic disc showed significant relative risk for all outcomes - retinopathy, moderate VA decline, onset of blindness. Increasing dose to the lens had significant relative risk with cataracts. The most prominent relationships had significant log-rank tests and hazard ratios, indicating that incidence rates were significantly different throughout the follow up duration. This included $D_{\text{macula}} > 52$ Gy and $D_{\text{OD}} > 42$ Gy related to retinopathy, and $D_{\text{lens}} > 16$ Gy related to cataract formation.

The failed log-rank test and hazard ratios for VA decline and onset of blindness indicate that the rate of vision decline was insignificant among high and low dose groups. It can be seen in Fig. 2C-F that the Kaplan-Meier curves intersect meaning the incidence rates are not different at all studies time points between high and low dose groups. Interestingly, VA decline and onset of blindness has significant relative risks, but such analysis does not consider time points, or rates. Incidence of VA decline may also be due to confounding variables, including endpoints assessed in this study (i.e., cataracts or radiation retinopathy). A larger patient population with adequate follow up would be necessary to strengthen these findings, but based on RR analysis, it is concluded that increased dose to the optic disc and macula dose may influence VA decline.

The studied patient demographics aligned with previous reports, including the median doses to the macula, optic disc and lens, [15,20,33,34]. Additionally, similar toxicity-dose relationships and survival differences have been reported among univariate analyses, hazard ratios, and Kaplan-Meier analyses [15,20]. The evaluated dose of $D_{\text{macula}} > 52$ Gy and $D_{\text{OD}} > 42$ Gy were like those found by Gündüz et al. who evaluated high retinopathy rates at $D_{\text{macula}} > 57$ Gy and $D_{\text{OD}} > 44$ Gy, and concluded that macula doses below $50$ Gy may be tolerable for eye plaque patients [33]. Their conclusion is strengthened by the results of this work. The reported rate of retinopathy (65 %) falls within the wide range found in previous studies (22–70 %). Rates for VA decline, and cataract formation were similar to those described in COMS Reports and previous studies [2,6,9,10,15,20,35,36].

Clinical implications

This study provides incidence rates of toxicity for $D_{\text{macula}}$, $D_{\text{OD}}$, or $D_{\text{lens}}$ (Table 4). Such format is similarly used by QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) allowing quick references for dose and estimated toxicities (Table 4) [31]. A reference table such as this may be helpful for tumors located in undesirable positions relative to the macula, where planning reveals that a dose will be above tolerance. In the case of high macula dose, the physician may be better informed to proactively prescribe anti-VEGF or other preventative therapies to reduce the risk of retinopathy [23,24]. Additionally novel preventative strategies might be considered such as vitreous replacements which help attenuate and reduce excess dose [37–39]. Strategies to attenuate dose to critical normal tissue should be further studied to reduce toxicity without sacrificing tumor control.

Limitations

Disadvantages of this study include the small sample size and consequential lack of long term follow up. After five years only a small portion of patients ($n = 15$) had continued follow-up data. Toxicities such as radiation retinopathy or moderate VA decline can take years to develop, and such rates are underestimated in patients with follow up data less than five years. The tails of cumulative incidence plots may be...
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confirm the results. These variables were accounted for in this work however future studies are necessary to
( Table 1 ). Glaucoma, retinal detachment, and macular degeneration
need for large patient populations with long term survival and toxicity

patients are regularly followed up by their ophthalmologist, it is assumed

hazard ratios and log-rank tests for blindness and VA decline study could
analysis and relative risk estimates, however the lack of significant

This study only used clinical factors; no cytogenetic or histological
factors were analyzed. It is difficult to evaluate the true effect of radi
data in eye plaque patients.

Toxicity: Variable: P: Mean with Toxicity Mean without Toxicity

<table>
<thead>
<tr>
<th>Radiation Retinopathy</th>
<th>Variable</th>
<th>P</th>
<th>Mean with Toxicity</th>
<th>Mean without Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Optic Disc (Gy)</td>
<td>0.03</td>
<td>55.5</td>
<td>35.6</td>
<td></td>
</tr>
<tr>
<td>*Distance (mm)</td>
<td>0.03</td>
<td>11.1</td>
<td>13.6</td>
<td></td>
</tr>
<tr>
<td>*Macula Dose (Gy)</td>
<td>0.001</td>
<td>87.6</td>
<td>39.7</td>
<td></td>
</tr>
<tr>
<td>*Macula Distance (mm)</td>
<td>0.01</td>
<td>9.8</td>
<td>12.7</td>
<td></td>
</tr>
<tr>
<td>Tumor Height (mm)</td>
<td>0.41</td>
<td>4.24</td>
<td>4.41</td>
<td></td>
</tr>
<tr>
<td>Plaque Diameter (mm)</td>
<td>0.06</td>
<td>17.6</td>
<td>16.6</td>
<td></td>
</tr>
<tr>
<td>*Age</td>
<td>0.04</td>
<td>67.9</td>
<td>61.3</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.30</td>
<td>30.6</td>
<td>29.4</td>
<td></td>
</tr>
</tbody>
</table>

| Moderate VA Decline   | *Optic Disc Dose (Gy)          | 0.01 | 59.0 | 41.6 |
| a                    |                                | 0.04 | 10.9 | 12.7 |
| b                    |                                | 0.02 | 89.6 | 58.4 |
| *Macula Distance (mm)| 0.01                           | 9.33 | 11.7 |
| Tumor Height (mm)    | 0.31                           | 4.33 | 4.04 |
| Plaque Diameter (mm) | 0.14                           | 17.5 | 16.8 |
| *Macula dose (Gy)    | 0.05                           | 95.2 | 64.4 |
| Macula Distance (mm) | 0.11                           | 9.42 | 11.1 |
| Tumor Height (mm)    | 0.09                           | 4.43 | 3.96 |
| Plaque Diameter (mm) | 0.11                           | 17.5 | 16.5 |
| *Age                 | 0.09                           | 65.9 | 60.1 |
| BMI                   | 0.36                           | 30.2 | 29.5 |
| *Optic Disc Distance (mm) | 0.04 | 10.5 | 12.7 |
| *Macula Dose (Gy)    | 0.05                           | 95.2 | 64.4 |
| Macula Distance (mm) | 0.11                           | 9.42 | 11.1 |
| Tumor Height (mm)    | 0.09                           | 4.43 | 3.96 |
| Plaque Diameter (mm) | 0.11                           | 17.5 | 16.5 |
| *Age                 | 0.22                           | 64.9 | 61.4 |
| BMI                   | 0.42                           | 30.1 | 29.6 |
| *Lens Dose (Gy)      | 0.003                          | 19.9 | 13.6 |
| Lens Distance (mm)   | 0.07                           | 15.9 | 16.6 |
| Tumor Height (mm)    | 0.06                           | 4.49 | 3.51 |
| Plaque Diameter (mm) | 0.38                           | 17.3 | 17.1 |
| *Age                 | 0.95                           | 62.9 | 58.6 |
| BMI                   | 0.27                           | 29.8 | 28.8 |

| Cataract              | *Lens Dose > 16 Gy             | 1.71 | 1.34 | 2.18|
|                       |                                | 1.71 | 1.34 | 2.18|
|                       | Proximity to Lens < 15 mm     | 1.30 | 0.94 | 1.78|
|                       | *Sex (M)                      | 1.20 | 0.90 | 1.63|
|                       | Smoking History              | 0.78 | 0.45 | 1.36|

Table 5
Two Sample T-Test Results. Toxicity endpoints and related variables.

Table 6
Relative Risk Estimates Relative risk (RR) estimates are shown for radiation retinopathy, VA decline and onset of blindness.

- Indicates significance (P ≤ 0.05) without confounding variables.
- Preexisting glaucoma removes significance.
- Preexisting macular degeneration removes significance.
- Preexisting retinal detachment removes significance.

less dependable as the number of patients declined. There is a strong need for large patient populations with long term survival and toxicity data in eye plaque patients.

This study only used clinical factors; no cytogenetic or histological factors were analyzed. It is difficult to evaluate the true effect of radiation on VA given the presence of confounding clinical factors. For example, 26 of the 52 patients had pre-existing eye condition(s) (Table 1). Glaucoma, retinal detachment, and macular degeneration were accounted for in this work however future studies are necessary to confirm the results. These variables were accounted for the univariate analysis and relative risk estimates, however the lack of significant hazard ratios and log-rank tests for blindness and VA decline study could be due to confounding variables that affect vision. Moreover, conditions such as cataract and retinopathy will both contribute to VA decline, making two outcomes difficult to distinguish. In addition, many patients received treatments to alleviate their side effects including anti-VEGF (n = 13) therapies for radiation-induced macular edema or laser therapy (n = 4) for neovascularization due to radiation retinopathy. There exists variability in treatment for retinopathy in our data, however since patients are regularly followed up by their ophthalmologist, it is assumed they all are receiving the standard of care. For the best clinical recommendations, a larger, more uniform sample size, or a prospective trial with long term follow up is needed to ensure adequate and accurate representation of the patient population.

The dose calculations performed in this study were homogeneous, water-only calculations made by the TPS. Heterogeneous dose estimates can be estimated according to published data in AAPM Task Group 129.
based on Monte Carlo calculations, however currently no TPS performs heterogenous dose calculation for COMS eye plaque therapy. The doses reported here are an overestimate without the Silastic seed carrier and gold-alloy backing heterogeneity considerations. AAPM Task Groups 43, 129, and 221 suggest reported dose to water until a heterogeneous TPS exists, dual-calculation reporting of both homo- and heterogenous doses are encouraged [3,7,29,30,40]. Homogenous doses were reported in this work to align with previous eye plaque dosimetry literature and to translate results to future patients with similar treatment planning methods. Additionally, doses were calculated as point doses which may lead to error, especially with larger OAR’s such as the lens, with such steep dose gradients presented by brachytherapy sources. The advancement of Monte Carlo model-based calculations for eye plaque brachytherapy has been proposed for $^{125}$I and $^{106}$Ru applicators to use patient specific geometry models [41]. Recent studies have analyzed the use 3D planning based on CT images to create more accurate dose plans based on OAR volume and placement in a realistic eye geometry [42,43]. When such methods are used clinically, relevant dose-outcome relationships should be analyzed.

Only $^{125}$I COMS plaques were used in this study, leaving questions remaining for other plaque manufacturers and isotopes, especially beta-emitting sources or even the recently-proposed dual-core eye plaque [44]. Similar studies need to be performed to make equivalent conclusions. While several studies have compared tumor control and toxicity across different isotopes, further work can consolidate specific dose–response relationships for all isotopes and plaque types to establish dose limits to OARs in the eye [34,45]. It is noted that isotopes with differing half-lives do not have directly translatable results [46]. A biological effective dose calculation would be required to compare OAR dose values, which is outside the scope of this work.

Despite the limitations presented, the data provided gives valuable information for treatment decisions in the clinic for eye plaque brachytherapy and encourages future work to improve ocular dose limit recommendations. For patients approaching high normal tissue dose during treatment planning, preventative strategies could be implemented such as vitreous replacements or pharmaceuticals. Depending on availability, options such as Gamma Knife® or proton therapy may be necessary for tumors close to normal tissues that would otherwise receive a remarkably high dose using eye plaques.

**Conclusion**

Eyes treated with the COMS $^{125}$I eye plaque technique commonly experience vision decline over time. Incidence rates and dose-toxicity
relationships are reported to encourage continuous work of defining ocular dose limits and dose reduction strategies. It was found that dose to the macula (>52 Gy) and optic disc (>42 Gy) may predict risk of radiation retinopathy, and vision decline. Dose to the lens (>16 Gy) may predict cataract formation. Patients can be counseled with these tolerances in mind.

Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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