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Determinants of Radiation Dose in Selective Ophthalmic Artery Chemosurgery for Retinoblastoma

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ABSTRACT

BACKGROUND AND PURPOSE: Retinoblastoma is the most common pediatric ocular neoplasm. Multimodality treatment approaches are commonplace, and selective ophthalmic artery chemosurgery has emerged as a safe and effective treatment in selected patients. Minimizing radiation dose in this highly radiosensitive patient cohort is critical. We explore which procedural factors affect the radiation dose in a single-center cohort of children managed in the UK National Retinoblastoma Service.

MATERIALS AND METHODS: A retrospective review was performed of 177 selective ophthalmic artery chemosurgery procedures in 48 patients with retinoblastoma (2013–2017). Medical records, angiographic imaging, and radiation dosimetry data (including total fluoroscopic screening time, skin dose, and dose-area product) were reviewed.

RESULTS: The mean fluoroscopic time was 13.5 ± 13 minutes, the mean dose-area product was 11.7 ± 9.7 Gy.cm², and the mean total skin dose was 260.9 ± 211.6 mGy. One hundred sixty-three of 177 procedures (92.1%) were technically successful. In 14 (7.9%), the initial attempt was unsuccessful (successful in 13/14 re-attempts). Screening time and radiation dose were associated with drug-delivery microcatheter location and patient age; screening time was associated with treatment cycle.

CONCLUSIONS: In selective ophthalmic artery chemosurgery, a microcatheter tip position in the proximal or ostial ophthalmic artery and patient age 2 years or younger were associated with reduced fluoroscopic screening time and radiation dose; treatment beyond the first cycle was associated with reduced fluoroscopic screening time.

ABBREVIATIONS: DAP = dose-area product; OA = ophthalmic artery; SOAC = selective ophthalmic artery chemosurgery

Retinoblastoma is the most common pediatric ocular neoplasm, occurring in approximately 1 in 20,000 live births. In the United Kingdom, approximately 40–50 new cases are diagnosed annually.¹ Retinoblastoma develops from a retinal cone precursor cell in response to bi-allelic inactivation of the *RB1* gene on chromosome 13.^{1,2} The *RB1* gene product is the retinoblastoma protein, a tumor suppressor. Gene mutations may be hereditary (40%) or sporadic (60%). Hereditary disease is more likely to present earlier with bilateral disease and be associated with other cancers.

Overall patient survival in retinoblastoma is high (exceeding 95%) in resource-rich settings, where detection and treatment of

disease are prompt.³ Several options exist for treatment, guided by the extent of tumor spread, as determined by the International Classification of Retinoblastoma (Table 1).⁴ Selective ophthalmic artery chemosurgery (SOAC) has emerged as a valid treatment technique for group A–D tumors, with substantial ocular salvage rates, particularly in lower tumor grades.^{5,6} Potential SOAC benefits include ocular preservation and less systemic toxicity associated with standard intravenous chemotherapy regimens. Exposure to ionizing radiation during angiography and fluoroscopic positioning of the delivery microcatheter are potential detriments. Adverse effects of external beam radiation therapy treatment used historically in retinoblastoma treatment are well established. These include cataract formation, ocular dryness, facial dysmorphism, and secondary neoplasms.⁷ Although radiation doses used in SOAC are substantially lower than in external beam radiation therapy, this patient group is exquisitely radiosensitive (familial retinoblastoma has a predilection for second tumor formation) and strategies to minimize radiation dose are imperative (according to the As Low As Reasonably Achievable principles).^{8,9} This can be achieved in SOAC by judicious adjustment of fluoro-

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Table 1: The International Classification of Retinoblastoma⁴

Group	Features
A	Tumor ≤ 3 mm
B	Tumor > 3 mm or macular location (≤ 3 mm to foveola), juxtapapillary location (≤ 1.5 mm to disc), clear subretinal fluid (≤ 3 mm from margin)
C	Tumor with subretinal and/or vitreous seeds ≤ 3 mm from tumor
D	Tumor with subretinal and/or vitreous seeds > 3 mm from tumor
E	Extensive retinoblastoma occupying $> 50\%$ of globe or neovascular glaucoma; opaque media from hemorrhage in anterior chamber, vitreous, or subretinal space; invasion of postlaminar optic nerve, choroid (> 2 mm), sclera, orbit, anterior chamber

scopic exposure settings, limiting screening times, and minimizing angiography.¹⁰ This study assessed SOAC radiation dose in a single center with the aim of informing further dose-reduction strategies. The study group was selected from the latter half of a 10-year institutional experience of over 320 SOAC procedures in > 100 patients, reflecting an experienced service with established protocols.

MATERIALS AND METHODS

We conducted a retrospective review of 177 consecutive SOAC procedures, performed between January 2013 and December 2017 in 48 patients with a diagnosis of retinoblastoma. This study was registered as a Service Evaluation with the hospital Clinical Audit Department and was exempt from approval from a local research ethics committee. All patients undergoing SOAC had group C or D tumors, and all had relapsed after first-line systemic chemotherapy. No patients underwent SOAC as a first-line treatment. Data collection encompassed review of medical records, angiographic imaging, and radiation dosimetry data, which were obtained from our system dose reports. These included total fluoroscopic time, skin dose, and dose-area product (DAP) (currently DAP is designated Kerma area product by the International Commission on Radiologic Protection¹¹). Twenty procedures in 14 patients were excluded due to incomplete dose reports. “Technical procedural failure” was defined as failure to deliver a complete planned dose of intra-arterial chemotherapy in the given treatment episode. There were no clinically apparent angiographic complications during this period.

SOAC Technique

Patients were selected for SOAC by a multidisciplinary team including oncology, ophthalmology, and neurointerventional radiology. Pediatric neurointerventional subspecialists with > 5 years’ postfellowship experience performed SOAC with the patient under general anesthesia. A 4F catheter was positioned in the ipsilateral internal carotid artery via a transfemoral approach following full intravenous heparinization (75 U/kg). A preliminary control biplane angiogram was obtained. In conventional anatomy, the ophthalmic artery was catheterized using a variety of over-the-wire and flow-directed microcatheters (typically Magic microcatheter 1.2F or 1.8F; Balt, Montmorency, France) using 0.007- or 0.008-inch wires such as Hybrid 0.007 (Balt), ASAHI CHIKAI 0.008 (Asahi-Intecc, Aichi, Japan), and Mirage 0.008 (Covidien,

Irvine, California). In variant anatomy, accessory ophthalmic supply from the external carotid artery was used (typically through the anterior division of the middle meningeal artery). A single patient had bilateral SOAC in a single session (2 episodes total). This was due to synchronous bilateral disease relapse, and these 2 treatment episodes were excluded from analysis because the doses could not be separated. In all other cases with bilateral disease, a single eye was treated at each session.

Before delivering chemotherapy, we confirmed stable tip position and antegrade ophthalmic artery contrast flow with evidence of choroidal blush by superselective biplane microcatheter angiography (On-line Figure). When a stable ostial position could not be achieved in the ophthalmic artery (OA) origin, the vessel was catheterized more distally. Microcatheter tip delivery position was recorded as “origin” when located at the ostium, “proximal” when in the OA proximal to the midpoint between the ostium and the angiographic angle, and “distal” when beyond this midpoint.¹² Chemotherapy was typically delivered during 30 minutes, with occasional short single-plane fluoroscopic pulses to confirm stable catheter tip position when there were stability concerns. No further angiography was performed.

Fluoroscopic Protocol

All procedures were performed on an Artis zee (Siemens, Erlangen, Germany) biplane flat panel angiography suite used exclusively for pediatric work. Digital subtraction angiography used both frontal and lateral intensifiers with automatic exposure control parameters set to maximal values of 3 μ Gy per frame at 4 frames per second. Fluoroscopic screening was performed with automatic adjustment of kilovolt and milliamperes-second, at 7.5 or 10 pulses per second. Detector dose was set to 29 or 36 nGy/p. Magnification during initial angiography was set at 32 cm on the frontal detector and 42 cm on the lateral detector and magnified to 22 or 16 cm on the lateral detector during superselective ophthalmic artery angiography/fluoroscopy.

The radiation dose was minimized by optimizing collimation, filtration, and reducing patient-to-detector distance and magnification when possible.

Statistical Analysis

Data are summarized by descriptive statistics. Mean and SD are reported for radiation dose parameters. By means of SPSS software, Version 25 (IBM, Armonk, New York), a 2-tailed independent-samples *t* test was used to compare the radiation dose parameters for patient age category, treatment cycle, and successful-versus-abandoned procedures. A Kruskal-Wallis test was used to compare radiation doses among years, injected vessels, and operators. Bland-Altman statistics were used to compare the association between screening times and abandoned procedures. $P \leq .05$ was considered statistically significant for all tests.

RESULTS

Forty-eight patients underwent selective ophthalmic artery chemosurgery (male/female ratio = 22:26). Thirty-three patients had bilateral retinoblastoma, and 15 had unilateral disease. In 177 procedures, 163 (92.1%) were technically successful. Fourteen (7.9%) procedures were unsuccessful, usually due to induced OA

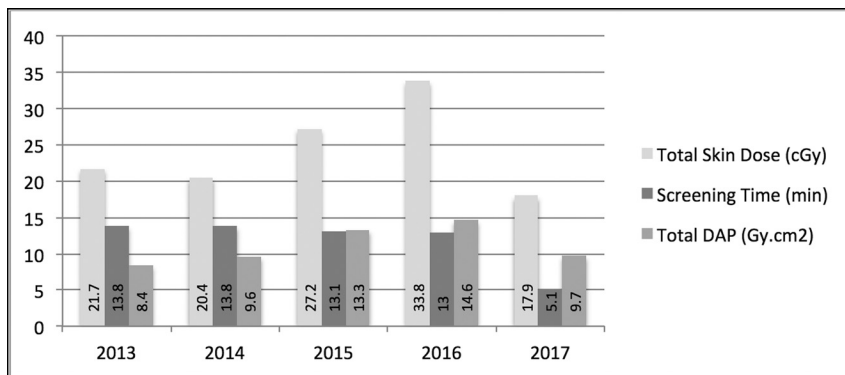


FIG 1. Mean screening times, total skin dose, and total DAP by year.

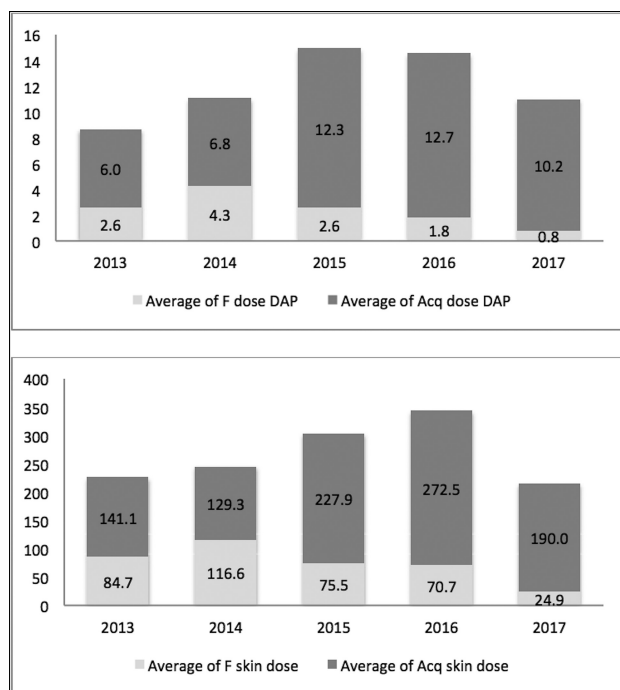


FIG 2. Angiographic acquisitions (Acq) were responsible for most of the radiation dose, and its proportion of the contribution to the overall dose gradually increased between 2014 and 2017. F indicates fluoroscopic.

ostial spasm. Repeat procedures were successful on subsequent attempts in all except 1 patient, in whom anomalous anatomy prevented stable microcatheter positioning.

The mean fluoroscopic time was 13.5 ± 13 minutes, (range, 1.5–67.2 minutes).

The mean dose-area product was 11.7 ± 9.7 Gy.cm² (range, 1.7–55.4 Gy × cm²).

The mean total skin dose was 260.9 ± 211.6 mGy (range, 43–1243 mGy).

All parameters were higher in abandoned procedures: screening time (35.7 ± 16 versus 11.5 ± 10.8 minutes) ($P < .01$), dose-area product (22 ± 13 versus 10.8 ± 8.8 Gy.cm²) ($P < .01$), and skin dose (543.7 ± 255.4 versus 236.6 ± 189.5 mGy) ($P < .01$). When screening time exceeded 25 minutes, the procedure was successful in only 11% of patients, with a mean DAP of 18.5 Gy.cm² and a skin dose of 470.7 mGy in this group.

There was a progressive reduction in screening time during the

study period, with increasing experience and latterly reflecting a move toward a more proximal/ostial OA catheter position, which was almost exclusive in 2017 (Fig 1). The total DAP and skin dose also fell in 2017. A greater proportion of the radiation dose came from angiographic acquisitions versus fluoroscopic screening (Fig 2).

In the 163 technically successful procedures, infusion was performed via the OA in 128 (78.5%) and via the external carotid artery collateral supply to the OA in 35 (21.5%). Of the 128 OA infusions, 67 (52%) were made at the origin/os-

tium, 17 (13%) at the proximal vessel, and 44 (35%) at the distal vessel. The screening times, total DAP, and total skin doses were lower with ostial or proximal OA microcatheter tip positions compared with more distal OA or external carotid artery positions (Table 2).

Among operators, there were no significant differences in screening time (12.3 ± 11 versus 10.5 ± 10.2 versus 14.4 ± 15 minutes) or total DAP (10.6 ± 7.9 versus 11.3 ± 9.9 versus 8.8 ± 7.1 Gy.cm²), though a significant difference was noted in total skin dose (258.1 ± 200.6 versus 207.4 ± 165.9 versus 295.6 ± 259.4 mGy).

There were significantly higher total DAP (12.8 ± 9.5 versus 10.8 ± 11.3 Gy.cm²) and total skin doses (281.9 ± 218.3 versus 194 ± 146.6 mGy) in procedures performed on children older than 2 years of age. Although the screening time was also greater in this age group (12.4 ± 10.4 versus 10.8 ± 11.3 minutes), this difference was not significant.

Mean screening time was significantly longer in the first cycle of treatment compared with follow-up cycles (12.7 ± 11.5 versus 8 ± 7.4 minutes). This screening time did not translate into a significant difference in radiation dose (total DAP, 10.8 ± 8.9 versus 11 ± 8.7 Gy.cm²; and total skin dose, 238.5 ± 200 versus 230.9 ± 154.6 mGy) between cycles, however.

DISCUSSION

We report the radiation dose for SOAC procedures during the second 5-year period of our 10-year experience.

The mean screening time in this cohort was 13.5 minutes and mainly reflects the duration of fluoroscopic radiation exposure. This has multiple determinants, including anatomic considerations, microcatheterization strategy, fluoroscopic protocol, and operator experience.¹³ Lower mean screening times were reported by Cooke et al¹⁰ and Boddu et al¹⁴ at 8.5 and 10.2 minutes, respectively. However in this cohort, there was a wide range of screening times (maximal time of 67.2 minutes), and a median screening time of 7.3 minutes is more reflective of local practice.

Dose-area product/Kerma area product and patient entrance dose/skin dose are considered more accurate surrogate measures of patient radiation exposure. The DAP is a product of the radiation dose within the field and the area of tissue irradiated. This influences but is not synonymous with patient dose (which incorporates additional factors, such as patient body habitus, x-ray

Table 2: Comparison among fluoroscopic screening time, total DAP, and total skin dose between ophthalmic artery and ECA branch injections

	Mean ($\pm$ SD)	P Value
Screening time (min)		
OA origin	9.2 ($\pm$ 9.65)	.0001
OA proximal	11.9 ($\pm$ 7.1)	
OA distal	14.3 ($\pm$ 11)	
ECA	12.5 ($\pm$ 13.5)	
Total DAP (Gy.cm ²)		
OA origin	10.2 ($\pm$ 9.5)	.016
OA proximal	6.9 ($\pm$ 2.9)	
OA distal	11.3 ($\pm$ 6.6)	
ECA	13.3 ($\pm$ 11)	
Total skin dose (mGy)		
OA origin	205.7 ($\pm$ 170.7)	.001
OA proximal	146.8 ($\pm$ 71.1)	
OA distal	271.4 ($\pm$ 168.9)	
ECA	295.7 ($\pm$ 254.7)	

Note:—ECA indicates external carotid artery.

beam quality, and radiation sensitivity of the irradiated tissue).¹⁵ The skin dose in our study measures the total skin dose (or cumulative radiation dose absorbed at the skin). Total skin dose differs from but correlates with¹⁶ peak skin dose. Peak skin dose correlates more closely with skin injury, but its calculation requires a priori analysis and is not the primary output parameter of the Siemens system. The DAP values in our series were higher than those reported by Boddu et al,¹⁴ reflecting a difference in procedural techniques. Ipsilateral internal carotid artery digital subtraction angiography was performed initially in all procedures to delineate vessel anatomy in our cohort, while others relied solely on lower dose fluoroscopic road-mapping techniques.

Figure 2 demonstrates a reduction in the component of radiation dose from fluoroscopy across the years (commensurate with reducing screening times), leading to a greater contribution to dose from angiographic acquisitions. Other dose-reducing methods such as lowering the fluoroscopic pulse rate and DSA frame rates and more active collimation and reduction of patient-intensifier distance are reflected in falling doses across time.¹⁷ Manufacturer innovations such as CAREposition (Siemens) have further helped reduce screening time. This technology allows patient repositioning in the imaging field without radiographic exposure using a moving outline box and crosshair on a last-image hold display. The procedural radiation exposure in this series remains below that described for cerebral angiography in children, but there is clearly room for further improvement.¹⁸

Extended procedures have a significant impact on radiation dose with diminishing returns. Our practice has evolved to abandon the procedure if protracted attempts at vessel catheterization are unsuccessful, particularly when faced with spasm in target vessels. In all except 1 patient, the first re-attempt was successful.

Our superselective approach (distal catheterization of the ophthalmic artery) provides a viable alternative in challenging anatomy but can be time-consuming and almost certainly contributes to increased screening times and radiation dose. Alternative strategies such temporary balloon occlusion of the ICA distal to the ophthalmic artery to redirect the microcatheter or chemotherapy into the target artery have been described by other groups.¹⁹ We have not resorted to this technique out of concern

for ICA damage and distal embolism. With our approach, there have been no vessel dissections or cerebral embolic complications in >350 procedures. The lowest radiation doses occurred with proximal and ostial microcatheter positions, and now superselective catheterization is only used when a stable ostial position cannot be achieved.

Patients younger than 2 years of age had significantly lower radiation exposure, explained by smaller patient size, active lowering of fluoroscopic dose, and aggressive collimation.

Screening times were higher in the first cycle of treatment, compared with subsequent cycles, a finding consistent with other groups.¹⁴ Once a successful catheterization strategy is identified, this generally proves reproducible. The reduction in screening time on subsequent treatment cycle was not reflected in reduced DAP or skin dose, however, because angiographic runs contributed to the bulk of that dose.

There are limitations of a retrospective single-center study. A number of patients were excluded from the study due to incomplete dose-data recording. In our practice, SOAC was only used as salvage therapy in C and D eyes relapsed after systemic chemotherapy, whereas most published cohorts tended toward broader indications (eg, B eyes) and with SOAC as first-line treatment.

CONCLUSIONS

SOAC is established as a safe and effective treatment for retinoblastoma in selected cases in which disease is limited to the orbit. Minimizing radiation dose must be a priority in this exquisitely radiosensitive patient cohort. Our data support a strategy of proximal or ostial OA microcatheter positioning and minimizing the use of angiographic runs in favor of fluoroscopic techniques. Procedures in children younger than 2 years of age were associated with reduced screening time and radiation dose. Screening times fall in subsequent treatment cycles as a patient-specific catheterization strategy is established.

Careful procedural planning, operator experience, judicious use of dose-reducing techniques, advances in angiographic imaging technology, and the use of specific imaging equipment parameters for pediatric populations all contribute to reducing radiation dose.

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